Effect of age and affection status on blood pressure, serum potassium and stature in familial hyperkalaemia and hypertension

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Abstract

Background. The rare autosomal dominant genetic disorder familial hyperkalaemia and hypertension which is caused by mutations in WNK4 kinase, is characterized by childhood hyperkalaemia and hypercalciuria, and appearance of hypertension in the third to fourth decade. Accompanying short stature is often described.

Methods. We determined height, blood pressure and blood and urinary biochemical parameters in members of a very large family of FHHt with the WNK4 Q565E mutation.

Results. The family has 57 members, 30 of whom (including 14 children) are affected. Prehypertension occurred in 7/11 affected and 1/10 unaffected children (P = 0.024). Serum potassium (SK) was ~0.5 mmol/L higher in affected children vs adults [5.98 ± 0.42 vs 5.46 ± 0.40 mmol/L, respectively (P < 0.0001)] (33 samples from 11 children and 36 samples from eight adults). SK of ≥6.0 mmol/L occurred in 16/33 children's samples and in 3/36 adults' samples (P = 0.0003). Hyperkalaemia in children is currently untreated. Children also had more severe hyperchloraemia and hypercalciuria. The family contains four large subfamilies, and each includes 8–10 siblings. In one subfamily, height Z-score was lower in affected vs unaffected subjects [−2.69 ± 0.36 vs −1.05 ± 0.16, respectively (P < 0.0001)]. In the other three subfamilies, no such difference was found.

Conclusions. Short stature is not part of FHHt with the WNK4 Q565E mutation. Children affected with FHHt have a high prevalence of prehypertension, and their hyperkalaemia is more severe than that of affected adults. Children may have a more severe defect in the basic mechanism that produces hyperkalaemia. We suggest that, in affected adults, the attenuation of hyperkalaemia and appearance of hypertension may be the result of a late rise in the activity of renal transporters or channels such as the epithelial sodium channel.

Keywords: children; hyperkalaemia; hypertension; short stature; WNK kinases

Introduction

Familial hyperkalaemia and hypertension (FHHt), also termed pseudohypoaldosteronism type II (PHA II), is a monogenic form of hypertension characterized by the combination of hyperkalaemia and hypertension [1,2]. The discovery that FHHt is caused by mutations in the WNK [With No K (lysine)] kinases WNK1 and WNK4 revealed a new metabolic pathway that regulates blood pressure and serum potassium concentration [3]. In patients with the WNK4 Q565E mutation, hypercalciuria [4–6] accompanies the hyperkalaemia; both are present at an early age [4,5], whereas hypertension appears later, in the third decade in males and in the fourth decade in females [6]. The factors contributing to the late appearance of hypertension are not known. Thiazide therapy is very effective in the correction of hyperkalaemia, hypercalciuria and hypertension [4].

An important feature of FHHt mentioned mainly in sporadic case reports is short stature [2]. The availability of the largest family with FHHt described in the literature, and its current expansion, enabled a detailed comparative study of stature in its affected and unaffected members. The family now includes 57 subjects, 30 of whom are affected.

Investigation of the expanded family, which includes the addition of 11 children (bringing the number of affected children to 14), revealed that affected children have increased prevalence of prehypertension, and that hyperkalaemia in affected children is significantly more severe than in adults affected by FHHt with the WNK4 Q565E mutation. This observation might shed some light on the mechanism for late appearance of hypertension in FHHt.

Materials and methods

The subjects studied here belong to a previously reported large family with FHHt and the WNK4 Q565E mutation [4–6]. All subjects included...
in the analysis were examined by us clinically and their genotype analysed. Children were defined as subjects ≤18 years of age. Affection status was determined by the presence of the WNK4 Q565E mutation as described previously [4–6]. All biochemical analyses were performed on subjects who had never been treated by thiazides due to the postulated long-term effects of these drugs [2].

**Determination of blood pressure**

This was measured by auscultation of the seated subject using an appropriate-sized cuff and a sphygmomanometer. In children, it was measured one to three times. Subjects with systolic and or diastolic blood pressure of <90th percentile for age gender and height were classified as having normal blood pressure. Subjects with systolic or diastolic blood pressure of >90th but <95th percentile were classified as suspected prehypertension. Subjects with systolic or diastolic blood pressure of >95th percentile were classified as suspected hypertension [7].

**Determination of height**

This was performed by the use of a standardized method. Each subject was measured using a fixed stadiometer with right-angle headpiece. Percentiles were determined according to the Centers for Disease Control and Prevention [8]. Heights were converted into standard deviation scores (Z-scores) using the National Center for Health statistics reference values. Low stature was defined as a height percentile of ≤5% (Z-score of −1.64).

**Serum potassium**

Blood was withdrawn in the morning with stasis and fist clenching, and serum was separated within 60 min. Normal range in our laboratory is 3.5–5.2 mmol/L.

**Determination of fractional excretion of potassium calcium and sodium**

This was done by determining serum and spot urine electrolytes and creatinine.

**Ethics**

The study was approved by the local ethics committee of Sheba Medical Center (Tel Hashomer, Israel). Informed consent was obtained from all subjects studied or from the parents of the children studied.

**Results**

**The extended pedigree**

Figure 1 shows the extended pedigree that now contains 57 members, 30 of them affected with FHHt; it includes the 46 previously described subjects [6] and the addition of 11 new subjects who were studied by us clinically and by genotype analysis. In four subjects, VI 12, VI 21, VI 28 and VI 29, blood was not withdrawn, and genotype analysis was performed by buccal smear. All of the other affected subjects had hyperkalaemia and hypercalciuria. Fourteen of these subjects are currently hypertensive, 13 are being treated by thiazide diuretics (all affected subjects of generations III, IV and V except for subjects V 3 and V 6) and five of these 13 are being additionally treated with calcium channel blockers. In three of these affected subjects, calcium channel blockers were added after many years of thiazide use, at an age of >50 years, possibly because of development of essential hypertension in these subjects with FHHt.
Prehypertension is prevalent in affected children

Blood pressure was examined in 21 children aged 3–17 years (mean 9.0 ± 4.0 years), 12 boys and nine girls. There were 11 affected children—five boys and six girls—with a mean age of 8.7 ± 4.2 years and 10 unaffected children—seven boys and three girls—with a mean age of 9.3 ± 3.9 years. Prehypertension occurred in seven of the 11 affected children, four of them boys, and in one unaffected 4-year-old boy (P = 0.024). The mean BMIs of affected and unaffected children did not differ.

Hyperkalaemia in affected children is more severe than in adults

Hyperkalaemia in affected children was found to be more severe than in affected adults (Table 1, Figure 2). We compared SK levels in affected adults and children: 33 serum samples from 11 affected children were compared with 36 samples from eight affected adults. Mean SK in the children was ~0.5 mmol/L higher than in the adults [5.98 ± 0.42 vs 5.46 ± 0.40 mmol/L, respectively (P < 0.0001)]. Forty-eight per cent of the children's serum samples (16/33) showed SK levels of ≥6.0 mmol/L, compared with only 8% (3/36) in adults (P = 0.0003). We also compared the mean individual SK levels of the 11 affected children with that of the eight affected adults, and these were also higher in children than in adults [6.00 ± 0.36 vs 5.48 ± 0.28 mmol/L, respectively (P = 0.003)]. A comparison of SK levels in the six affected girls with that in the five affected boys showed higher SK levels in the former, but this was not statistically significant [6.18 ± 0.34 vs 5.81 ± 0.30 mmol/L, respectively (P = 0.09)]. To rule out the possibility that the higher SK values in affected children results from haemolysis during phlebotomy, we compared SK in unaffected children and adults, and found that they were not higher in the former than in the latter (Table 1). We also compared serum chloride and urinary calcium in affected children and adults. In accordance with the more severe hyperkalaemia found in children, hyperchloraemia was also more severe than in adults. Mean chloride concentration in 35 serum samples from eight affected adults was 108.4 ± 1.3 mmol/L, and mean chloride concentration in 29 serum samples of 11 affected children was 110.3 ± 1.8 mmol/L (P < 0.0001). Unaffected children and adults had similar serum chloride concentrations (Table 1). Hypercalciuria was also more severe in affected children than in adults. Mean calcium-to-creatinine ratio in 33 urine samples from eight affected adults was lower than that found in 24 urine samples from 12 affected children [0.60 ± 0.25 vs 0.83 ± 0.36 mmol calcium/mmol creatinine, respectively (P = 0.012)]. This difference does not result from lower creatinine excretion in children since unaffected children and adults had similar values of urinary calcium-to-creatinine ratio (Table 1). Affected subjects had higher serum aldosterone concentrations than unaffected subjects [308 ± 140 vs 217 ± 105 pmol/L, respectively (P = 0.052)]; however, this parameter in affected children was similar to that in affected adults, and serum aldosterone concentration in unaffected children was similar to that in unaffected adults.

Fractional excretion of potassium calcium and sodium

Since no systematic data are available regarding these parameters in affected and unaffected subjects with FHHt, we

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Table 1. Age, height and biochemical values in affected and unaffected adults and children

<table>
<thead>
<tr>
<th></th>
<th>Affected adults</th>
<th>Affected children</th>
<th>P-value</th>
<th>Unaffected adults</th>
<th>Unaffected children</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.8 ± 10.0</td>
<td>7.5 ± 2.9</td>
<td>&lt;0.0001</td>
<td>26.2 ± 10.6</td>
<td>7.5 ± 4.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Height Z-score</td>
<td>−2.69 ± 0.36</td>
<td>−1.30 ± 0.92</td>
<td>0.002</td>
<td>−1.13 ± 0.24</td>
<td>−1.67 ± 0.97</td>
<td>0.24</td>
</tr>
<tr>
<td>SK (mmol/L)</td>
<td>5.46 ± 0.40</td>
<td>5.98 ± 0.42</td>
<td>&lt;0.0001</td>
<td>4.26 ± 0.25</td>
<td>4.05 ± 0.19</td>
<td>0.027</td>
</tr>
<tr>
<td>SCl (mmol/L)</td>
<td>108.4 ± 1.3</td>
<td>110.3 ± 1.8</td>
<td>&lt;0.0001</td>
<td>104.1 ± 1.9</td>
<td>104.3 ± 1.6</td>
<td>0.72</td>
</tr>
<tr>
<td>UCa (mmol calcium/</td>
<td>0.60 ± 0.25</td>
<td>0.83 ± 0.36</td>
<td>0.012</td>
<td>0.33 ± 0.10</td>
<td>0.23 ± 0.17</td>
<td>0.11</td>
</tr>
<tr>
<td>mmol creatinine)</td>
<td>(33 sam, 8 sub)</td>
<td>(33 sam, 11 sub)</td>
<td></td>
<td>(10 sam, 10 sub)</td>
<td>(15 sam, 15 sub)</td>
<td></td>
</tr>
<tr>
<td>Serum aldosterone</td>
<td>300 ± 143</td>
<td>316 ± 146</td>
<td>0.83</td>
<td>212 ± 138</td>
<td>220 ± 83</td>
<td>0.87</td>
</tr>
<tr>
<td>(pmol/L)</td>
<td>(7 sam, 7 sub)</td>
<td>(7 sam, 7 sub)</td>
<td></td>
<td>(6 sam, 6 sub)</td>
<td>(9 sam, 9 sub)</td>
<td></td>
</tr>
</tbody>
</table>

SK, serum potassium; SCl, serum chloride; UCa, urinary calcium; sam, samples; sub, subjects.

*Subjects shown in Figure 3.

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Fig. 2. Serum potassium concentration in adults (closed circles) and children (closed triangles) affected by FHHt, and in unaffected adults (open circles) and children (open triangles). Thirty-six serum samples of eight affected adults, 33 serum samples of 11 affected children, 10 serum samples of 10 unaffected adults and 15 serum samples of 15 unaffected children are shown. Mean ± SD is shown.
Table 2. Fractional excretion of potassium, calcium and sodium

<table>
<thead>
<tr>
<th>Fractional excretion (%)</th>
<th>Affected (n = 16)</th>
<th>Unaffected (n = 13)</th>
<th>Controls (n = 12)</th>
<th>P-value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K</td>
<td>4.61 ± 2.00</td>
<td>9.22 ± 5.50</td>
<td>11.50 ± 4.40</td>
<td>0.0003</td>
</tr>
<tr>
<td>Ca</td>
<td>2.05 ± 0.89</td>
<td>0.64 ± 0.51</td>
<td>1.04 ± 0.50</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Na</td>
<td>0.72 ± 0.31</td>
<td>0.70 ± 0.31</td>
<td>0.63 ± 0.23</td>
<td>0.8</td>
</tr>
</tbody>
</table>

calculated these values in 16 affected, 13 unaffected and 12 control subjects. Table 2 shows that, as expected, the fractional excretion of potassium in affected subjects was reduced by about 50% compared with that found in unaffected subjects. However, individual data showed a pronounced overlap, with 8/13 unaffected subjects falling in the range of the affected subjects. This is in contrast to the almost absolute lack of overlap between SK in affected and unaffected subjects (Figure 2). In 69 serum samples from 19 affected subjects, mean SK was 5.71 ± 0.48 mmol/L compared with a mean of 4.14 ± 0.23 mmol/L in 25 samples from 25 unaffected subjects (P < 0.0001). Only one unaffected subject had a SK level (4.8 mmol/L) in the range of that found in affected subjects. As expected from the hypercalciuria of FHHt, we found an increase in the fractional excretion of calcium in affected compared with unaffected subjects (Table 2). Marked overlap between individual values in these groups was observed here as well. Fractional excretion of sodium was similar in affected and unaffected subjects (Table 2).

**Height in the family**

The pedigree shown in Figure 1 includes four large subfamilies, all progeny of subject IV 2; subfamily A includes subjects IV 2 and V 3–V 12, subfamily B subjects V 3 and VI 5–VI 12, subfamily C subjects V 6 and VI 13–VI 21 and subfamily D subjects V 7 and VI 22–VI 29. In subfamily A, mean height Z-score was indeed lower in the seven affected subjects than in the four unaffected subjects [−2.69 ± 0.36 vs −1.05 ± 0.16, respectively (P < 0.0001)]. However, in the other three subfamilies, there was no such difference. In subfamily B, the six affected members were taller (albeit insignificantly) than the three unaffected children [height Z-score −1.27 ± 1.18 vs −2.36 ± 1.00, respectively (P = 0.22)]. In subfamilies C and D, mean height Z-scores were similar in affected and unaffected members. In subfamily C, they were −2.13 ± 1.03 vs −1.84 ± 0.88, respectively (P = 0.65), and in subfamily D they were −1.16 ± 1.38 vs −0.86 ± 0.31, respectively (P = 0.68). All subjects in subfamily A were >18 years. In the other three subfamilies, range of ages was 3 months to 18 years. The unaffected fathers in subfamilies A, B, C and D had height Z-scores of −1.65, −0.68, −1.23 and +0.02, respectively. Analysis of 34 out of 35 subjects in these four subfamilies with available stature measurement (Figure 3) showed no difference in the mean Z-score of the affected vs the unaffected subjects [−1.87 ± 1.01 vs −1.51 ± 0.85, respectively (P = 0.2)]. An additional analysis of the same data showed that very low stature (Z-score of <−2.0) was more prevalent among affected subjects in these four subfamilies (8 out of 17), than among unaffected subjects (5 out of 17); however this difference did not reach statistical significance (P = 0.48). The eight affected adult subjects who were not descendants of subject IV 2 (mean age 51.2 ± 18.3 years) had a mean height Z-score of −1.0 ± 1.2, a higher value than that found in the affected children shown in Table 1.

In an apparent support of a possible direct association of short stature with FHHt is the clinical case of subject VI 31. At the age of 5 years, she was presented with short stature. Her height Z-score was −2.74. SK was 6.5–6.9 mmol/L, and serum bicarbonate was 19 mmol/L. IGF-1 concentration was 8.8 mmol/L. Growth hormone levels in clonidine-stimulation test were normal. Her affected mother, V 14, had a height Z-score of −3.14 at the age of 13 years [4]. Her SK was 6.0–7.2 mmol/L, and bicarbonate was 18.5 mmol/L. She was treated by thiazide diuretics and when she was 18 years old her height Z-score was −1.39. Although it is unclear whether her growth was accelerated by the thiazides, her daughter, subject VI 31, was started on thiazide therapy.

The relation between short stature and IGF-1, severity of hyperkalaemia, hyperchloraemia (reflecting metabolic acidosis) and hypercalciuria was assessed. Higher rather than lower IGF-1 concentrations were found in seven affected compared with three unaffected children (all between the ages of 3 and 10 years, and prepubertal) [9.9 ± 2.8 vs 5.4 ± 1.4 mmol/L, respectively (P = 0.03)]. Of the 10 affected children with known SK levels, six had low stature (Z-score <-1.64), and their mean SK was 5.98 ± 0.41 mmol/L, not different than the mean SK in the four taller children, which was 6.18 ± 0.17 mmol/L (P = 0.37). A potential cause for the short stature is metabolic acidosis in FHHt. However, the bicarbonate level in subject VI 31 for example (a very short subject) was 19 mmol/L, similar to the mean bicarbonate levels of all the affected subjects including taller ones [19.5 ± 1.4 mmol/L [5]]. Among the affected children, hyperchloraemia was similar in the six low-stature and four taller children [110.7 ± 1.3 vs 111 ± 1.8 mmol/L, respectively (P = 0.7)], Urinary calcium was not higher in the low-stature vs taller children affected with FHHt (data not shown).
Discussion

Monogenic disorders give us the opportunity to observe and study the clinical effects of a mutated gene. This has been the case with the rare autosomal dominant disorder FHHt. The discovery that mutations in the kinases WNK1 and WNK4 cause FHHt led to extensive research, which revealed a cascade or network of kinases that ultimately stimulate the Na–Cl cotransporter (NCC) [9–11], thus apparently explaining the hypertension and hyperkalaemia in FHHt. In vitro experiments showed that WNK4 is involved in the regulation of other transport systems as well, including the renal outer medulla potassium channel (ROMK) [12], ENaC [13,14], paracellular chloride transport [15] and calcium transport [16]. It is not clear which of these effects is physiologically relevant. Moreover, WNK4 could potentially have other unknown effects. Close investigation of clinical features of FHHt may point to such effectors.

A clinical feature that is considered part of the clinical syndrome of FHHt is short stature [2]. With the availability of more children to investigate stature in FHHt, it became feasible to perform the first systematic study of blood pressure in children with FHHt and to compare serum potassium in affected children and adults. We found that affected children have a higher prevalence of prehypertension compared with unaffected children in the family. This means that children with FHHt should be followed closely for the appearance of hypertension. This is especially true for boys who may have a higher incidence of prehypertension than girls. It is also in agreement with our previous finding that hypertension appears earlier in adult males (at 28 years of age) than in adult females (at 38 years of age) [5]. The prevalence of prehypertension in the affected children (7/11) was much higher than that found in the US among children aged 8–17 years (8–10%) [17]. Since all FHHt-affected children will ultimately develop hypertension as adults [4–6], a follow-up study of this family may improve our understanding of the relationship between childhood prehypertension and hypertension [18].

In addition, we found that hyperkalaemia in affected children is more severe than in affected adults. Mean SK was ~0.5 mmol/L higher in children than in adults. Moreover, about 50% of SK level tests in children revealed values of ≥6.0 mmol/L, while in adults such hyperkalaemic values were found in only 8% of the tests. The finding of higher SK, serum chloride and urinary calcium levels in affected children is not an artefact since it does not occur in unaffected children. This observation has two implications. The first deals with the practical question of whether to treat these children. As described previously, thiazide therapy is very effective in the treatment of FHHt [4]. Our current therapeutic policy is to treat affected subjects only upon detection of hypertension or if hypercalciuria is present in the affected subject along with decreased bone mineral density. Do affected children require thiazide therapy just for hyperkalaemia? Hyperkalaemia is a major concern in patients with chronic renal failure under dialysis, whose prognosis worsens with increased severity of hyperkalaemia [19]. During decades of follow-up of members of the family studied here, as well as in the literature, no cases of sudden death have been reported in FHHt. It is possible that, similar to the decreased sensitivity of patients with renal failure to chronic hyperkalaemia [20], children with FHHt also develop decreased sensitivity to chronic hyperkalaemia.

The second issue is the mechanism governing the increased severity of hyperkalaemia in children with FHHt. Since aldosterone is a major regulator of SK, we compared its concentration in affected children and adults; however, no significant difference was found. Is a diet richer in potassium the basis for the increased hyperkalaemia in children? In a transgenic mouse model of FHHt, Lalioti et al. demonstrated a dramatic rise in SK upon feeding these mice a high potassium diet [21]. We did not measure dietary potassium in children or adults, but a big difference is unlikely. Another potential contributing factor to the more severe hyperkalaemia seen in children may be increased physical activity [22]. However, mean SK of boys, who may have higher physical activity, showed a non-significantively lower value than that measured in girls. We therefore presume that the basic defect that is responsible for the hyperkalaemia in FHHt is more pronounced in children. Whether hyperkalaemia in FHHt occurs only as a consequence of enhanced activity of NCC in the distal nephron or whether the renal potassium channel ROMK is involved [11,21,23] is still under debate. In support of the possibility that the basic renal defect is responsible for the increased severity of childhood hyperkalaemia is the finding that both hyperchloremia, which reflects metabolic acidosis, and hypercalciuria, which accompanies hyperkalaemia in FHHt, are also more severe in children than in adults. We therefore suggest that in adults compared to children with FHHt, there is an attenuation of the basic defect causing hyperkalaemia but not hypertension, or there is development of compensatory mechanisms as compared to children with FHHt. A potential compensatory mechanism may be the acquisition of higher activity of the maxi-K channels in the distal nephron. This was demonstrated in the developing rabbit kidney [24] and has been suggested to explain the transient neonatal hyperkalaemia in Bartter syndrome with inactivating mutations of ROMK [25]. It is interesting that in adults with FHHt, hypertension appears while hyperkalaemia is attenuated. A pathophysiological mechanism that may be at the basis of both these clinical manifestations is a rise in the activity of ENaC. This was indeed found in the knockin model of WnkD561A/+ mice [23].

We report here that the fractional excretion of potassium in affected subjects with FHHt is about 50% of that in unaffected subjects. It is interesting that in the knockin mouse model of FHHt, fractional excretion of potassium was higher, 70–75% of that in wild-type mice [23,26]. In both FHHt mouse models [21, 23, 26], there was an overlap in individual SK levels in the wild-type and mutant mice, in contrast to the nearly complete lack of such overlap in the family reported here.

Regarding short stature in FHHt, this has been reported in some mainly sporadic but also familial cases [27,28]. The availability of a very large family with FHHt and the WNK4 Q565E mutation enabled us to study this issue in detail. When initially reported as the first affected family, more than three decades ago, we did not consider af-
fected members to have short stature [29]. As described in Results Section, our pedigree includes two affected members, a daughter and her mother, who presented with very low stature. In the mother, thiazide therapy was accompanied by an increase in height Z-score. Analysis of our pedigree shows that indeed in subfamily A (see Results Section) affected subjects were of significantly lower stature than unaffected subjects; however, in the other three subfamilies, B, C and D (see Results Section), no association was found between affection status and short stature. Low IGF-1, hyperkalaemia, metabolic acidosis and hypercalciuria were considered to be potential causes of the short stature, but this could not be shown. Hyperkalaemia, hyperchloraemia and hypercalciuria were all of similar severity in affected children regardless of stature. Only two families with FHHt and short stature have been described [27,28]. In one family, with an undefined molecular defect, which included four adults and two children, three of the adults had a height percentile of <3%, and the two children were of normal height [27]. In the other family, which included three affected adults and four affected children, only one adult was short, with a height percentile of 5% [28]. The latter family bears the same WNK4 Q565E mutation as the family described in this report [30]. Height is considered to be a polygenetic trait, and genome-wide association studies have recently identified common genetic variants that contribute to height variation [31]. It is possible that some FHHt families with a still unidentified genetic defect harbour a mutation in a gene that affects growth. In any case, we recommend that a very low stature child with FHHt and the WNK4 Q565E mutation, especially if severely hyperkalaemic, should have a trial of thiazide therapy. Only further experience can validate this approach.

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Conflict of interest statement. None declared.

References

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A comparison of cystatin C- and creatinine-based prediction equations for the estimation of glomerular filtration rate in black South Africans

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Abstract

Background. Serum creatinine (S-Cr)-based prediction equations are commonly used for estimating glomerular filtration rate (GFR). However, S-Cr concentration is also affected by other factors such as tubular secretion, muscle mass, diet, gender and age. Serum cystatin C (S-Cys C)-based prediction equations have been proposed as an improved potential alternative as S-Cys C levels are not influenced by many of the factors that affect creatinine concentration other than GFR. This may be of great benefit to patients with low muscle mass such as those infected with human immunodeficiency virus who are at increased risk for the development of renal impairment. The aim of this study was to develop and evaluate a S-Cys C-based prediction equation for different stages of renal disease in black South Africans.

Methods. One hundred patients with varying degrees of renal function were enrolled in the study. The plasma clearance of ⁵¹Cr-EDTA, a gold standard method, was used to measure GFR (mGFR). In addition, serum was analysed for S-Cr and S-Cys C on each participant. This dataset was split into a development dataset (n = 50) and a test dataset (n = 50). The development dataset was used to formulate a S-Cys C- and S-Cr-based prediction equation using multiple linear regression analysis. These equations together with the four-variable MDRD and CKD-EPI equation were then tested on the test dataset.

Results. In the test dataset, accuracy within 15% of measured GFR was 68% for the S-Cys C equation and 48% for the S-Cr equation. Root mean square error for S-Cys C eGFR was 10.2 mL/min/1.73 m² for those patients with mGFR <60 mL/min/1.73 m² and 11.9 mL/min/1.73 m² for those patients with mGFR >60 mL/min/1.73 m². Root mean square error for S-Cr eGFR was 10.7 mL/min/1.73 m² for those patients with mGFR <60 mL/min/1.73 m² and 25.5 mL/min/1.73 m² for those patients with mGFR >60 mL/min/1.73 m².

Conclusions. In this study, S-Cys C-based prediction equations appear to be more precise than those of S-Cr for those patients with mGFR >60 mL/min/1.73 m² and may therefore be of benefit in the earlier detection of renal impairment.

Keywords: creatinine; cystatin C; glomerular filtration rate; MDRD

Introduction

Glomerular filtration rate (GFR) is considered the ‘gold standard’ in the diagnosis of chronic kidney disease (CKD) and is also accepted as the best overall measure of kidney function [1,2]. GFR can be measured as the renal clearance of exogenous markers such as inulin, ⁵¹chromium ethylenediaminetetraacetic acid (⁵¹Cr-EDTA), technetium-labelled diethylene-triamine-pentacetate (⁹⁹mTc-DTPA) and iohexol. However, these exogenous markers are impractical for routine clinical use due to their limited access and high cost. Endogenous GFR markers include serum creatinine (S-Cr) and cystatin C (S-Cys C). S-Cr is the most commonly used marker in the clinical laboratory to assess GFR; however, it has multiple limitations [3]. For example, creatinine concentration is...