Indian Society of Nephrology
Southern Chapter

Volume 8, Issue 1, 2015

Newsletter

In February 2015, at Calicut, The Governing Body and the Executive Committee of ISNSC have been reconstituted. We are presenting important photographs of the ISNSCCON 2015. World Kidney Day has been celebrated in several of South Indian Nephrology centres. We are presenting photographs of these celebrations. In page 3 and 4 we are carrying the text version of Tanker Award Presentation and the Dr.Niyamatullah Award winning essay.

The Governing Body

Dr RamdasPisharody
Chairperson
Dr R. Padmanabhan
Vice Chairperson
Dr KN Arun
Vice Chairperson
Dr. R Ram
Hon. Secretary
Dr. Desai Madhav
Hon. Treasurer
Executive Committee
Dr G Swarnalatha (Andhra Pradesh)
Dr Vincent Lloyd (Karnataka)
Dr SenthilNayagan (Tamil Nadu)
Dr Sreelatha M (Kerala)
Dr. Praveen (Nellore)
Hon. Secretary


Inauguration function


A section of audience


A section of audience


Dr. Dinakaran President ISNSC 2013-15


Dr. MLN Murthy


Dr. Ramdas Pisarody President ISNSC 2015-16


Dr. Thomas Mathew


Dr. Richard Glossack


Dr. Sreelatha, Organizing Secretary


Dr. Carmine Zoccali


Dr. C. Ravindran Principal Government Medical College Calicut


Honouring of the Founder Members of ISNSC


Winners of Tanker award & Dr. Niyamatullah award

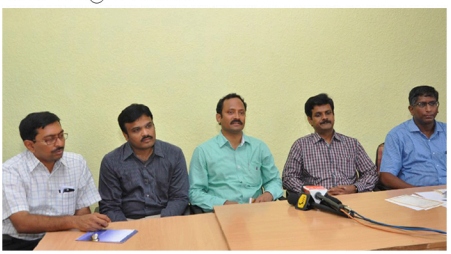
World Kidney Day Celebrations 2015

SRM Medical College Hospital -Madras

All nephrologists in Guntur and Mr. Rajesh Kumar, SP Guntur district participated in the meet.

DR.AVULASRINIVAS | Aswini Hospitals Guntur 522001 | email: avulasrinivas@hotmail.com

1. Screening camp: 500 patients were screened. History and risk profile noted. S. creatinine and blood sugar were done.



2. Press meet on spreading awareness of kidney diseases .

Celebrated World Kidney Day at Caritas Hospital, Kottayam, Kerala. Public meeting, Health talk and Kidney disease detection camp formed part of the day. Around 200 subjects were screened. Also there was Nephrology quiz competition for hospital staff.

DR SURESH GA | DR BINOY THOMAS | DR AJISH JOHN, Nephrologists, Caritas Hospital, Kottayam, email: ajishjohnvtk@gmail.com

Inaugural meeting

DR S KRISHNAN Apollo-Secunderabad54 Krishnapuri Colony, West Marredpally,Secunderabad 500 026 A.P. India
Phone 91 - 40 – 27806766 email: poojakrish54@yahoo.com

Cake cutting by a 86-year old dialysis patient in our unit on the World Kidney Day

DR.ARPANAIYENGAR, Professor and Head, Deparment of Pediatric Nephrology, St.John's Medical College Hospital, Bangalore email: arpanaiyengar@gmail.com

Magic Show at Children's Kidney Care Centre, St. John's Medical College Hospital, Bengaluru.

2. A few moments of "Magic" to bring smiles on the suffering faces of children with kidney diseases.

DR.SANKARANSUNDAR MD,DNB(Nephrology)
Director&Chief Nephrologist KANTI Ranked Top 5 in India by The WEEK Magazine Columbia Asia Hospitals Bangalore.
visit us at www.kanti.com www.columbiaasia.com

1. Dr Sundar addressing the Police and Home Guards on Preventing Kidney disease.

2. Kidney Screening of Police and Home Guards by Columbia Asia Hospitals

World Kidney Day Celebrations 2015

DR.DILIPRANGARAJAN NU hospitals, Bangalore email: dr.dilip@nuhospitals.com

1. Patients at the Kidney Screening Camp

2. Patient's blood collection at the Screening Camp

3. Nephro-Urologytalk in TV on WKD

The World Kidney Day function is an annual feature of Deccan Institute of Nephrology and Renal Transplantation, Deccan Hospitals, Rajbhavan Road, Hyderabad.The Chief Guest of the evening was the Managing Director of the Hospital, Mr.Damodar Reddy. Invited audience, 150 people in number, included patients and their attendants. Guest speakers were three Renal transplantation patients who shared their experience. Two of the patients had completed 24 years since transplantation. The third patient, who had completed ten years after cadaver renal transplantation shared his experience in hemodialysis as well as Conitnuous Ambulatory Peritoneal Dialysis (CAPD) prior to renal transplantation. The medical staff spoke about the History, Aims and Objectives of World kidney Day. The theme for the World Kidney Day 2015, "Kidney Health for All " and "Eight Golden rules" to reduce the risk of kidney disease were explained. Different modes of renal replacement therapy and Cadaver organ donation were discussed. A quiz program on kidneys was conducted, with an initial multiple choice written screening round followed by oral quiz program for ten best performers. Prizes were given for the winners. Entertainment program included Dances by invited artists. Snacks and tea were served.The event was a huge success.

Nephrology Consultants: DR.K.S.NAYAK, DR.S.V.SUBHRAMANYAM, DR.N.PAVAN KUMAR RAO. email: sreepada11@gmail.com

World Kidney Day Walkathon" on 14/03/2015

Dr.M.Jayakumar, email: mjk_mmc@yahoo.co.in

DR RAJESH R NAIR Professor Deparment of Nephrology, Amrita Institute of medical sciences Kochi email: drrajeshr70@gmail.com

1. Health checkup and awareness camp conducted at the District Collectorate, Ernakulam. It was inaugurated by the Hon Assistant Collector Sri.Mrinmayi Joshi. Awareness lectures were delivered by Drs. George Kurian, Rajesh R Nair and Anil Mathew.

2. Screening for proteinuria detection were conducted in various primary health centres of Ernakulam district

DR.SAMPATH KUMAR, email: drksampath@gmail.com

1.Public lecture

2.Kidney health Booklet in Tamil being released and received by 2 of my transplant patients.2.Public lecture

DR.SANTHOSHVARUGHESE email: santosh.vellore@gmail.com

1. Renal dietery advice

2. Screening camp for diabetes and hypertension

DR. KP JAYA KUMAR Govt Medical College, Kottayam. email: drkpjk@gmail.com

1. The function 'vilakkutheliyikkal' by Dr.RemlaBeevi

2. Light show

POLYMORPHISM OF THE CYP3A5 GENE AND ITS EFFECT ON TACROLIMUS BLOOD LEVEL

Sreeja S. Nair[1],Noble Gracious[1],Jacob Georg[1] ,Sreeja.S.[2],T.S. Anish,[3]R. Radhakrishnan [2]

From the1Department of Nephrology, Government Medical College; 2Laboratory Medicine and Molecular Diagnostics, Rajiv Gandhi Centre For Biotechnology;3Department of Preventive and Social Medicine, Government Medical College

Abstract Objectives:

Tacrolimus is the cornerstone for immunosuppression in renal transplant and is metabolized by the cytochrome P450A CYP3A subfamily of enzymes in the liver and small intestine.A polymorphism in intron 3 of the CYP3A5gene affects the expression of this enzyme and tacrolimus trough blood levels.The purpose of this study was to identify the proportion of CYP3A5 gene polymorphisms in South Indian renal transplant patients and determine the effect of CYP3A5 gene polymorphisms on tacrolimus trough blood levels in patients with and without CYP3A5 expression.

Introduction

Tacrolimus is the corner stone of immunosuppression in renal transplant. It is a macrolide antibiotic compound that acts by inhibiting the calcineurin pathway by binding to FK binding protein.1However, it has a narrow therapeutic index and requires therapeutic drug monitoring to prevent graft rejection as a result of inadequate immunosuppression with low drug levels or toxicity due to high drug levels.Tacrolimus is metabolized by the CYP3A subfamily of enzymes in the liver and small intestine. Although both CYP3A4 and CYP3A5 are involved in the metabolism of tacrolimus, previous studies have shown that polymorphisms in CYP3A5 genes are responsible for interindividual variations in bioavailability of tacrolimus.2 A polymorphism in intron 3 of the CYP3A5gene affects the expression of this enzyme. The CYP3A5*3 allele (G at position 6986) produces a cryptic splice site and encodes an abnormal spliced mRNA with a premature stop codon;thus, individuals who are homozygous for this allele (CYP3A5*3/*3) are called nonexpressors.Presence of CYP3A5*1allele (A at position 6986) produces normal mRNA, resulting in a high expression of this enzyme in the intestine and in the liver; individuals expressing at least one CYP3A5*1 allele are called expressors.Therefore, expressors can be either homozygous (CYP3A5*1/*1) or heterozygous (CYP3A5*1/*3).3,4 Previous studies showed that expressors achieved 2-fold lower tacrolimus concentrations-to-dose ratio compared with nonexpressors.5-9Therefore, we aimed to find the proportion of nonexpressors and expressors and clarify the role of CYP3A5 polymorphism on tacrolimus drug levels in our renal transplant population.

Materials and Methods *Patients*

We included 25 adult patients who underwent renal transplant at Government Medical College, Trivandrum, Kerala, India. The study was approved by the ethics committee of the institution before the study began, and the protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration. Written informed consent was obtained from all patients. All patients received tacrolimus (dose,0.1 mg/kg bodyweight)with prednisolone and mycophenolate mofetil.Tacrolimus 12-hour trough blood level was determined on postoperative day 6 using a chromatographic method (liquid chromatography-tandem mass spectrometry assay). The lower limit of quantification of the assay was 0. 003ng/mL.

Genotype analyses. Genotype analyses of all patients were performed to identify the CYP3A5 allele. Nucleic acid isolation was performed using a standard magnetic bead-based extraction protocol according to the manufacturers (MagJET DNA and RNA Purification Kits,Thermo Fisher Scientific Corporation, Massachusetts,USA)Custom-designed primers synthesized from human cytochrome P450 PCN3 mRNA (cytochrome P450, family3,subfamily A,polypeptide 5) complete cDNAs were used for polymerase chain reaction amplification of the target. The polymerase chain reaction protocol was a standardized procedure for the selected primer sequence done using thermal cycler (Applied Biosystem, Thermo Fisher Scientific Corporation. Massachusetts,USA). Postamplification detection was performed by restriction fragment length polymorphism analysis using SspI endonuclease(New England Biolabs Inc, Massachusetts,USA).

Statistical analyses

Data were reported as mean ±standard deviation (SD) or mean (range, minimum to maximum) for all quantitative estimates.Tacrolimus trough blood levels between 2 groups were compared with independent ttest. Statistical analysis was done using software (SPSS for Windows, Version 16. 0, SPSS Inc., Chicago, IL, USA).

Results

Characteristics of study population In the 25 renal graft recipients who were included in the study, there were 22 males and 3 females (Table 1). The mean age was 32 ± 20 years and body weight was 58 ± 11 kg. There were 3 patients who received induction therapy (2 patients received antithymocyte globulin and 1 patient received basiliximab).Mean donor age was 44±12 years.At 1month after transplant, the incidence of biopsy-proven acute rejection was 20% (all T-cell-mediated rejection). There were 8 graft biopsies obtained from the study population in the first month after transplant,and the incidence of tacrolimus nephrotoxicity in this subgroup was 8%. Frequency of CYP3A5 genotypes and relation to tacrolimus level The CYP3A5*1/*1, *1/*3, and *3/*3 genotypes were detected in 5 (20%), 5 (20%), and 15 (60%) of the 25 graft recipients(Table1).Mean tacrolimus trough level in the CYP3A5*1/*1 group was 5.154 ng/mL (range, 4.42 to 6.5 ng/mL), CYP3A5*1/*3 group was5.348 ng/mL (range, 3.1 to 9.87ng/mL) and CYP3A5*3/*3 group was 9.483 ng/mL.(range, 4.5 to 14.1ng/mL). Tacrolimus level difference between expressors and nonexpressors was significant when compared with independent t test. (t,-4.28; degrees of freedom, 23; P ≤ .001). Effect of CYP3A5genetic polymorphisms on acute rejection episodes and tacrolimus nephrotoxicity

Biopsy-proven acute renal graft rejection on biopsies obtained at 1 month after transplant was compared between the 3 CYP3A5 genotype groups. Acute rejection episodes were significantly more frequent for CYP3A5*1 homozygotes (2 out of 5 40%) than patients with CYP3A5*1/*3 (1out of 5-20%) or CYP3A5*3/*3 genotypes (2 out of 15-13%). We examined the relation between CYP3A5 genetic polymorphism and biopsyproven nephrotoxicity due to tacrolimus use; 8renal biopsies were obtained during 1month, and 2 biopsies (both in nonexpressors) had evidence of calcineurin-induced toxicity.

Discussion

Tacrolimus is a potent immunosuppressive drug used in solid organ transplant.1However, it has a narrow therapeutic range, which is further complicated by wide variation in intraindividual and interindividual variability in bioavailability of the drug.Tacrolimus is metabolized by CYP3A4 and CYP3A5 in the liver and small intestine. Genetic polymorphisms in CYP3A5 affect the interindividual variability in tacrolimus trough blood levels.2

In our study, we evaluated the effect of CYP3A5genetic polymorphisms on tacrolimus daily dose requirements in a cohort of kidney transplant recipients. Our results showed that carriers of at least 1 active allele (CYP3A5*1) needed significantly higher doses of tacrolimus than patients homozygous for CYP3A5*3 (CYP3A5 nonexpressors).This result relied on the fact that carriers of CYP3A5*1allele exhibit high levels of CYP3A5 expression and enzymatic activity, leading to higher daily dose requirement to achieve sufficient trough levels of tacrolimus. Such results have been reported previously in the literature concerning this polymorphism.5-10

A previous study by Patel and associates studied the effect of CYP3A5 polymorphism on tacrolimus drug dosing in North Indian renal allograft recipients.11To our knowledge, the present study is the first study to show the association between CYP3A5 genetic polymorphism and tacrolimus drug level in a South Indian population.

We evaluated the risk of biopsy-proven acute rejection during the first month after transplant. We observed that patients with CYP3A5*1/*1genotype had a higher risk of developing acute graft rejection episodes than CYP3A5*3homozygotes. This observation is in agreement with the fact that carriers of the wild-type allele (CYP3A5*1) have higher levels of CYP3A5 expression, higher metabolic clearance of tacrolimus, and low trough concentrations resulting in acute rejection.A previous study by Quteineh and coworkers showed that CYP3A5*1homozygotes had increased risk of acute rejection episodes (38%) than patients with CYP3A5*1/*3(10%) or CYP3A5*3/*3(9%) genotypes (P = .01).12They also reported that few rejection episodes occurred after the first month after transplant, and overall rejection episodes were more important during the first month after transplant. This showed the importance of performing tacrolimus daily doses early posttransplant, when there is a greater risk of developing acute rejection episodes.12

We studied the relation between CYP3A5 genotype and biopsy-proven tacrolimus nephrotoxicity.We observed increased occurrence of nephrotoxicity in CYP3A5 nonexpressors.This was expected because of high trough blood levels in these patients. However,we were limited by the small number of biopsies to substantiate this finding. The previous study by Quteineh and associates showed no relation between the development of tacrolimus-related nephrotoxicity and CYP3A5genetic polymorphism.12 In conclusion, our results confirmed that CYP3A5 genetic polymorphism is an important factor in determining tacrolimus daily requirements and adjusting tacrolimus trough concentrations. Furthermore, it was shown in our study that genetic polymorphism is a risk factor for developing acute rejection episodes. Screening for this polymorphism in patients waiting for solid organ transplant could be helpful to predict the best individualized tacrolimus oral dose and may prevent early acute rejection related to insufficient immunosuppression.

References

1. Halloran PF. Immunosuppressive drugs for kidney transplantation. N Engl J Med. 2004; 351(26):2715-2729.

2. Kamdem LK, Streit F, Zanger UM, et al. Contribution of CYP3A5 to the in vitro hepatic clearance of tacrolimus. Clin Chem. 2005;51(8): 1374-1381.

3. Kuehl P, Zhang J, Lin Y, et al.Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nat Genet. 2001;27(4):383-391.

4. Hustert E, Haberl M, Burk O, et al. The genetic determinants of the CYP3A5 polymorphism.Pharmacogenetics. 2001;11(9):773-779.

5. Thervet E, Anglicheau D, King B, et al. Impact of cytochrome p450 3A5 genetic polymorphism on tacrolimus doses and concentration-to-dose ratio in renal transplant recipients. Transplantation. 2003;76(8):1233-1235.

6. Anglicheau D, Legendre C, Thervet E. Pharmacogenetics in solid organ transplantation: present knowledge and future perspectives. Transplantation. 2004;78(3):311-315.

7. Tada H, Tsuchiya N, Satoh S, et al.Impact of CYP3A5 and MDR1(ABCB1) C3435T polymorphisms on the pharmacokinetics of tacrolimus in renal transplant recipients. Transplant Proc. 2005;37(4):1730-1732.

8. Mourad M, Mourad G, Wallemacq P, et al. Sirolimus and tacrolimus trough concentrations and dose requirements after kidney transplantation in relation to CYP3A5 and MDR1 polymorphisms and steroids. Transplantation. 2005;80(7):977-984.
9. Macphee IA, Fredericks S, Mohamed M, et al. Tacrolimus pharmacogenetics: the CYP3A5*1allele predicts low dose-normalized tacrolimus blood concentrations in whites and South Asians. Transplantation. 2005;79(4):499-502.

10. Zuo XC, Ng CM, Barrett JS, et al .Effects of CYP3A4 and CYP3A5 polymorphisms on tacrolimuspharmacokinetics in Chinese adult renal transplantrecipients: a population pharmacokinetic analysis.Pharmacogenet Genomics. 2013;23(5):251-261. doi: 10.1097/FPC.0b013e32835fcbb6.

11. Patel M, Gumber M, Kute V, et al.Influence of CYP3A5polymorphism on tacrolimusdrug dosing in Indian renal allograft recipients:initial experience [International Conference on Human Genetics and 39th Annual Meeting of Indian Society of Human Genetics poster, abstract]. MolecCytogen. 2014,7(suppl 1):P98.doi:10.1186/1755-8166-7-S1-P98.

12. Quteineh L, Verstuyft C, Furlan V, et al. Influence of CYP3A5genetic polymorphism on tacrolimus daily dose requirements and acute rejection in renal graft recipients.Basic ClinPharmacolToxicol.2008;103(6):546-552.doi: 10.1111/j.1742-7843.2008.00327.x.

Table 1.Comparison of the Clinical Characteristics of the Study Population*

Characteristic	CYP3A5*1/*1	CYP3A5*1/*3	CYP3A5*3/*3
No. of patients	5 (20%)	5 (20%)	15 (60%)
Age at transplant (y)	16(12 to 22)	33 (22 to 47)	36 (20 to 50)
Sex(male/female)	4/1	5/0	13/2
Age of donor (y)	44(32to52)	46(37 to 52)	43(33 to 58)
Hemoglobin (g/dL)	10.2(8.8 to 11.8)	10.0(8.4 to 11.0)	9.8(8.6 to 10.8)
Blood urea (mg/dL)	18(16 to 26)	20(15 to 28)	21(16 to 27)
Creatinine (mg/dL)	1.6(0.9 to 1.8)	1.5(1.0 to 1.7)	1.6(0.9 to2.4)
Potassium (mmol/L)	4.2(4.0 to4.4)	4.4(4.0 to 5.6)	4.4(3.8 to 5.6)
Total bilirubin (mg/dL)	1.0(0.8 to 1.1)	0.8(0.6 to 1.0)	0.9(0.6 to 1.1)
Alanine aminotransferase (U/L)	32(26 to 38)	34(26 to 36)	36(26 to 40)
Aspartate aminotransferase (U/L)	28(26 to 30)	27(24 to 32)	30(25 to 38)
Albumin (g/dL)	3.5(3.0 to 3.8)	3.6(2.8 to 4.0)	3.5(2.8 to 4.2)

Comment [E1]: Data from Results text.

*Data reported as number (%), mean (range, minimum to maximum), or number

DR. NIYAMATULLAH ESSAY WRITING COMPETITION 2014
SOUTHERN CHAPTER OF INDIAN SOCIETY OF NEPHROLOGY (ISNSC)
TOPIC: AGEING AND THE KIDNEY

Dr. Arvind Krishnakumar,
3rd Post Graduate Student,
M.D. General Medicine, Madras Medical College,Chennai.

AGEING AND THE KIDNEY

Ageing is that inevitable process in the human body which occurs with the progress of one physical dimension that cannot be modified - time. Almost all organs and organ systems undergo predictable modifications in their structure and function as time passes. Although a heterogenous process, with different organs in the same person ageing at different rates, the pattern remains almost uniform in most human beings who lead a normal life. The rate at which an organ ages may be influenced by many factors, a few being the genetic make-up of the individual, lifestyle habits, and environmental factors.

Among the organs and systems involved, some of the most significant changes due to ageing occur in the kidney and the urinary tract. As it is well known, the kidney functions not only as an excretory organ but as a multifunctional unit, with additional endocrine, osmoregulatory and neurohormonal functions as well.

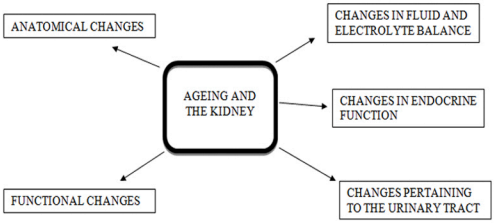


Figure 1 - Ageing in kidney

STRUCTURAL CHANGES IN THE KIDNEY

Gross Structural Changes

The kidney increases in size till the fourth decade of life where it reaches a maximum size of 12 cm in length and 400 g in weight. After this there is a gradual decline in the mass by 10% per decade1.

Wang et al studied the variation in the decline in cortical and medullary volumes of the kidney with ageing2. Volumes were measured with contrast enhanced computed tomography (CECT) images. Cortical volumes declined with age in both genders. As for medullary volumes, it increased with age in men, while in women, it increased with age till 50 years, after which it showed a decreasing trend.

There is an increase in renal parenchymal cysts in terms of size, number and frequency, with respect to age. In addition to simple cysts, other parenchymal cysts, both benign and malignant, are also seen to have increased incidence with advancement of age.

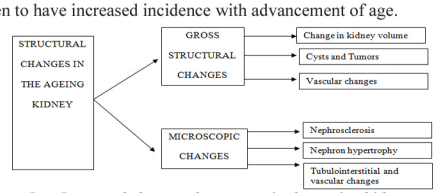


Figure 2 - Structural changes that occurs in the ageing kidney

Microscopic Changes

Nephrosclerosis is generally defined as the presence of two or more of the following - 1)Glomerulosclerosis; 2)Tubular atrophy; 3) Interstitial fibrosis; and 4)Arteriosclerosis. Nephrosclerosis is the characteristic pathological finding in the ageing kidney. This is attributed to the ischemic injury of the nephrons as a result of hyalinosis and arteriosclerosis of the arteries3.

Concordant to the age related nephrosclerosis, there also occurs a hypertrophy of the remaining functioning nephrons, characterised by an increase in overall tuft cross sectional area4. It is still unresolved whether or not this glomerular hypertrophy may predispose to glomerulosclerosis5.

In the tubulointerstitial compartment ageing causes tubular dilation and atrophy and infiltration with mononuclear cells. These changes are best observed in the outer medulla6. Some tubules develop small diverticuli, and these diverticuli can harbour bacteria, therefore predisposing to recurrent and resistant urinary tract infections6.

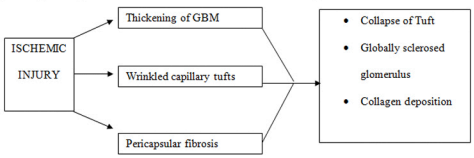


Figure 3 - Pathogenesis of microscopic changes in the ageing kidney. GBM – Glomerular Basement Membrane.

Ageing of the vascular bed is observed by generalised arteriosclerosis, and hypertrophy of the intima and media. An objective evidence of intimal-medial thickening is by measuring medial thickness/lumen diameter ratio6.

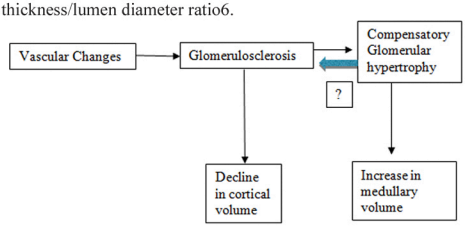


Figure 4 - Relation in the microscopic changes with the gross pathological changes in the ageing kidney

These changes occur independently with age but are accelerated in the presence of diabetes and hypertension7.

FUNCTIONAL CHANGES WITH AGEING

Changes in renal function can be observed by observing:

1) Glomerular Filtration Rate (GFR)
2) Renal Plasma Flow
3) Osmoregulatory functions
4) Endocrine functions

Glomerular Filtration Rate Changes

The GFR, ideally measured by inulin clearance, shows a progressive decreasing trend as a person ages, the decrease being more in men than in women. This fall in GFR is significantly affected by blood pressure. This is substantiated by the fact that 30-35% individuals who are normotensive show no decrease in creatinine clearance with age6.

The main question being asked is - what method should be used to measure estimated GFR in the elderly? The Cockcroft Gault formula has been used since ages as the standard equation for estimating GFR, although its limitations rose many questions of doubt regarding its accuracy. Although the MDRD (Modifications of Diet and Renal disease) formula was a relative improvement over the Cockcroft Gault equation, neither of the two have been validated in people over 70 years. The main reason behind this is the variation in creatinine production in the elderly due to decreased muscle mass. A creatinine level of 1.2 mg/dL in an 85 year old woman would estimate the GFR to be 45 ml/min/1.73 m2, which would classify the patient to have Stage 3 CKD. However this serum creatinine level may be an age-related adaptation of kidney function without any evidence of kidney disease.

A relatively less variable compound as compared to creatinine is serum cystatin C. The KDIGO (Kidney Diseases: Improving Global Outcomes) guidelines recommends the use of Cystatin C to estimate the GFR in adults with eGFR(Creatinine) of 45 - 59 ml/min/1.73m2 who do not have other markers of kidney damage (eg. albuminuria) if confirmation of CKD is required8.

In view of all the above mentioned issues, the Berlin Initiative Study was conducted9. The study was a cross sectional cum longitudinal approach on subjects aged more than 70 years. A new GFR equation was developed using Iohexol clearance as the gold standard.

Renal Plasma Flow

The Renal Plasma flow declines with ageing due to the presence of atherosclerotic arteries and subsequent decrease in arterial compliance. The mean flow at 40 years of age is 650 ml/min whereas at 90 years it comes down to as low as 290 ml/min6. The decline is better observed in hypertensive than normotensive individuals. Another observation made was the decline in flow involved in cortical areas more than the medulla.

Changes in Osmoregulatory functions with Ageing

Elderly individuals are more prone for dyselectrolytemias. Even a slight disturbance in sodium and water balance will cause symptomatic dysnatremias. There is an impaired response to an increase as well as a decrease in serum sodium levels. There is a concentrating defect at the medullary level and so the responses to hyperosmolality are reduced. This predisposes the patient to hypernatremia10. In a volume-overloaded elderly, there also occurs a defective ability to dilute urine, so they are predisposed to hyponatremia as well. This is often exacerbated by the use of medications like thiazides, and serotonin reuptake inhibitors (SSRIs) that are used more commonly in this age group11.

Other common electrolyte disturbances include hyperkalemia and hypercalcemia. Acid-base balance is usually adequately balanced in the elderly. However, an additional acid load would be difficult to excrete in such patients and this inability is revealed at times of stress (For instance, when the patient develops sepsis).

Changes in Osmoregulatory functions with Ageing

Elderly individuals are more prone for dyselectrolytemias. Even a slight disturbance in sodium and water balance will cause symptomatic dysnatremias. There is an impaired response to an increase as well as a decrease in serum sodium levels. There is a concentrating defect at the medullary level and so the responses to hyperosmolality are reduced. This predisposes the patient to hypernatremia10. In a volume-overloaded elderly, there also occurs a defective ability to dilute urine, so they are predisposed to hyponatremia as well. This is often exacerbated by the use of medications like thiazides, and serotonin reuptake inhibitors (SSRIs) that are used more commonly in this age group11.

Other common electrolyte disturbances include hyperkalemia and hypercalcemia. Acid-base balance is usually adequately balanced in the elderly. However, an additional acid load would be difficult to excrete in such patients and this inability is revealed at times of stress (For instance, when the patient develops sepsis).

Endocrine Issues

Erythropoietin (EPO) release in response to low hemoglobin is blunted in individuals above 60 years12. These individuals also have lower levels of 1, 25 hydroxyvitamin D levels, due to a mechanism similar to that occuring in CKD.

Since the kidneys are the primary mode of excretion of insulin, a decline in renal function with age was associated with a decrease in clearance of insulin.

THE MOLECULAR BASIS OF RENAL AGEING

A number of mechanisms have been proposed to explain the changes that occur in the kidneys with age. In general, cellular ageing is related to genomic instability, telomere loss, and oxidative damage.

Telomeres are short complexes of protein and DNA that are located at the ends of chromosomes. The DNA of telomeres is synthesized by the enzyme telomerase. Somatic cells do not have this particular enzyme and so the telomeres shorten with every cellular division. Eventually, a critically short telomere is detected by the cell, which then activates p53 and p16 and the cell undergoes apoptosis. In the ageing kidney, especially in the cortex, it is seen that telomeres shorten faster with older age13.

Oxidative damage also plays an important role in the process of cellular ageing. There is an increased oxidative stress and lipid peroxidation that occurs with ageing and this results in an increase in advanced Glycated end products (AGEs), an Upregulation of AGE receptors and downregulation of AGE-R1 (a receptor protective against the injury mediated by AGE)3 . AGEs, through various mechanisms, impair the ability of renal cells to respond to hypoxia. This further accentuates the damage caused by hypoxia due to arteriosclerosis of the renal vascular tissue.

One of the most important models describing ageing in the kidneys is related to the expression of the Klotho protein. Klotho is an anti-ageing gene that encodes a membrane protein synthesized in the distal tubules of nephrons and in the choroid plexus in the brain. It binds to a cell surface receptor and represses intracellular signals of insulin and insulin-like growth factor 116. An increase in oxidative stress, as occurs in ageing, reduces the expression of Klotho.

Many questions regarding the molecular pathogenesis still remain unanswered and there is a need for further studies to substantiate current models and to bring out newer, more refined models for the pathogenesis of ageing.

CLINICAL SIGNIFICANCE OF AGEING IN KIDNEYS

It is important to know the changes that occur in the kidneys with ageing as they have many clinical implications:

1. Chronic Kidney Disease or Age Related Dysfunction?

As mentioned before, it is difficult to distinguish CKD and age related decline in GFR in the elderly, especially when the GFR is 45-59 ml/min/1.73m2 in the absence of other markers of renal disease. As per KDIGO guidelines, it is better to use serum cystatin C to estimate GFR in individuals of this category.

2. There is an increased incidence of Acute Kidney Injury (AKI) in the Elderly

There are many predisposing factors for AKI in the elderly. Polypharmacy, with many drugs affecting the kidneys via some primary or secondary mechanism, tops the list. Prolonged use of ACE inhibitors and NSAIDs blunts the neurohormonal response to a decrease in blood pressure. Increased us of SSRIs also increases the risk of obstructive uropathy.

The causes of AKI remain similar to those in other age groups, although there is an increase in the incidence of post renal obstructive uropathy and sepsis in the elderly. There also occur difficulties in adopting appropriate treatment strategies in these patients due to the presence of multiple comorbidities.

3. Urinary Tract Infection (UTI) is a common cause of Fever

It is observed that asymptomatic bacteruria and symptomatic UTIs increases with ageing in both men and women17. Whereas males have an increased risk due to prostatic hypertrophy and urinary calculi; a high prevalence of cystoceles and uterine prolapse poses an increased risk of UTIs in postmenopausal women. Their clinical presentation also varies, with symptoms ranging from classic UTI symptoms like dysuria and pyuria, to an encephalopathy-like picture. This makes clinical diagnosis a challenging task.

4. Renal Replacement Therapy (RRT) in the Elderly

With increased survival, the incidence of CKD has risen in the geriatric population. Therefore, along with this increased incidence, comes an increase in the need for RRT.

With regard to an elderly patient, the decision to initiate RRT is more challenging than in younger adults. Besides medical issues and comorbidities, non-medical factors like family support, difficult transportation and income play important roles as barriers18.

The ideal time for initiating RRT is also crucial. The IDEAL (Initiating Dialysis Early and Late) study found no benefit in early initiation19. Some studies have even identified more harm than benefit in HD in elderly pateints20. There are some scores that prognosticate and help in decision making in the elderly, an example being a 6-month prognostic risk score by Couchoud et al21.

Risk Factors	Points
Total dependence for transfers	3
BMI <18.5 kg/m^2	2
Peripheral vascular disease stage 3 or 4	2
Congestive heart failure stage 3 or 4	2
Severe behavorial disorder	2
Unplanned dialysis initiation	2
Active malignancy	1
Diabetes Mellitus	1
Dysrhythmia	1

TOTAL SCORE AND 6-MONTH MORTALITY RATE CORELATION

0 – **8%**
1–8 – **10%**
2 – 14-**17%**
3-4 – **21-26%**
5-6 – **33-35%**

Figure 5 – 6-month risk score for initiating dialysis by Couchoud et al17.

In Europe, some centres adopt a nondialytic approach called maximum conservative management (MCM) 22. Although mortality rates are higher in patients receiving MCM than in dialysis, the former group had fewer hospitalizations.

The next question is whether to start the patient on HD or peritoneal dialysis (PD). Both have their own pros and cons. Whereas HD is more effective and a supervised procedure, elderly patients may not tolerate HD because of higher risk of fluid and electrolyte shifts, and cardiovascular mortality. On the other hand, PD provides safer ultrafiltration, is a home – based procedure and there is no need for vascular access, and so becomes an attractive option for the elderly. However the decreased efficiency and higher risk of peritonitis become barriers in the use of PD.

Whatever be the primary disease, transplantation is the treatment of choice for end stage renal disease (ESRD). Studies have shown an increased mortality in wait-listed ESRD patients compared to post transplantation patients23. This benefit is also observed when expanded criteria donor (ECD) kidneys are used – a 25% reduction in mortality rate is seen in those who undergo transplantation24.

Because immunocompetence reduces in the elderly, the immunosuppressive therapy required is much lower than in younger patients. There is also a decreased incidence of rejection episodes but an increased risk of infection25. An increased risk of chronic allograft nephropathy is observed with higher risk for older donor age. The best benefit of survival is observed in patients with ESRD due to hypertension and Diabetes.

To conclude, managing disease in the aged kidneys is a challenge in all aspects of clinical medicine – in the clinical diagnosis, investigations, as well as therapy. The best option for ESRD in the elderly still remains renal transplantation. A simplified management algorithm is provided below for the management of elderly patients with ESRD.

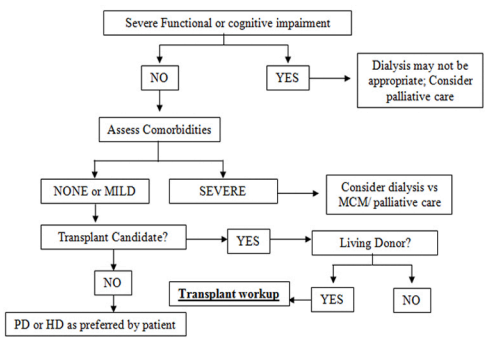


Figure 6 – Approach to an elderly patient with ESRD. HD – Hemodialysis. PD – Peritoneal Dialysis. MCM – Maximum conservative management