Insulin resistance and pancreatic beta-cell function in patients with hypertensive kidney disease

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Abstract

Background. Insulin resistance and hyperinsulinaemia have been reported among patients with chronic renal failure. However, little is known concerning insulin sensitivity among patients with hypertensive kidney disease (HKD), especially in those with moderate or severe renal dysfunction.

Methods. We examined and compared 30 patients with HKD, 30 normotensive patients with chronic kidney disease (CKD-NT), 30 normal controls and 30 patients with hypertension and normal renal function (HTN). Moderate and severe renal dysfunction were defined according to the K/DOQI definitions (estimated glomerular filtration rates between 15 and 59 ml/min per 1.73 m²). The homeostasis model assessment of insulin resistance (HOMA-R) and three surrogate indexes based on 75 g oral glucose tolerance test results were used to determine insulin sensitivity.

Results. A trend to higher HOMA-R values in the HTN and HKD groups than in the other groups was noted, but the difference was not statistically significant. The insulin sensitivity index (ISI) proposed by Stumvoll et al. was significantly lower in the HTN, HKD and CKD-NT groups than in controls and was significantly lower in HKD than in the HTN and CKD-NT groups. The insulin sensitivity index proposed by Gutt et al. was significantly lower in HKD than in the control and HTN groups and showed a trend to being lower in HKD than in CKD-NT. The same patterns prevailed in the oral glucose ISI. We assumed that subjects whose ISI values decreased below the mean value minus 2-SD in the control group manifest apparent insulin resistance. According to this criterion, ~40% of HKD subjects were in an insulin-resistant state; only <10% of HTN subjects and ~10–30% of CKD-NT subjects were insulin resistant.

Conclusions. HKD with moderate to severe renal dysfunction is associated with insulin resistance.

Keywords: hypertensive kidney disease; insulin resistance; insulin sensitivity indexes

Introduction

Hypertension has been considered one possible important cause of end-stage renal disease [1]. Currently, cardiovascular disease is the main cause of morbidity and mortality among patients with chronic renal failure [2]. Hypertension is strongly associated with insulin resistance [3]. Chronic renal failure is also an insulin-resistant state associated with hyperinsulinaemia [4–6] and renal dysfunction is relatively common among patients with long-standing primary hypertension. Therefore, the increased risk of cardiovascular disease among patients with hypertensive kidney disease (HKD) might be correlated with insulin resistance. Interestingly, it has been known that insulin resistance and hyperinsulinaemia are present even in the early stages of chronic kidney disease [7–9]. However, those data were obtained from patients with either IgA nephropathy or adult polycystic kidney disease (APKD). Only a few patients with HKD were included in those studies. There is little information concerning both insulin sensitivity and insulin secretion among patients with HKD. To address this issue, we did a cross-sectional study to examine insulin sensitivity in HKD patients with moderate to severe renal dysfunction.

Subjects and methods

Patients

Subjects were recruited from the outpatient clinics of the First Department of Internal Medicine of Nara Medical University.
Hospital. Consecutive patients were included until four groups of 30 subjects each were formed as follows: control group (CON), HKD group and the comparison groups of hypertension alone with normal renal function (HTN) and chronic kidney disease without hypertension (CKD-NT). Briefly, normal renal function was defined according to the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) definitions [estimated glomerular filtration rate (GFR) ≥90 ml/min per 1.73 m²] [10]. The CON subjects had normal blood pressure and normal glucose tolerance (fasting plasma glucose <6.1 mmol/l and 2 h plasma glucose <7.8 mmol/l). HKD was defined according to the Schlessinger criteria [11]. Those criteria include a family history of hypertension, left ventricular hypertrophy (by electrocardiography), proteinuria ≥2+ on dipstick urinalysis, hypertension preceding any evidence of proteinuria or serum creatinine elevation and absence of nephrotoxin exposure, congenital renal disease or systemic disease. Of those who met the Schlessinger criteria, the subjects with moderately and severe renal dysfunction according to the K/DOQI definition (estimated GFRs between 15 and 59 ml/min per 1.73 m²) were included in the HKD group. Other hypertensive subjects with normal renal function (estimated GFR ≥90 ml/min per 1.73 m²) were enrolled in the HTN group. Normotensive subjects with moderate and severe renal dysfunction (estimated GFRs between 15 and 59 ml/min per 1.73 m²) were enrolled in the CKD-NT group. Hypertension was defined as one or more of systolic blood pressure >140 mmHg, diastolic blood pressure >90 mm Hg and use of antihypertensive medication. The exclusion criteria were age <20 or >75 years, known history of diabetes mellitus of antihypertensive medication. The exclusion criteria were age <20 or >75 years, known history of diabetes mellitus (fasting plasma glucose ≥7.0 mmol/l or use of anti-diabetic medications), secondary hypertension, serious systemic disease or kidney failure (estimated GFR <15 ml/min per 1.73 m²). This study was performed in accordance with the Helsinki Declaration and written informed consent was obtained from each participant.

**Laboratory methods**

Proteinuria was defined as a positive reaction on dipstick testing. Haematuria was defined as red blood cells >4 per high-power field in urinary sediments. Serum creatinine was measured by an autoanalyzer and creatinine clearance was calculated using the Cockcroft–Gault formula [12].

**Oral glucose tolerance test**

A standard 75g oral glucose tolerance test (OGTT) was performed after a 10h overnight fast. Plasma samples were obtained at 0, 30, 60, 90, 120 and 180 min after glucose loading. Plasma glucose was determined using a glucose oxidase autoanalyzer and plasma immunoreactive insulin was measured by an enzyme immunoassay (Entym Insulin Test; Roche, Basel, Switzerland). The insulinenic index, a widely used index of early-phase insulin response, was defined as the ratio of the increment of plasma insulin to that of plasma glucose at 30 min after glucose loading [13]. To assess plasma glucose response and total insulin secretion, we used the area under the response curve for plasma glucose and insulin (AUC-G and AUC-I, respectively) and a trapezoidal rule.

**Evaluation of insulin sensitivity**

Based on the data from the above-described OGGT, we used the homeostasis model assessment of insulin resistance (HOMA-R), as proposed by Matthews et al. [14], to calculate an index from the product of the fasting concentrations of plasma insulin and plasma glucose divided by 22.5. The insulin sensitivity index (ISI), as proposed by Stamvoll et al. [15] (ISI-S), was calculated using the values obtained in the above-described 75 g OGTT values:

\[
\text{ISI-S} = 0.226 - 0.0032 \times \text{BMI} - 0.0000645 \\
\times \text{insulin} (120 \text{min}) - 0.00375 \times \text{glucose} (90 \text{min})
\]

The ISI as proposed by Gutt et al. [16] (ISI-G) was also calculated using the 75 g OGTT values:

\[
\text{ISI-G} = m/[\text{glucose} (0 \text{min}) + \text{glucose} (120 \text{min})] \\
\times 0.5/\log[\text{insulin} (0 \text{min}) + \text{insulin} (120 \text{min}) \times 0.5]
\]

where m is the glucose uptake rate in peripheral tissues, calculated as:

\[
m = [75000 \text{mg} + \text{[glucose} (0 \text{min}) - \text{glucose} (120 \text{min})] \\
\times 0.19 \times \text{BW}/120 \text{min}
\]

Furthermore, the oral glucose insulin sensitivity (OGIS) index was calculated using Mari’s formula, as described elsewhere [17].

The mean values minus 2-SD of each surrogate index in the CON group was chosen as the cut-off limit for apparent insulin resistance.

**Statistical analysis**

Data are presented as means±SD. Comparisons among groups were performed using analysis of variance followed by post-hoc testing with Scheffe’s test. The significance of differences among percentages was evaluated with the chi-square test. A P-value of <0.05 was considered significant.

**Results**

**Clinical characteristics of subjects**

Table 1 shows the clinical characteristics of the subjects in each of the CON, HTN, HKD and CKD-NT groups. Age was significantly higher in HTN, HKD and CKD-NT than in CON and was significantly higher in HKD and CKD-NT than in HTN. Body mass index (BMI) was similar between CON and HKD, but it was significantly higher in the HTN and HKD groups compared with CKD-NT. As expected, blood pressure was significantly higher in the HTN and HKD groups than in CON and CKD-NT. Heart rate was similar among the four groups. There were no differences between HTN and HKD with regard to the use of angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers, dihydropyridine (DHP) or non-DHP calcium channel blockers, alpha-blockers or diuretics. The use of beta-blockers showed a trend to being higher in HKD than in HTN (13.3% vs 3.3%), but the difference was not statistically
significant. The number of patients with heavy proteinuria tended to be larger in CKD-NT than in HKD. The numbers of patients with haematuria were similar between HKD and CKD-NT. Serum lipid concentrations were similar among the four groups. Creatinine clearance was significantly lower in HKD and CKD-NT than in CON and HTN.

Metabolic data

Table 2 shows metabolic data of the CON, HTN, HKD and CKD-NT groups. Fasting plasma glucose was slightly higher in HTN and HKD than in CON, whereas fasting plasma insulin was comparable between the four groups. The 2 h plasma glucose was significantly higher in HTN, HKD and CKD-NT than in CON and was significantly higher in the HKD and CKD-NT groups than in HTN. The 2 h plasma insulin was significantly higher in HKD and CKD-NT than in CON and HTN and it was also significantly higher in HKD than in CKD-NT. AUC-I was significantly higher in HKD compared with CON and HTN. The insulinogenic index was significantly lower in the HKD and HKD groups and showed a trend to being lower in the CKD-NT group than in CON. HOMA-R showed a trend to being higher in HTN and HKD than in the other groups (but not statistically significant). ISI-S was significantly lower in HTN, HKD and CKD-NT.

Table 1. Clinical characteristics of subjects

<table>
<thead>
<tr>
<th></th>
<th>CON</th>
<th>HTN</th>
<th>HKD</th>
<th>CKD-NT</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.0±8.1</td>
<td>55.1±7.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>67.3±7.0&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>67.4±4.5&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>21/9</td>
<td>23/7</td>
<td>14/16</td>
<td>17/13</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.1±2.7</td>
<td>24.2±2.2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>23.5±2.4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>22.0±2.9</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>115.2±9.7</td>
<td>146.5±15.0&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>141.6±18.2&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>115.1±5.6</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>66.3±9.4</td>
<td>85.0±13.6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>82.9±11.9&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>65.9±9.9</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>82.5±8.6</td>
<td>105.3±13.4&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>102.5±13.1&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>82.2±10.5</td>
</tr>
<tr>
<td>Heart rate (beats per min)</td>
<td>72.2±9.7</td>
<td>74.6±10.6</td>
<td>70.6±14.2</td>
<td>70.0±13.5</td>
</tr>
<tr>
<td>ACEI/ARB use (%)</td>
<td>0</td>
<td>36.6</td>
<td>3.3</td>
<td>0</td>
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<tr>
<td>DHP-CCB (%)</td>
<td>0</td>
<td>30.0</td>
<td>6.7</td>
<td>0</td>
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<tr>
<td>Non-DHP-CCB (%)</td>
<td>0</td>
<td>13.3</td>
<td>13.3</td>
<td>0</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alpha-blocker (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.41±1.12</td>
<td>5.75±1.75</td>
<td>5.06±1.12</td>
<td>4.98±1.27</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.35±0.88</td>
<td>1.66±1.11</td>
<td>1.60±0.88</td>
<td>1.20±0.68</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.22±0.31</td>
<td>1.49±0.62</td>
<td>1.32±0.32</td>
<td>1.01±0.33</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>58.6±12.6</td>
<td>61.6±10.5</td>
<td>95.8±27.9&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>89.6±29.2&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Proteinuria ≤2+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Proteinuria ≥3+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Haematuria</td>
<td>0</td>
<td>0.0</td>
<td>40.0</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>112.5±19.2</td>
<td>109.0±15.4</td>
<td>51.3±8.4&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>50.9±8.2&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data are means±SD, n or %. SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CCB, calcium channel blocker.

<sup>a</sup>P<0.01 vs CON; <sup>b</sup>P<0.05 vs CON; <sup>c</sup>P<0.01 vs HTN; <sup>d</sup>P<0.05 vs CKD-NT; <sup>e</sup>P<0.05 vs CKD-NT.

Table 2. Metabolic data on the four groups studied

<table>
<thead>
<tr>
<th></th>
<th>CON</th>
<th>HTN</th>
<th>HKD</th>
<th>CKD-NT</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG (mmol/l)</td>
<td>4.98±0.40</td>
<td>5.35±0.50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.28±0.57&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.17±0.53</td>
</tr>
<tr>
<td>FPI (pmol/l)</td>
<td>36.8±14.8</td>
<td>36.4±17.2</td>
<td>40.4±23.3</td>
<td>32.0±17.0</td>
</tr>
<tr>
<td>2h plasma glucose (mmol/l)</td>
<td>6.11±0.89</td>
<td>7.01±1.39&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8.02±1.48&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7.92±1.64&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>2h plasma insulin (pmol/l)</td>
<td>213±90</td>
<td>208±88</td>
<td>384±228&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>294±164&lt;sup&gt;b,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>HOMA-R</td>
<td>1.36±0.55</td>
<td>1.47±0.83</td>
<td>1.62±1.07</td>
<td>1.26±0.74</td>
</tr>
<tr>
<td>ISI-S (&lt;times&gt;10&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>112±12</td>
<td>105±7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>93±21&lt;sup&gt;d,f&lt;/sup&gt;</td>
<td>103±14&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>ISI-S &lt;88 (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>13.3</td>
</tr>
<tr>
<td>ISI-G</td>
<td>87±16</td>
<td>76±12&lt;sup&gt;b&lt;/sup&gt;</td>
<td>61±15&lt;sup&gt;c&lt;/sup&gt;</td>
<td>68±21&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>ISI-G &lt;55 (%)</td>
<td>0</td>
<td>3.3</td>
<td>36.7</td>
<td>26.7</td>
</tr>
<tr>
<td>OGIS index</td>
<td>548±54</td>
<td>500±53&lt;sup&gt;b&lt;/sup&gt;</td>
<td>451±72&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>484±9&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>OGIS &lt;440 (%)</td>
<td>0</td>
<td>10.0</td>
<td>43.3</td>
<td>33.3</td>
</tr>
<tr>
<td>Insulinogenic index</td>
<td>98.0±70.1</td>
<td>67.1±52.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>68.6±49.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>70.1±44.4</td>
</tr>
<tr>
<td>AUC-I</td>
<td>687±307</td>
<td>618±246</td>
<td>912±450&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>762±348</td>
</tr>
</tbody>
</table>

Data are means±SD or %. FPG, fasting plasma glucose; FPI, fasting plasma insulin.

<sup>a</sup>P<0.01 vs CON; <sup>b</sup>P<0.05 vs CON; <sup>c</sup>P<0.01 vs HTN; <sup>d</sup>P<0.05 vs HTN; <sup>e</sup>P<0.05 vs CKD-NT; <sup>f</sup>P<0.05 vs CKD-NT.
than in CON and was significantly lower in HKD than in HTN and CKD-NT. ISI-G was significantly lower in HTN, HKD and CKD-NT than in CON and was significantly lower in HKD than in HTN. The OGIS index displayed the same pattern. Furthermore, we assumed that subjects whose ISI-values decreased below the mean value minus 2-SD in CON manifest apparent insulin resistance. According to this criterion, ~40% of the HKD subjects were in an insulin-resistant state, whereas <10% of the HTN subjects and ~10–30% of the CKD-NT subjects were insulin resistant.

Discussion

This study is the first to use surrogate indexes of insulin sensitivity based on 75 g OGTT results to demonstrate that HKD is associated with insulin resistance. In fact, the HKD patients had significantly lower ISI-S, ISI-G and OGIS indexes compared with normal controls. These findings are in general agreement with observations in other renal diseases using different methodological approaches – a euglycaemic–hyperinsulinaemic clamp or a frequently sampled intravenous glucose tolerance test with the minimal-model technique [7,9]. In these studies, evidence of insulin resistance was found in both IgA nephropathy and APKD patients [7,9]. In our study, we also show that HKD subjects were insulin resistant when compared with HTN subjects, despite both groups having similar BMI. HKD and HTN subjects both also had similar blood pressures and fasting plasma insulin levels. Mean age was higher in HKD than in the HTN group, so the role of aging in insulin resistance could not be excluded [18]. Nevertheless, it has been reported that age per se explains only 1.1% of the variability in insulin activity [19]. Factors other than age, such as physical fitness or dehydroepiandrosterone sulphate (DHEAs), should be taken into account. However, we have no data to provide on these factors.

Additionally, our HKD patients were more insulin resistant compared with CKD-NT patients, despite similar renal functions. The HKD patients showed significantly lower values in ISI-S compared with CKD-NT patients. The ISI-G and OGIS indexes also showed a trend to being lower in HKD than in CKD-NT. We think that these differences cannot be explained only by the reduced metabolism of insulin in the presence of renal damage. Another factor that might be involved in insulin sensitivity is sympathetic activity. Sympathetic activation appears to play an important pathogenic role in obesity-associated insulin resistance and hypertension [20]. Indeed, HKD patients had a significantly higher BMI compared with CKD-NT patients (23.5±2.4 vs 22.0±2.9 kg/m²; P < 0.05). We think that these differences are quite small and even in our HKD group most subjects are not obese (BMI <30 kg/m²). It has been recognized also that renal failure represents a condition of increased sympathetic activity and this hyperactivity is associated with tissue insulin resistance [21]. We cannot rule out the possibility that the HKD patients have different sympathetic activity compared with the CKD-NT patients. Further research will be necessary to resolve this problem.

This study has several limitations. First, HKD has been defined in several different ways. To confirm the diagnosis of HKD in them, patients should have a renal biopsy [22]; however, patients with suspected HKD infrequently undergo renal biopsies and the diagnosis of HKD is made merely by exclusion of other renal diseases on clinical grounds. To date, two established sets of criteria have been proposed to distinguish HKD from other renal diseases [11,23]. We used the Schlessinger criteria [11]. These criteria include family history of hypertension, left ventricular hypertrophy noted on electrocardiography, proteinuria ≥2+ on dipstick urinalysis, hypertension preceding any evidence of proteinuria or elevated creatinine and absence of nephrotoxin exposure, congenital renal disease or systemic disease. In the present study, all HKD subjects satisfied the criteria. On the other hand, the criteria of the African American Study of Kidney Disease and Hypertension Study Group [23] are more rigorous than the more commonly applied criteria used in our study. We did not apply those criteria in the belief that African-Americans are more likely to develop end-stage renal disease from hypertension than other ethnic groups. In the CKD-NT group, only a few patients had renal biopsy. Two patients had pathological changes consistent with moderate mesangio proliferative glomerulonephritis (non-IgA nephritis), two had focal glomerulosclerosis and one had chronic interstitial nephritis. None of the patients had amyloidosis. In the remainder of cases, clinical evidence seems to point to ‘probable’ renal atherosclerotic disease.

Second, the validity of the simple indices of insulin resistance in use must be considered. The euglycaemic–hyperinsulinaemic clamp technique is the standard method for measuring insulin sensitivity, but its invasiveness and high cost have limited its use in clinical practice. Other techniques for measuring insulin sensitivity, such as a frequently sampled intravenous glucose tolerance test with minimal-model analysis, also are similarly invasive and difficult to adapt to clinical use. Currently, HOMA-R is the surrogate measure of choice for assessing insulin resistance. Indeed, in the present study, HOMA-R showed a trend to being higher in HTN and HKD than in the other groups (but not statistically significant). However, HOMA-R gives little information on insulin action in peripheral tissues (it is thought to reflect mainly hepatic insulin resistance). It seems likely that HOMA-R is an indirect marker of insulin resistance, because it is influenced by the degree of compensatory hyperinsulinaemia. In particular, it has been recognized that the compensatory function of pancreatic beta cells in Japanese people is lower than that observed in Caucasians [24]. Clearly, most Japanese people are less obese than other ethnic groups: fasting
hyperinsulinaemia is less common in Japanese people. Therefore, the usefulness of HOMA-R in the relatively lean Japanese may be limited. We also used other surrogate indexes of insulin sensitivity calculated from fasting state values and results of OGTTs (ISI-S, ISI-G and OGIS index). These surrogate indexes have been compared with the index calculated using the euglycaemic–hyperinsulinaemic glucose clamp technique (clamp-IR) and in our previous report they were shown to be valid measures of insulin resistance in Japanese people [25]. In that report, ISI-S showed the strongest correlation with clamp-IR ($r = 0.641$, $P < 0.001$) and ISI-G showed a somewhat weaker correlation ($r = 0.526$, $P < 0.001$). In contrast, there was a weak inverse correlation between HOMA-R and clamp-IR ($r = -0.227$, $P = 0.047$). More recently, similar results were obtained comparing the OGIS index and clamp-IR ($r = 0.726$, $P < 0.001$) [26]. Therefore, we believe that these surrogate indexes calculated from 75 g OGTT results are valid for clinical use, especially in the relatively lean Japanese people. In the present study, ISI-S decreased significantly in the HKD group. A fact further supported by the parallel decrease of both ISI-G and OGIS index. However, the results of this study may be applicable only to the Japanese, because ethnic difference exists in insulin sensitivity.

In conclusion, HKD with moderate to severe renal dysfunction is associated with insulin resistance.

**Conflict of interest statement.** None declared.

**References**


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