Renal Function and Histopathology in the Elderly

Hiroshi Sato, Takao Saito, and Kaoru Yoshinaga

The Second Department of Internal Medicine, Tohoku University School of Medicine, Sendai City, 980, Miyagi, Japan

AGING AND RENAL FUNCTION

Decline of renal function with aging is the most dramatic among all the organ systems. Functioning cells are gradually lost and physiologic reserve capacity is reduced. The glomerular filtration rate, which is low at birth, approaches adult level by 3 years, and is maintained at approximately 140 ml/min/1.73 m² until the age of 25 to 34 years. Thereafter, it declines linearly by approximately 8 ml/min/1.73 m² per decade (1,2). The glomerular filtration rate of healthy octogenarians is only half or two-thirds of that measured in young adults.

These functional changes are accompanied by corresponding structural changes in the kidney. The two kidneys, which weigh approximately 50 g at birth, increase to between 270 g and 350 g in the third and fourth decades, but subsequently decline to less than 200 g by the ninth decade. The loss of renal mass is principally initiated in the cortex, with relative sparing of the medulla.

The number of functioning glomeruli declines roughly in accord with the changes in renal weight. Up to the age of 40 years, sclerotic glomeruli constitute less than 5% of the total. With increasing age thereafter, the incidence of sclerotic glomeruli increases, so that sclerosis involves 10% to 40% of the total glomerular population by the eighth decade (3–5). Kasiske (6) has shown that the mean percentage of sclerotic glomeruli in 60-year-old subjects with minimal vascular disease was approximately 5%, and that the number of obsolete glomeruli correlates directly with the severity of atherosclerosis. However, the size of the remaining glomeruli with no sclerosis increases with age (7,8), and is associated with ultrastructural and biochemical alterations of the glomerular constituents (to be discussed later in this chapter).

The precise mechanisms of the age-related changes in the kidney have not hitherto been elucidated. At least two separate subcomponents seem to exist in the aging process of the kidney. One component is an essential renal change resulting from the natural aging process, and is common to all human beings to some degree. Another is the influence of some pathophysiologic conditions that can take place
intermittently or continuously throughout the person’s life. Hypertension, dehydration, drug abuse, glomerulonephritis due to immunologic injury, and various infections including pyelonephritis would be examples of such conditions (9,10). Lindeman (10) suggested that nephropathic environmental factors or common pathologic processes were mainly responsible for the age-related renal dysfunction. Virtually all the histological changes observed in the aged kidney may be induced not only by the natural aging process but also by miscellaneous pathologic factors such as those mentioned above. There is great difficulty in distinguishing the purely age-related effects from the other effects. It is thus inevitable that the ensuing discussion relates to renal changes in general without defining or analyzing specific etiologies.

Our study on patients with chronic glomerulonephritis has revealed an age-dependent decline in renal function, evaluated by creatinine clearance value (Fig. 1). The gradient of renal function decrease in our study is quite similar to that shown by Rowe et al. (1), who studied healthy adults without any specific renal diseases. From this observation, the aging process is assumed to have effects on all individuals whether or not they suffer from renal disease.

RENAL MORPHOLOGICAL CHANGES IN THE ELDERLY

Several investigators have shown that there is an increase in the mesangial matrix and a progressive thickening or folding of the glomerular basement membrane (GBM) and tubular basement membrane in the aged kidney (2,7,11–13). Figure 2 shows our results of ultrastructural examinations on the GBM thickness in 167 patients with renal diseases, excluding membranous glomerulonephritis, hereditary nephritis, diabetes, amyloidosis, and transplanted kidney. The method of Osawa et al. (14) was used in measuring GBM thickness. As shown in this figure, the GBM thickness

![FIG. 1. Cross-sectional difference in creatinine (Ccr) clearance value with age. Values plotted indicate mean ± SEM. ○, mean value in each age group studied by Rowe et al. (1) on normal subjects (n = 548); ●, mean value in our study on patients with chronic glomerulonephritis (n = 215).]
In Cockayne's syndrome (15), a congenital anomaly characterized by the accelerated aging process of multiple organs, the GBM is extremely thickened to approximately 3 times the normal thickness. These intraglomerular morphological changes are probably associated with an age-related increase in extracellular material such as laminine and type IV collagen, which is the main component of the GBM and mesangial matrix (16, 17). Furthermore, biochemical analysis of the GBM demonstrates decreased sulfation of the glycosaminoglycans, an alteration that could reduce the net negative charge and render the GBM more permeable to macromolecules (18), leading to an increase in urinary protein excretion and to a progressive glomerular sclerosis (19, 20).

The functional and morphological interglomerular imbalance that develops with aging is also an important factor in the progression of glomerular sclerosis. Thus, as sclerosis progresses, some glomeruli fall into capillary collapse or segmental sclerosis, resulting in a decreased filtration rate, while the remaining glomeruli show morphological hypertrophy and functional hyperfiltration in an attempt to preserve the total kidney function. This compensatory hyperfiltration is assumed to be one of the main mechanisms of progressive glomerulosclerosis; it induces further GBM injury, cellular impairment, and an expansion of the mesangial matrix (2, 21).

Figure 3 shows schematically the many paths leading to the development of glomerular sclerosis. The aging process, as well as the presence of systemic hypertension, diabetes, hyperlipidemia, arteriosclerosis, and so forth, is an important factor behind the multi-faceted incidence of glomerular injury. Furthermore, food intake is also a variable that can have considerable effects. In various experimental models that included aging animals of many species, the degree and the frequency of the glomerular sclerosis were affected by dietary manipulations. Limitation of total energy intake was originally shown to delay the development of glomerular lesions (22, 23). Afterward, a low protein diet (20–23) and restriction of dietary phosphorus (24) were shown to reduce proteinuria and to delay the age-related glomerular
sclerosis, even when total energy intake was not restricted. It seems likely that dietary intake of carbohydrates in humans has little effect on the kidney, whereas protein intake influences renal size, structure, and function, mediated by intrarenal hemodynamic alterations (2,21). Renal blood flow and glomerular filtration rate rise with a high protein diet (25), resulting in renal hypertrophy. Brenner et al. (21) suggested that the protein-rich diet characteristic of modern Western society can alone induce chronic renal hyperfiltration and hyperperfusion and thereby contribute to the functional and structural deterioration of the aging kidney.

EVENTUAL RENAL FAILURE IN THE ELDERLY

In aged adults, not only glomerular filtration rate but also urine concentrating ability and the adaptive capacity for responding to changes in the intake of electrolytes and water are significantly impaired (26). Thus, various abnormal conditions such as overhydration, dehydration, or electrolyte imbalance are easily brought on by only a mild exogenous or endogenous stimulus, for example, bacterial or viral
infection, surgical operation, decreased water intake, drug ingestion, and so forth (most of these events might be completely harmless to healthy young adults). In particular, a state of dehydration, which is easily and frequently induced without any subjective symptoms in older patients, may facilitate the expression of nephrotoxicity of various drugs, such as antibiotics, diuretics, contrast media, and non-steroidal anti-inflammatory drugs (NSAIDs), and can sometimes result in severe renal failure. Figure 4 shows the clinical course of a 64-year-old nephrotic patient who developed acute renal insufficiency after the combined administration of NSAIDs and diuretics. Creatinine clearance decreased from 57 to 13 ml/min, and blood pressure was significantly increased, probably due to water retention. The aged kidney is clearly at high risk of eventual failure, especially when the number of functioning nephrons is further reduced by acquired renal diseases.

Another problem is the discrepancy of the relationship between serum creatinine and the creatinine clearance value. The reduction in creatinine clearance with age is accompanied by a reduction in creatinine production, which reflects the decrease of muscle in body mass that occurs with age (1). Therefore, the relationship of serum creatinine to creatinine clearance changes with age; although creatinine clearance

![Graph showing adverse effects of combined administration of indomethacin and furosemide on renal function.](image)

FIG. 4. Adverse effects of combined administration of indomethacin and furosemide on renal function, observed in a nephrotic 64-year-old woman with membranous glomerulonephritis.
RENAL FUNCTION AND HISTOPATHOLOGY

decreases from 120 ml/min at age 20 years to 60 ml/min at age 80 years, serum creatinine concentration remains nearly constant at a level of approximately 1 mg/dl. The approximate creatinine clearance in adult men can be derived from the serum creatinine value with the following formula:

\[
Ccr = \frac{(140 - \text{age})[\text{lean body weight (kg)}]}{72 \times \text{serum creatinine (mg/dl)}}
\]

In adult women, the clearance is approximated by multiplying the calculated value by 0.85 (2,27). The practical implication of these observations is that kidney function in older patients may sometimes be unexpectedly decreased, even if they have a normal serum creatinine value. Renal function reserve capacity may be even further decreased (25). Consequently, it is important for clinicians to pay attention to renal function at all times during the medical treatment of aged patients.

ACQUIRED KIDNEY DISEASES IN THE ELDERLY

Finally, we would like to comment on the spectrum and the character of the superimposed kidney disease in the elderly. The incidence of primary renal disease in elderly people may not be significantly greater than in younger adults. However, in contrast to younger age groups, crescentic glomerulonephritis, renal vasculitis including periarteritis nodosa, membranous glomerulonephritis, diabetic nephropathy, and renal amyloidosis are relatively more common in patients over 60 years of age (28-30). Most of these diseases are frequently resistant to steroid therapy or other medical treatment, and tend to progress slowly or rapidly to end-stage renal failure. On the other hand, steroid-sensitive minimal change disease is still observed in approximately 10% of cases of the nephrotic syndrome in the elderly (29,30). Some cases of the membranous glomerulonephritis, crescentic glomerulonephritis, and renal vasculitis may also respond to steroids or other drugs. Therefore, even in the elderly, histological diagnosis by renal biopsy is required to decide on an adequate treatment procedure, as long as the condition of the patient permits the execution of such a biopsy.

REFERENCES


**DISCUSSION**

*Dr. Hodkinson:* I should like to make a comment on creatinine. You made the point that the relationship of serum creatinine to renal function changes with age because of the reduction in muscle mass in old people. This deserves special emphasis. In some of our elderly patients with chronic illness there is so much wasting that a normal serum creatinine may be found in the presence of frankly abnormal renal function. We did some work a few years ago (1) that showed that urea was a better predictor of renal function than creatinine in old age even when creatinine is adjusted for body weight, which is really only saying that adjustment for body weight is not very good. The geriatrician's experience is quite different from the usual nephrological opinion that urea is useless and creatinine is the gold standard.
Dr. Chandra: I have a comment relating to possible mechanisms of changes in renal function with age. There are animal models of autoimmune renal diseases, some of which are genetic, in which deterioration in renal function can be prevented by a low-energy, low-protein diet. My hypothesis is that in some aging individuals, autoimmune processes, which can be induced by viral infections, may be the reason for deterioration in renal function. Such autoimmune processes may be modified or arrested by a low-protein or low-energy intake.

Dr. Havlik: Although I realize that in many cross-sectional models there is not an important relationship between dietary protein intake and blood pressure, I wonder whether there is any new information on this. Could there be a correlation between dietary protein intake and blood pressure to the extent that quite minor increases in blood pressure over a long period might influence renal function?

Dr. Sato: Systemic hypertension does not correlate with dietary protein. It is much more dependent on dietary salt intake. However, high-protein diet may cause intrarenal, intraglomerular hypertension, mediated by mesangial hyperfunction and intrarenal vascular reaction. Intraglomerular hypertension over a long period might induce progressive glomerular sclerosis and renal dysfunction.

Dr. Durnin: It seems unlikely that there would be a relationship between dietary protein intake and hypertension or any sort of renal dysfunction. I don’t think there is any evidence to show that individuals with widely varying protein intake have any differences in kidney function.

Dr. Nestel: There is evidence from studies in vegetarians and in animal models that the type of protein can influence the blood pressure. Diets rich in plant proteins appear to lead to substantially lower blood pressures than diets rich in animal proteins, in the absence of any systematic change in mineral intake.

Dr. Sato: In cases of healthy adults, influence of dietary protein on renal function may be negligible. It seems unlikely that dietary protein alone can induce renal damage by itself. But, it is possible that a high-protein diet may accelerate the renal damage caused by other pathological factors. In other words, a protein-rich diet could be harmful to the kidney that is already affected by acquired renal diseases, particularly when glomerular filtration rate is evidently decreased. I believe a few elderly people must have acquired kidney disease with insidious and subclinical renal insufficiency. A lot of experimental and clinical studies demonstrated beneficial effects of a low-protein diet on the progression of renal failure (2–5). On the other hand, restriction of dietary protein may cause a malnutritional condition. So, careful consideration is required for practical diet programming.

REFERENCES

Endocrine Function in the Elderly

H. Malcolm Hodkinson

University College London, London NW1 OPE, England, United Kingdom

Many different changes in endocrine function with age have been described. To give just some of many possible examples, there are increases in the levels of growth hormone in women, rises in thyroid stimulating hormone, modest decreases in triiodothyronine, and increased sensitivity of response to antidiuretic hormone (1). Levels of norepinephrine rise (2) and there are altered circadian patterns for cortisol, norepinephrine, and growth hormone (3). There are falls in renin and aldosterone levels (4) and a rise in parathyroid hormone levels, although this seems to be entirely due to decreased renal excretion (5). Pancreatic polypeptide and gastrin show rises with age, although other gut hormones do not appear to change (6).

However, these and many other described changes are generally small and of doubtful importance in a practical sense. They are certainly dwarfed by the important and major changes in sex hormones and gonadotropins, and this chapter will therefore concentrate on this area.

Changes in sex hormones and trophic hormones occur in both sexes with aging. Obviously the changes are far more dramatic in women in relation to the abrupt cessation of estrogen secretion by the ovary at the time of menopause. However, although there is no abrupt change in testicular function with age, there is a gradual diminution of Leydig cell function so that testosterone levels fall progressively. Gonadotropins rise in both sexes in response to these falls in sex hormone production.

ESTROGENS IN POSTMENOPAUSAL WOMEN

Within a few months of menopause, levels of the most potent estrogen, estradiol, fall markedly, whereas those of estrone fall only a little so that it then becomes the main estrogen (7). The ovary loses its ability to convert androstenedione to estrone and testosterone to estradiol. The greatly reduced production of estradiol now relies on peripheral conversion of its plasma precursors estrone, androstenedione, and, to a smaller extent, testosterone, as there is no direct secretion by the ovaries or adrenals (8). Similarly, the production of estrone is almost entirely by peripheral conversion of circulating androstenedione in adipose tissue. Androstenedione is in turn secreted mainly by the adrenals, although ovarian secretion does continue at about half its premenopausal level (8). As adipocytes are the site of these peripheral
conversions, estrogen production, particularly that of the more potent estradiol, is more efficient in obese postmenopausal women (9). This explains the protective effect of obesity against postmenopausal osteoporosis that has been shown in many studies.

ANDROGENS IN POSTMENOPAUSAL WOMEN

The postmenopausal ovary continues to produce the androgens androstenedione and testosterone, although at somewhat reduced rates (8), while adrenal secretion of these two hormones and of dihydroepiandrosterone continues unchanged (10). As conversion of androgens to estrogens in the ovary no longer takes place, the net result is that total androgen levels are somewhat higher.

GONADOTROPINS AFTER MENOPAUSE

Levels of luteinizing hormone (LH) and of follicle-stimulating hormone (FSH) reach a maximum some 2 to 3 years after menopause (7) and remain elevated throughout later life by approximately four- and sixfold, respectively (11). Administration of estrogens to postmenopausal women causes LH and FSH to fall, indicating that the feedback loop is still intact and that the elevations can be regarded as secondary to the changes in the sex steroid hormones (11).

SEX HORMONE AND GONADOTROPIN CHANGES IN MEN

Although there are no abrupt changes in men comparable to menopause in women, androgens do fall somewhat with age (12) so that the main androgen, testosterone, as well as α-dihydrotestosterone have lower blood levels in elderly men. There do not seem to be any corresponding changes in estrogen levels; estrone, the most important estrogen in men, shows no age relationship (13). The position regarding gonadotropins is less clear-cut, with some workers finding no change with age, whereas others report some increase in LH beyond the age of 60 years (13).

CONSEQUENCES OF MENOPAUSE

The physical consequences of menopause such as atrophic changes in the genital tract, breast, skin, and other organs and tissues influenced by estrogens are well recognized. No less important, however, are the many metabolic consequences of estrogen withdrawal, not all of which are so well appreciated. Osteoporosis is perhaps the most serious and obvious of such changes, but there are various other changes that we should examine.
Biochemical Changes Following Menopause

Many biochemical analyses show age changes that could confound or obscure changes due to menopause itself. However, studies of women in the age groups during which natural menopause is experienced allow us to compare age-matched groups of women who are premenopausal or postmenopausal and so to allow fully for age effect. McPherson and colleagues were among the first to look systematically for such menopausal effects (14). They found that 7 of the 17 analyses they studied showed significant changes attributable to menopause itself!

Links to Bone Metabolism

McPherson et al. found a group of changes that can be linked to postmenopausal osteoporosis. Serum alkaline phosphatase and calcium showed significant elevations and there was also a nonsignificant rise in serum inorganic phosphate. Similarly, Crilly and colleagues (15) found a significant rise in both serum alkaline phosphatase and the urinary excretion of hydroxyproline. Taken together, these findings point strongly to linkage to the phase of rapid postmenopausal bone loss consequent upon estrogen withdrawal and preventable by estrogen administration. Thus, extra calcium and phosphate are released from bone into the bloodstream by the increased osteoclastic activity. This also gives increased collagen removal by destruction of bone matrix, leading to increased excretion of its degradation product, hydroxyproline. As osteoblastic activity is highly geared to osteoclastic activity, the rise in alkaline phosphatase is also readily explicable. It is of interest that the rises in phosphate and calcium persist into old age, where women have significantly higher values than men (16).

Estrogen also appears to have other effects that are relevant to bone physiology. Osteomalacia is widely recognized as being far more likely to affect old women rather than men. This may be due to differences in vitamin D metabolism between the sexes, for elderly women have significantly lower values of serum 25-hydroxycholecalciferol than men even when differences in age, dietary intake of vitamin D, and sunlight exposure are fully allowed for (17). Furthermore, the difference is quite substantial: women have values about 70% of those of men when other factors are balanced.

Urea and Electrolytes

McPherson and his colleagues also found significant elevations of blood urea and of serum bicarbonate and sodium after menopause. The changes reduced the differences between men and women in each case, although significant but small sex differences remained. This would suggest that sex hormones have important influences on renal function.

They also found that serum iron and serum aspartate aminotransferase rose
significantly postmenopausally, again having the effect of bringing values closer to those for men. The change in serum iron could perhaps be ascribed to the cessation of menstrual iron loss, but there is no obvious explanation for the change in aspartate aminotransferase.

Uric Acid

Others have shown a significant postmenopausal elevation of serum uric acid (18), confirming the nonspecific trend found by McPherson and colleagues (14). Again, this brings female values closer to those for males and is paralleled by a rising incidence of acute gout in older women.

CONCLUSION

By far the most impressive hormonal changes occurring with aging are the changes in sex hormones and gonadotropins after menopause. Reduced estrogens in older women set in motion many physiological changes, some of which appear to be seriously deleterious (most particularly those underlying the development of postmenopausal osteoporosis, which is perhaps better regarded as an integral part of normal aging than as a disease).

Other hormonal changes appear to be relatively minor in nature in comparison with these and, although they may be of academic interest, do not seem to have major practical importance.

REFERENCES

12. Zumoff B, Strain GW, Kream J, et al. Age variation of the 24-hr mean plasma concentrations of


DISCUSSION

Dr. Meredith: Are you aware of any longitudinal studies looking at the rather complicated endocrine changes after the menopause?

Dr. Hodkinson: There are several such studies going on but none has yet come up with any clear answers. Such studies are certainly needed. In particular, we need to come up with better predictors of postmenopausal osteoporosis.

Dr. Guesry: You have dealt with only half the population. What about men? Do you think there is any need to treat elderly men with growth hormone and testosterone, as has already been suggested, or do you think this is unnecessary?

Dr. Hodkinson: I suspect this is unnecessary, but it depends on what the aim is. If we are talking about bone disease, the problem of osteoporosis is predominantly a female one. On any kind of cost-benefit equation we shall not do well if we start treating men with testosterone to prevent osteoporosis. However, this is certainly not the case for hormonal treatment in women. Osteoporosis in older women is an immense problem. If we could only predict those who are destined to suffer most severely, the cost-benefit equation would be highly favorable.

Dr. Nestel: What is your bottom line advice on hormone replacement in postmenopausal women? When one reads about this subject it appears that, as well as getting relief from menopausal symptoms, women on estrogens have half the coronary thrombosis mortality of those not receiving estrogens, quite apart from the beneficial effects on osteoporosis.

Dr. Hodkinson: I don’t think it is yet possible to give definitive advice. However, we have to decide why we are giving hormone replacement therapy (HRT). Treatment is often given for the rather nebulous entity that is considered to be the menopausal syndrome. However, many of the symptoms ascribed to this have been shown to be more common before the menopause—headaches, for example. If replacement therapy is given with a view to preventing bone disease or vascular disease, we are talking about long-term treatment and I believe this to be quite onerous for the women who receive it. There is also the financial aspect to consider, apart from any possible risk of long-term replacement therapy (although I believe these have been exaggerated). My view is that we can afford to be very positive about HRT but we need to be highly selective in applying it.

Dr. Nestel: What do you mean by selective?

Dr. Hodkinson: We need to be able to identify groups of people whose risk is greater than average.

Dr. Nestel: So for the possible prevention of coronary heart disease, you would select only those women who have other risk factors for the condition?
Dr. Hodkinson: Yes, broadly. But one is looking at the osteoporosis problem as well. You need to combine the two: if you have high risk of either bone disease or ischemic heart disease the benefits of treatment of both are going to be very much better.

Dr. Chandra: Since the workshop is on nutrition, I wonder if you can speculate on the role of nutritional factors in modulating the hormonal changes you have described. Referring back to Dr. Guesry's question about HRT in males, we know that nutritional factors modulate testosterone levels so if we accept that in the elderly the frequency of nutritional deficiencies increases, then this may in part explain the lower testosterone levels. Testosterone is a very sensitive index of zinc intake, so even if only 20% of the population has marginal zinc deficiency in this age group, this could account for some of the differences in hormone levels. Is there any information to suggest that decline in estrogen output might be related to diet and nutrition rather than to primary gonadal failure?

Dr. Hodkinson: Decline in estrogen is a biologically programmed event. I don't think we can implicate diet in this. I accept that there are nutrients that may have an effect on the production of individual steroid hormones, but we are not talking about one estrogen. There is a plethora of estrogens and to determine whether zinc deficiency affects estrogen production you would have to measure them all—a daunting task and unlikely to yield a clear result unless there is a major effect. However, I think there is little doubt that there are interactions between hormonal status and dietary factors. Osteoporosis and osteomalacia are relevant examples. I am sure there are interactions in both directions.

Dr. Ballard-Barbash: Our National Cancer Institute has unearthed a number of studies that have examined the effect of dietary factors on estrogen metabolism. It has been postulated that several of these, including fat, alcohol, and fiber, have effects on estrogens. Early findings have confirmed effects on estrogen metabolism in several instances.

Dr. Durnin: It has been reported that exercise affects endocrine function in elderly men. Do you have any information on this?

Dr. Meredith: This also occurs in young men. Lower testosterone levels regularly occur in runners, and this is true for older men as well.