Review Article:

Ageing and kidney: a primer

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ABSTRACT

Ageing is an inevitable process that affects all organs and kidneys are no way an exception. There is an urgent need to understand ageing as a holistic process. The changes occurring in ageing kidneys resemble to those occurring in chronic kidney disease. However, many differences exist between them. Old age is a risk factor for acute kidney injury and increased risk of urinary tract infections and asymptomatic bacteriuria. Serum creatinine is a suboptimal indicator of renal function in the elderly because loss of muscle mass in elderly decreases creatinine production. Serum cystatin-c measurement, with reference values adjusted for age represents a promising marker to measure renal function in the elderly. The default management strategy for renal failure in elderly is more of conservative in developing countries when compared to developed countries where there is changing trend from conservative to initiation of renal replacement therapy. The decision when to initiate renal replacement therapy is more challenging. Haemodialysis or peritoneal dialysis each has its own advantages and disadvantages.

Key words: Ageing, Kidney


INTRODUCTION

Ageing is an universal phenomenon that affects all organisms. Despite the fact that it is inevitable, a precise definition for ageing and the interplay of complex mechanisms in the process of ageing are largely unknown. Generally, people over 60 years of age are considered as “old” and constitute the elderly segment of population. Women usually consider themselves old at a younger age than men because onset of menopause and arrival of grand-children are considered signs of ageing in women. In India, traditionally elderly persons live with family of the eldest son. This assured that the eldest son, and his family took care of the elderly. The growth in science and technology in the last decade has had a tremendous impact on the life expectancy of the individual and with changing traditions, is posing a great risk for elderly population and the economic, social and emotional needs of elderly appears to be unmet. The Indian aged population is currently second largest in the world absolute number of people above 60 years will increase from 76 million in 2001 to 137 million by 2021 this fast increase in elderly population leads to higher dependency ratio. Population based studies documented that elderly usually suffer from impaired renal function. According to National Health and Nutrition Examination survey (NHANES III), 35% of the elderly population had stage 3 CKD. Renal transplantation is emerging as a separate speciality by itself. With live renal donor prospects ever increasing in elderly, there is an urgent need to understand ageing and know ageing as a holistic process.

This topic received special attention in 9th World Kidney Day an annual event jointly sponsored by the International Society of Nephrology and the International Federation of Kidney Foundation. Conservative management
remains the default management strategy for renal failure in elderly in developing countries when compared to developed countries where there is changing trend to ward initiation of renal replacement therapy (RRT). Though it is generally accepted that old age per se is not a contraindication for renal transplantation, elderly have multiple co-morbidities which influence the decision for instituting transplantation. Nonetheless, renal transplantation appears to reduce mortality among patients of all ages. Further, use of expanded criteria for deceased donors and more liberal use of older living donors help in reducing the mortality.

KIDNEYS FROM BIRTH TO DEATH

One of the oldest definitions of ageing states that it is “a gradual weakening of cell reactivity based on the biophysical and biochemical changes of cell matter, on the changes in its physicochemical structure, on the gradual loss of the cell capacity for reproduction and regeneration of its biochemical structural elements”. The kidneys develop from the intermediate mesoderm initially as nephrogenic cord which gives rise to pronephros, mesonephros and metanephros. The initial two structures are temporary in the course of development and the metanephros is a permanent structure.

New born and infants

Kidneys in new born differ considerably in their length and width; while the right kidney is wider than the left kidney, it is shorter than the left one. In comparison with adult, new born kidney glomeruli occupy a much larger cortex volume during the first two months of life. The main characteristic feature of neonatal glomeruli is polymorphism in shape and size. The foetal lobulations usually disappear over time but persist in babies whose birth weight is low; they are also characterized by distinct echogenic cortex and hypoechogenic pyramid. Mature juxtramedullary nephrons contribute to the filtration capacity where as superficial cortical glomeruli contribute to the blood flow. An important character of neonatal kidney is its reduced ability to concentrate the urine increasing the risk of dehydration when intake of fluids is restricted. Concentration ability is reduced because of decreased glomerular filtration rate (GFR) and anti-diuretic hormone (ADH) sensitivity on distal tubules is reduced.

Children and young adults

During this period there is maturation of all the structures of the kidney. The length of the kidney correlates well with child’s height. The adult kidney is 10 cm-12 cm in length, 5 cm-6 cm in width, and is about 3 cm thick. The weight of a single male adult kidney is about 150 g, while in women it is about 135 g. A mature kidney is functional in all its activities. These include excretion of the metabolic products and surplus water, maintenance of the constant composition of body liquids, preservation of the acid-base balance, and endocrine function by the production and release of erythropoietin, renin and 1,25 dihydroxycholecalciferol.

Elderly

In a classic autopsy study, the authors evaluated kidney tissue samples from 105 individuals, who had died suddenly and in whom known renal disease or hypertension was absent from birth to 101 years of age, changes occurring in kidneys with ageing were described. It has also been observed that kidney mass decreases from fourth decade of life at the rate of 10% per decade, and this reduction is more pronounced in cortex than medulla. The salient anatomical changes seen in kidneys with ageing are summarized in Table 1.

Mechanism of functional changes and its significance

Old kidney is more vulnerable to toxic effects of drugs and its metabolites. One of the popular models which explain the changes in ageing kidney is the Brenner hypothesis which states
that an altered control of glomerular haemodynamics increases glomerular plasma flow and intra-capillary pressure, leading to glomerulosclerosis. Glomeruli spared from this process are hyperperfused and hypertrophied and these functional adaptations serve to maintain GFR. However, this process becomes “maladaptive” in the long term, due to development of glomerular hypertension. The reduction in renal plasma blood flow is greater than the decrease in GFR, resulting in increased filtration fraction in elderly persons, explanation for decreased renal blood flow is because varied response to vasoactive substances and increased resistance in afferent and efferent arterioles.

The capacity of an old kidney to preserve sodium as a response to its insufficient intake is lowered. The lower capacity of the distal tubule for the reabsorption of sodium is explained by interstitial fibrosis or by a lower activity of the renin-angiotensin aldosterone system. Due to tubular atrophy and tubular-interstitial scarring, sodium-potassium adenosine triphosphatase (Na⁺-K⁺ ATPase) activity is reduced in the elderly, resulting in a high risk for hyperkalemia. Elderly subjects are more prone than young individuals to develop acidosis mainly because of the incapacity to increase ammonia and hydrogen ion synthesis. Impaired proton pump activity in the cortical collecting duct is a critical element leading to deranged response to acid load in the elderly. In addition, there is a reduction in the major urea transporter in the inner medullary collecting duct, which could result in decreased urea reabsorption and thus cause a reduction in medullary osmolality leading to lack of concentrating ability of urine. The plasma volume is decreased in the elderly because of increase in atrial natriuretic peptide (ANP)-related excretion of sodium and water, and also due to the translocation of liquids into intercellular space by high permeability of the capillaries known as oedematogene effect. The decreased sulfation of the glomerular basement membrane glycoaminoglycans accounts for the increased permeability of basement membrane to macromolecules. Functional changes which occur in ageing are summarised in Table 2.

### Table 1: Anatomical changes in the various structures of kidney with ageing

<table>
<thead>
<tr>
<th>Structure</th>
<th>Anatomical change</th>
</tr>
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<tbody>
<tr>
<td>Glomerular changes</td>
<td>Decrease in number of glomeruli</td>
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<tr>
<td></td>
<td>Hypertrophy of functional glomeruli</td>
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<td></td>
<td>Progressive folding and thickening of glomerular basement membrane</td>
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<td></td>
<td>Glomerulosclerosis</td>
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<td></td>
<td>Podocyte alteration</td>
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<td></td>
<td>Increase in mesangial matrix</td>
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<tr>
<td>Tubulointerstitial changes</td>
<td>Decrease in tubular length and number</td>
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<tr>
<td></td>
<td>Tubular atrophy</td>
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<tr>
<td></td>
<td>Interstitial fibrosis</td>
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<tr>
<td></td>
<td>Increased diverticulae of distal convoluted tubule</td>
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<tr>
<td>Vascular changes</td>
<td>Hyaline deposition</td>
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<tr>
<td></td>
<td>Arteriosclerosis</td>
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<tr>
<td></td>
<td>Aglomerulus circulation</td>
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<td></td>
<td>Increased vessel tortuosity</td>
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</tbody>
</table>

Source: reference 10

### Senescence Vs chronic kidney disease

Most of the changes occurring in ageing kidneys resemble those occurring in chronic kidney disease like low GFR and inability to respond to fluid and salt overload. However, differences exist between them. Anaemia as a
consequence of a low serum erythropoietin secretion is a characteristic feature in CKD. In the elderly proximal tubular function is preserved in the old and their serum erythropoietin and haemoglobin levels are normal.\textsuperscript{15} Even though the fractional excretion (FE) of urea is increased in old age as well as in CKD, serum urea level is normal in the elderly while it is increased in CKD. Serum levels and FE of calcium, magnesium and phosphorus are normal in the healthy elderly individuals, while increased FE of these substances is evident in CKD.\textsuperscript{15} Further in CKD patients FE of potassium increases as GFR decreases under the influence of the aldosterone hormone. However, in healthy very old people the FE of potassium is relatively diminished in relationship to GFR suggestive of relatively low serum aldosterone and aldosterone resistance. Parathyroid hormone (PTH) and active vitamin D levels are normal in the old, while PTH is increased and active vitamin D is decreased in CKD and in healthy very old people.\textsuperscript{15}

UNDERSTANDING THE MECHANISMS AND PATHOPHYSIOLOGY OF AGEING KIDNEY

Various pathophysiological mechanisms involved in ageing act together and their complex interactions generate multiple hits leading to ageing. These are summarized in Figure 1.

Gender also appears to play a role. The rate of progression of CKD tends to be slower in females. The impact of gender on the renin angiotensin system (RAS) relates to the interaction between $17\beta$-estradiol and angiotensin II. The $17\beta$-estradiol decreases tissue levels and activity of both angiotensin II and angiotensin converting enzyme (ACE).\textsuperscript{16} Conversely, testosterone tends to increase RAS activity. Spontaneous gene mutations in somatic and mitochondrial deoxyribonucleic acid (DNA) accumulate with normal aging in kidney cells. Functional genomic studies showed that over 500 genes are differently expressed in human kidneys across age-strata encompassing neonate’s (8 weeks) and elderly kidneys (88 years).\textsuperscript{14}

Klotho is perhaps the most powerful “aging-suppressor” gene. In the kidney, Klotho is predominantly expressed in the distal convoluted tubule. It exerts a series of potentially reno-protective actions\textsuperscript{17,18} including (i) reduction of oxidative stress via inhibition of the insulin/insulin like growth factor 1 (IGF1) signalling and induction of the

| Table 2: Functional changes in the various structures of kidney |
|-------------------|---------------------------------------------|
| Structure         | Functional change                           |
| Glomerular        | Decrease in glomerular filtration rate       |
| Tubular           | Impaired water balance                       |
|                   | Impaired sodium balance                      |
|                   | Decreased capacity to dilute urine           |
|                   | Decreased capacity to lower urine pH         |
|                   | Increased potassium retention                |
|                   | Increased sensitivity to vasoconstrictor     |
|                   | Decreased sensitivity to vasodilators        |
| Vascular          | Decrease in effective renal plasma flow      |
|                   | Increased post glomerular vascular resistance|
|                   | Increased filtration fraction                |
| Endocrine         | Decreased plasma renin activity and aldosterone|
|                   | Impaired erythropoietin response to anaemia  |
|                   | Decreased production of active vitamin D3    |

Source: reference 14
manganese superoxide dismutase; (ii) fine tuning of calcium phosphorus homeostasis by down regulation of vitamin-D synthesis and phosphaturia; (iii) modulation of calcium channel activity in renal tubular cells; and (iv) regulation of endothelium-dependent vascular reactivity. Sustained oxidative and metabolic stress, angiotensin-II, down-regulate Klotho messenger ribonucleic acid (m-RNA) expression. This function of Koltho gene is depicted in Figure 2.

Assessment of renal function in elderly

Serum creatinine is a suboptimal indicator of renal function in the elderly because loss of muscle mass in elderly decreases creatinine production, creatinine values are influenced by protein intake and hydration status. The reference range of creatinine considered as normal in the healthy young is inappropriately high in the elderly and serum values in the upper normal range may underlie early renal dysfunction. In a 20-year-old individual a creatinine value of 1 mg/dL may correspond to an estimated GFR of 120 mL/min while the same in 80 years-old persons might reflect an estimated GFR of 60 mL/min. Traditional formulas for estimating creatinine clearance are unreliable in elderly because of presence of multiple co-morbidities. Creatinine clearance is estimated by Cockcroft and Gault (CG) formula and modification of diet in renal diseases (MDRD) equation. The MDRD equation is generally considered more accurate than the CG formula to estimate GFR but the estimates between these two formulae differ in that the MDRD GFR may be 60% higher than the CG-GFR in patients over 65 years of age. Serum cystatin C measurement, especially when compared with reference values adjusted for age, represents a promising marker to measure renal function in the elderly.

Comparison of published studies across the world on ageing and kidney

Changes in the renal function associated with aging have been estimated in 9 cross-sectional and in 3 cohort studies. In these studies average decrease in GFR ranged from 0.4 to 2.6 mL/min (Table 3).

Clinical implications of ageing and kidney

In people aged over 65 years, pharmacokinetics are influenced more by the loss of kidney function than by the aging process of any other organ. A GFR of 30 to 60 mL/min, suggestive of stage 3 kidney disease, is observed in 15% to 30% of elderly people. Drug dosing must be adjusted to both changing pharmacokinetics and pharmacodynamics. Old age is a risk factor for acute kidney injury (AKI). In older patients, AKI has a very poor prognosis especially when it is associated with sepsis, and multi-organ failure with mortality rates as high as 75%. Old patients are not only more likely
to develop AKI, with the associated increased mortality and morbidity, but also more likely to have impaired recovery of renal function. They are also more likely to develop chronic renal disease and end-stage renal disease (ESRD) from AKI. Therefore, it is important to look for it and diagnose it early, and to treat it when it occurs. Elderly are at an increased risk of urinary tract infections (UTI) and asymptomatic bacteriuria, males have an increased risk because of prostatic hypertrophy and females are at risk because of uterine prolapse. Diagnosis of UTI in elderly is often challenging as sometimes it presents like encephalopathy.

**Renal replacement therapy and elderly**

The decision when to initiate RRT is more challenging. A number of nonmedical factors like family support, difficulties in transportation and lack of income act as barriers. IDEAL study has found no benefits of early initiation of RRT. Also haemodialysis (HD) peritoneal dialysis (PD) have their own advantages and disadvantages. Elderly patients have difficulty...
to tolerate HD because of large amounts of fluid and electrolyte shifts and associated cardiovascular mortality. PD is a home-based procedure, free from vascular access but efficiency is low and high risk of peritonitis. Renal transplantation is the treatment of choice for any ESRD. Specific issues in elderly are as they are less immunocompetent, degree of immunosuppression required is less and incidence of rejection is less in elderly. However, there are increased chances of infection. A simplified approach in the management of ESRD in elderly is shown in Figure 3.

Figure 3: Approach to a elderly patient with ESRD

ESRD = end-stage renal disease; RRT = renal replacement therapy

Ageing has been defined as “the collection of changes that render human beings progressively more likely to die”. Whether aging is a disease or a consequence of being human is a million dollar question which has no perfect answer. Renal ageing is a complex multi factorial process. To what extent histopathological changes correlate with disease needs further research. Progress in genomics and genetics provides new insight in understanding ageing. Proper lifestyle modifications including the adoption of low calories with high content in anti-oxidants currently represent the most pragmatic approach to maintain kidney health. As most of the studies on newer therapeutic treatments in kidney disease exclude elderly there is an urgent need to include them and apply the newer therapeutic benefits.

REFERENCES


