Changes in Renal Function with Aging among Japanese

Tatsuo Hosoya, Ryoichi Toshima, Kimiyoshi Icida, Akira Tabe and Osamu Sakai

Renal function was assessed in 329 inpatients who were presumably free of renal disease or water-electrolyte imbalance and the relationship between renal function and aging and sexual differences were investigated. Serum creatinine levels were slightly increased with aging, and were significantly higher in males than in females. Urinary creatinine excretion significantly decreased with aging; this decline was more pronounced in males. Urinary creatinine excretion was significantly higher in males. Creatinine clearance also decreased significantly with aging and this tendency was still observed after correction for body surface area. Sexual differences played no part in creatinine clearance. There was a significant increase in the serum B2-microglobulin level with aging. In addition, the Ccr of the aged Japanese population was lower in comparison with western counterpart. The findings suggest the need for special consideration in conducting clinical tests or administering drugs to this segment of the population in Japan.

(Internal Medicine 34: 520-527, 1995)

Key words: aging, renal function, creatinine clearance, serum creatinine

Introduction

Nephrons undergone physiological attrition and the glomeruli are reduced in size and become hyalinized with increasing age (1). Arterial intimal thickening (2), interstitial fibrosis, and tubular atrophy have also been reported. In regard to changes in renal function due to aging, some studies have shown decreases in renal blood flow, glomerular filtration rate (GFR) (3, 4), urine acidifying and concentrating ability (5, 6) and the production of renal hormones (6, 7). However, there have been no detailed studies on large numbers of Japanese patients concerning changes in renal function associated with aging. Since Japan has a large aging population, the opportunity for physicians to examine the elderly has been increasing. It seems very important to have an accurate understanding of changes in renal function associated with aging in Japanese as reflected in routine clinical tests of renal function. Such changes provide a basis for evaluating drug dosage and schedule, as well as the feasibility of using contrast media. In this study, the changes in renal function due to aging are assessed in a large number of male and female subjects.

Subjects and Methods

The subjects were 329 inpatients with no renal disease, water-electrolyte imbalance, or exposure to any drugs that affect the kidney function (diuretic, antihypertensive or nephrotoxic agents). Table 1 lists age, sex, body height and weight of the subjects. We collected 24-hour urine specimens three times. Fasting blood samples were collected early in the morning of the day scheduled for the start of the collection of urine specimens. Blood and urine creatinine and B2-microglobulin (B2-MG) levels, and urine N-acetyl-β-D glucosamidase (NAG) were determined. The 24-hour urinary excretion of each substance and creatinine clearance (Ccr) were calculated from these test results. Since both body height and weight significantly decreased with aging and sexual differences were significant in these values, the actual test data were compared with those after correction for body surface area for the 24-hour urinary creatinine (UcrV) and Ccr. The results of the renal function tests were expressed in mean values for the 3 days.

Creatinine and B2-MG were analyzed with an autoanalyzer by the creatine amidohydrolase method and by the latex agglutination test, respectively. Urine NAG levels were determined by a method using sodium-cresolsulfonphthaleinyl-N-acetyl-β-D-glucosamide.

The subjects were divided into a control group of those under 50 years of age, a 50s group for those 50 or over but under 60, a 60s group for those 60 years or over but under 70, a 70s group for those 70 or over but under 80, and an 80s group for those 80...
Table 1. Characteristics of Subjects

<table>
<thead>
<tr>
<th>Ages (y)</th>
<th>Male (cases)</th>
<th>Female (cases)</th>
<th>Total (cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>50</td>
<td>23</td>
<td>73</td>
</tr>
<tr>
<td>50–59</td>
<td>48</td>
<td>29</td>
<td>77</td>
</tr>
<tr>
<td>60–69</td>
<td>37</td>
<td>40</td>
<td>77</td>
</tr>
<tr>
<td>70–79</td>
<td>37</td>
<td>34</td>
<td>71</td>
</tr>
<tr>
<td>80≥</td>
<td>19</td>
<td>12</td>
<td>31</td>
</tr>
<tr>
<td>Total (cases)</td>
<td>191</td>
<td>138</td>
<td>329</td>
</tr>
</tbody>
</table>

<50 mean age, Male ; 37.2
Female; 31.7
Minimum age, Male ; 19
Female; 17
Maximum age, Male ; 90
Female; 88

Height (cm)

<table>
<thead>
<tr>
<th>Ages (y)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>169.9±7.22</td>
<td>156.5±3.97</td>
</tr>
<tr>
<td>50–59</td>
<td>164.5±5.93***</td>
<td>152.2±4.29***</td>
</tr>
<tr>
<td>60–69</td>
<td>163.8±5.70***</td>
<td>149.2±6.07***</td>
</tr>
<tr>
<td>70–79</td>
<td>159.0±5.42***</td>
<td>147.8±5.75***</td>
</tr>
<tr>
<td>80≥</td>
<td>158.4±5.26***</td>
<td>144.2±6.52***</td>
</tr>
</tbody>
</table>

Body weight (kg)

<table>
<thead>
<tr>
<th>Ages (y)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>65.0±12.1</td>
<td>49.3±6.39</td>
</tr>
<tr>
<td>50–59</td>
<td>56.3±9.10***</td>
<td>52.8±8.69</td>
</tr>
<tr>
<td>60–69</td>
<td>61.7±10.5</td>
<td>51.9±8.08</td>
</tr>
<tr>
<td>70–79</td>
<td>51.5±8.56***</td>
<td>46.0±9.25</td>
</tr>
<tr>
<td>80≥</td>
<td>49.7±6.65***</td>
<td>43.5±9.69*</td>
</tr>
</tbody>
</table>

*; P<0.05, ***; P<0.001: Comparison with less than 50 years old. x; P<0.05, xxx; P<0.001: Comparison between male and female.

Results

There was a tendency toward increases in the Scr level with aging in all subjects (Fig. 1). At the same time, however, there were instances of marked deviations and no clearcut pattern was observed. Changes in Scr by age and sex were investigated. Scr was found to be slightly increased with aging (Fig. 1). The Scr level was significantly (P<0.001) higher in the female group in their 80s than in the female control groups. The Scr level was higher in males, showing a significant sex-related difference in this parameter in all age groups except for the 80s group (Fig. 1). When Scr was similarly assessed using values corrected for body surface area, a tendency forward an increase with aging was evident for all subjects (P<0.001, upper Fig. 2). The sex differences had a minimal effect on the Scr level (lower Fig. 2).

When the Scr levels, corrected for body surface area, were examined by multiple regression analysis and the one-way layout method, the Scr level was found to rise with aging and there were significant differences (P<0.05) among the three groups. There was a significant (P<0.05) sex difference in the Scr level (markedly higher in males) in the group composed of those between 50 and 65 (Fig. 3).

There was a significant (P<0.001) negative correlation between the actual UcrV and age (upper Fig. 4). When the actual UcrV levels were examined by age and sex, it was found that they tended to decrease significantly with age regardless of sex in all groups (lower Fig. 4), and this tendency was particularly
Figure 2. Upper: Correlation between age and Scr levels corrected for body surface area. Lower: Changes in Scr levels corrected for body surface area by age and sex. — Male, ◦ Female. *; P<0.05, **; P<0.01: Comparison with the <50 years group.

Figure 3. Scr levels corrected for body surface area were assessed by multiple regression analysis and the one-way layout method according to age and sex. — Total, — Male, ◦ Female. *; P<0.05: Comparison by age. ×; P<0.05: Comparison by sex.

notable in males. UcrV was higher in males and the differences were significant in all except for the 80s group (Fig. 4). The relationship between the UcrV level corrected for body surface area and age was investigated in all subjects. As in the actual levels of UcrV, there was a significant (P<0.001) negative correlation, as shown in the upper part of Fig. 5. The changes in UcrV according to age and sex also tended to be similar to those of the actual UcrV levels (lower Fig. 5).

When the UcrV levels, corrected for body surface area, were examined by multiple regression analysis and the one-way layout method, these levels were shown to decrease with aging with significant (P<0.01) differences among the three groups. The UcrV level was significantly (P<0.01) higher in males in all three groups (Fig. 6). A significant (P<0.001) negative correlation was found between actual Ccr values and age for all subjects. Changes in the actual Ccr levels by age and sex were also investigated. The actual Ccr level significantly decreased with age for both sexes. Unlike Scr and UcrV, however, there were no sex differences in actual Ccr values. The correlation between Ccr and values corrected for body surface area, and changes in corrected Ccr by age and sex showed tendencies similar to those of the actual Ccr values. When corrections similar to those in UcrV were made, sex differences were no longer observed (Fig. 7). In the 80s group, the corrected Ccr was 54.5±16.9 ml/min in males and 52.5±23.1 ml/min in females.

When the Ccr levels corrected for body surface area were examined by multiple regression analysis and the one-way layout method, there were significant (P<0.01) differences among the three groups. As shown in Fig. 8, there was no sex difference.

There was a significant (P<0.001) positive correlation between the serum B2 MG level and age: serum B2 MG significantly increased with age (upper Fig. 10). The serum B2 MG level was significantly higher in males 70 years of age or over and females 50 years of age or over compared to the control group. This pattern was consistent with the decrease in Ccr due
Renal Function and Aging

Figure 4. Upper: Correlation between actual UcrV levels and age. Lower: Changes in the actual levels of UcrV according to age and sex. -●-Male, -○-Female. **; P<0.01: Comparison with the <50 years group. xxx; P<0.001: Comparison by sex.

Figure 5. Upper: Correlation between UcrV levels corrected for body surface area. Lower: Changes in UcrV levels corrected for body surface area according to age and sex. -●-Male. -○-Female. *; P<0.05, **; P<0.01: Comparison with the <50 years group. xx; P<0.01, xxx; P<0.001: Comparison by sex.

to aging but serum B2 MG levels varied widely; their relation to age was not as marked as that of UuaV or Ccr in the elderly. There were no sex differences in the serum B2 MG level in any of the age groups (Fig. 9).

The relationship between urinary excretion of B2 MG and age was assessed. There was a great variation among the subjects; and no correlation was found between these two parameters in all subjects. There were no consistent patterns with regard to age-related differences in the changes in urinary excretion of B2 MG. Nor was there any sex-specific change (upper Fig. 10).

There was no correlation between urinary excretion of NAG and age, nor any consistent pattern in regard to changes in the urinary excretion of NAG. However, the urinary NAG level did tend to be less in females, with significant differences in all ages except for the 60s and 70s groups (lower Fig. 10).

Discussion

It is very important in clinical practice to determine renal function accurately. Renal function is known to decline with aging (3, 4, 8), therefore the renal function of the aged must be accurately understood for implementing drug therapy, for tests using contrast media, and evaluating clinical test results. It is, in fact, well known that the incidence of adverse effects of drugs and contrast media is higher in the elderly. However, there have only been a few extensive studies on this subject in Japan (8).
In particular, there have been no reports compiling results obtained at multiple institutions. Confronted with this situation, we investigated the relationship between aging and renal function in large numbers of subjects at many institutions in cooperation with the members of the Third Subcommittee of the Ministry of Health and Welfare, Specific Diseases-Progressive Renal Dysfunction Study. The renal function test parameters examined were those frequently used in routine clinical practice (Scr, UcrV, Ccr, serum β₂ MG, 24-hour urine β₂ MG, and 24-hour urine NAG). Because the subjects were inpatients without renal disease in the various institutions with which the individual members of the subcommittee are affiliated, it was possible to collect blood and urine specimens for 3 days. The mean of the samples of 3 days were used as the results of the individual renal function tests for more precise determination. The urinary contents of β₂ MG and NAG were determined in 24-hour urine, not in sporadic urine specimens. As shown in Table 1, significant differences in body height and weight were noted by age and sex. Body surface area is closely correlated with renal metabolism and kidney size. By correcting for body surface area, the variation in Ccr can be reduced (9, 10). Therefore, both the actual and corrected Scr, UcrV and Ccr were used for the calculations. The Scr level rose slightly with age. The UcrV level decreased with age, and this trend was more pronounced in males. Both the Scr and UcrV levels were higher in males, but these sex differences were reduced by correcting for body surface area. It is believed that creatinine is produced in muscles at a constant rate and that the amount...
produced is proportional to the total muscle mass (11). The results for Scr and UcrV, therefore, suggest that muscle mass is greater in males and the decrease in mass due to aging is more marked in males. These results suggest that the difference in mass was corrected by body surface area, and even after this correction, Scr remained elevated, UcrV decreased with age, and sex differences persisted.

Although Ccr significantly decreased with age, there were no sex differences, unlike Scr or UcrV. The correlations between Ccr and age and changes in Ccr according to age and sex after correction for body surface area still showed tendencies similar to those of the actual Ccr. There were no sex differences even after correction for body surface area. When Scr, UcrV, and Ccr corrected for body surface area were examined using multiple regression analysis and the one-way layout method, there was a significant difference in the comparison of each parameter among the 3 groups. Among these 3 parameters, Ccr exhibited the most significant reduction regardless of sex, suggesting that it may be possible to establish reference values of Ccr for the three age groups. McQueen et al (12) reported a close correlation between Ccr and inulin clearance in healthy subjects. In patients whose GFR is compromised by renal disease, however, the Ccr/inulin clearance ratio is known to be elevated (13). The present study included only patients without renal disease. Therefore, the Scr, UcrV and Ccr data suggest that GFR significantly decreases with age in both sexes, even after body surface area correction to compensate for the decrease in muscle mass with aging and sex differences in muscle mass. Epstein (3), Wesson et al (4), and Alder et al (5) also reported reductions in GFR associated with aging in their studies using European and American subjects. According to their data, GFR for those over 70 years of age was over 70 ml/min for both males and females. These figures are higher than those of the present study but are in agreement with those of
Dohi et al (8) who used Japanese subjects. In other words, those results indicate that GFR or Ccr for the aged in Japan is lower in comparison with their western counterparts. There have been no reports on changes in the Ccr/inulin clearance ratio in the presence of the compromised GFR associated with aging and without renal disease. It is also unclear whether body surface area calculated on the basis of body height and weight accurately reflects the decreases in muscle mass due to aging. The results of a follow-up study of changes in renal function due to aging in the same patients by Lindeman et al (14) suggested considerable individual differences in renal hypofunction due to aging. Changes in the Ccr/inulin clearance ratio due to aging should be investigated in the future. Reductions in muscle mass due to aging should also be accurately determined by computed tomography and dual-photon absorptiometry. Follow-up studies should also be conducted in many of the same patients. It is hoped that age-specific criteria for Ccr will be established based on such studies to be used in clinical practice. We believe that the results of the present study will provide the fundamental data for these studies.

The serum B2 MG level is regarded as being positively correlated with Scr and serves as an index of glomerular function (15). In the present study serum B2 MG was also positively correlated with age and the results were consistent with the increase in Scr and decrease in Ccr due to aging. Among the elderly, however, there were wide variations in serum B2 MG values and their relation to age was not as definite as in Scr or Ccr. The explanation for this difference seems to require assessment of the relationship between aging and the production or catabolism of B2 MG. Urinary contents of B2 MG and NAG are considered to be indicators of proximal tubular disorders (16). There was no correlation between the urinary excretion of B2 MG or NAG and age and there were wide variations in values among the patients. Therefore it was impossible to identify changes in tubular function due to aging by using these two parameters.

The authors hope that in the future renal function studies in the elderly, particularly on Ccr, can be accurately interpreted and age-specific reference values be established and used in clinical practice.

Acknowledgments: This study was supported in part by a program project grant of The Ministry of Health and Welfare (director: Dr. Kiyoshi Kurokawa). The authors express their thanks to each participating institution, and the members of the Third Subcommittee of the Ministry of Health and Welfare.

References

Renal Function and Aging


