Insulin resistance and the progression of IgA glomerulonephritis

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Abstract

Background. IgA glomerulonephritis (IgAGN) has a highly variable prognosis with 15–40% of patients progressing to end-stage renal disease. Hypertension, proteinuria and renal insufficiency are risk factors associated with poor prognosis. The role of insulin resistance is unclear in IgAGN.

Methods. From a retrospective cohort of IgAGN patients, a total of 174 patients (104 males) were invited for two visits at the clinic, 11 and 16 years (median times) after IgAGN was diagnosed in renal biopsy. Of all the patients, 63% had been diagnosed at least 10 years before the first visit. Progressive disease was defined as cystatin-C exceeding normal limits and showing over 20% elevation between the first and second visits, or kidney transplantation or start of dialysis. Plasma insulin, homeostasis model assessment of insulin resistance (HOMA-IR) index and cystatin-C were obtained for analysis from 118 patients.

Results. IgAGN was progressive in 19.5% of the patients on the second visit. Insulin level and HOMA-IR of the first visit showed significant association with the progression of IgAGN (P = 0.019 and 0.005, respectively).

Conclusions. Our results show that in addition to the known risk factors age, hypertension, proteinuria and hyperuricaemia, plasma insulin level and calculated HOMA-IR are associated with the progression of IgAGN.

Keywords: cystatin-C; HOMA-IR; IgA glomerulonephritis; insulin; progression

Introduction

Metabolic syndrome is a cluster of atherosclerotic risk factors consisting of obesity, hypertension, dyslipidaemia, hyperuricaemia and hyperinsulinaemia. Chronic renal insufficiency (CRI) is also characterized by a high incidence of cardiovascular complications, while insulin resistance and hyperinsulinaemia are common in patients with end-stage renal disease (ESRD) [1–2]. The CRI-associated factors involved in derangements of glucose metabolism are probably related to anaemia, calcitriol deficiency, PTH excess, metabolic acidosis and accumulation of uraemic toxins [3].

Although the metabolic clearance of insulin may be impaired and its action prolonged during impaired kidney function, the postulated mechanisms of insulin resistance in CRI include inadequate insulin secretion, augmented hepatic glucose output, and resistance to the actions of insulin in peripheral tissues [4]. Moreover, insulin resistance is an independent predictor of cardiovascular mortality in the ESRD population [5]. Over the past decade, a body of evidence has accumulated showing the existence of insulin-resistance also in mild to moderate CRI, or even before the impairment of kidney function [6–10]. Two population studies have reported a significant relationship between chronic kidney disease and insulin resistance [11,12].

The course of IgA glomerulonephritis (IgAGN) is highly variable with ~15–40% of patients eventually progressing to ESRD, with hypertension, renal insufficiency and proteinuria being the classical risk factors for poor prognosis [13]. In our earlier study, hypertriglyceridaemia and hyperuricaemia at the time of the diagnosis were also found to be associated with a progressive course of IgAGN [14]. Insulin resistance has previously been associated with hypertension in IgAGN [15], but the influence of hyperinsulinaemia on the prognosis of IgAGN has remained unresolved. Therefore, the aim of our study was to examine the
association of plasma insulin concentrations with the progression of IgAGN.

**Subjects and methods**

**Patients**

The original population consisted of patients living in Pirkanmaa Health District in Finland (total population about 440,000) in whom IgAGN was diagnosed during a period of 11 years, between 1 January 1980 and 31 December 1990 (223 patients). IgAGN was defined as a glomerulonephritis with IgA as the sole or main glomerular immunofluorescence finding in renal biopsy. From this retrospective group, a cohort was invited twice for a physician’s appointment. Before the first visit, 30 patients had died, 15 had moved away from the district, whereby the rest of the original population were invited to attend the first visit. They were then invited for the second visit ~6 years after the first one. A description of the study flow is depicted in Figure 1.

For the first visit, a total of 174 patients (104 males) responded, out of which 168 (97%) came for the visit, while six (3%) only filled out and returned the questionnaire. At the time of the first visit, the median patient age was 48.5 years (range 17–85) and the median time from the renal biopsy was 11 years (range 6–17). All patients had been diagnosed at least 5 years, 63% at least 10 years and 26% at least 15 years before the first visit. In the case of the second visit, 10 (6%) patients had died, 114 (70% of the living ones) patients came for the visit, 30 (18% of the living ones) only filled out and returned the questionnaire. The median patient age was 54 years (range 17–90) and the median time from the biopsy was 16 years (range 7–24). A total of 100% of the patients had been diagnosed at least 5 years, 97% at least 10 years and 63% at least 15 years, before that visit. The median time from the first signs of IgAGN (episode of macroscopic haematuria, discovery of microscopic haematuria or proteinuria or renal insufficiency) was 14 years (range 7–57 years) on the first visit, and 19 years (range 7–64 years) on the second visit. The causes of death were confirmed from the patient files or from the death certificates kept by Statistics Finland. Six patients had died from cardiovascular diseases, two patients had died from malignancy, one from uraemia and one from intracerebral haemorrhage.

The study protocol was approved by the Ethics Committee of the University Hospital of Tampere, Finland.

**Clinical data**

At the time of the renal biopsy, there were no cases of systemic lupus erythematosus or liver cirrhosis. A total of 12 patients presented with some manifestation of Henoch–Schönlein purpura, and one developed them later. Both primary and secondary IgAGN were thus included in this study. Clinical renal findings of both visits are presented in Table 1.

Data on medication, concurrent diseases, smoking and alcohol drinking habits as well as anthropometric measures, blood pressure and laboratory variables were recorded during the visits. For the present analyses, the criterion of hypertension was the use of antihypertensive medication or systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg. The use of antihypertensive and lipid lowering medications is presented in Table 2.

A patient was considered as having diabetes mellitus if the fasting venous blood glucose level was ≥7.1 mmol/l or the patient was earlier diagnosed to have the disease. Six patients had diabetes mellitus at the time of renal biopsy, and during the follow-up 19 new diabetic patients emerged. Thus the number of diabetic subjects was 25 by the time of the second visit.

The median body mass index (BMI) was 26 kg/m² (range 18–45) on the first visit and 27 kg/m² (18–43) on the second visit, whereby the patients were slightly overweight and the tendency increased in the course of time. The median values for systolic blood pressure were 140 mmHg (104–190) on the first visit and 142 mmHg (90–224) on the second visit. Diastolic values were 89 mmHg (60–118) and 88 mmHg (52–120), respectively. Of the patients, 13% smoked on the first visit and 16%, on the second visit. The percentages of ex-smokers was 33 and 31, respectively.
analysed in the laboratory of Tampere University Hospital using the serum samples and spot and collection urine samples. All blood samples were obtained after an overnight fast. Low density lipoprotein cholesterol was calculated using the Friedewald-formula providing that the triglyceride value was <4.0 mmol/l.

**Statistical analyses**

The SPSS package was used for statistical analyses, and the two-sided P-value <0.05 was taken as the level for statistical significance. The correlations between two continuous variables were calculated using Pearson bivariate correlations if both variables were normally distributed, and Spearman bivariate correlations if one or both variables were non-normally distributed. The associations between categorical variables and continuous non-normally distributed variables were calculated using Mann–Whitney U-test or Kruskall–Wallis-test depending on the number of categories. The associations between categorical variables and normally distributed variables were analysed with Student’s t-test. The relationships between categorical variables were analysed with χ²-test.

**Results**

**Correlations between serum insulin concentrations and other continuous variables of the first visit**

The insulin values correlated (all correlations are Spearman correlations) significantly with BMI (r = 0.501, P = 0.0001), systolic blood pressure (r = 0.237, P = 0.002), but not with diastolic blood pressure (r = 0.130, P = 0.092). Significant correlations were also found between serum insulin and total cholesterol (r = 0.155, P = 0.044), HDL-cholesterol (r = −0.462, P = 0.0001), triglyceride (r = 0.616, P = 0.0001), urate (r = 0.370, P = 0.0001) and glucose (r = 0.362, P = 0.0001) concentrations. Proteinuria did not significantly correlate with insulin values (r = 0.127, P = 0.103). The insulin concentrations of the first and second visits significantly correlated with each other (r = 0.629, P = 0.0001).

**Progression of IgAGN**

The median cystatin-C concentrations on the first and second visits were 0.77 mg/l (range 0.44–5.70) and 1.06 mg/l (0.59–2.93), while the median MDRD estimates of GFR on the first and second visits were 77.3 ml/min (4.9–164.8) and 71.2 ml/min (11.9–127.5), respectively. On the first visit, 21/168 (13%) patients had impaired kidney function, including seven patients who had undergone kidney transplantation (with either normal or elevated cystatin-C values). This number included four patients who had undergone kidney transplantation (with either normal or elevated cystatin-C values). On the second visit, 26/120 (22%) patients presented with impaired kidney function, including seven patients with kidney transplants. One of these patients had undergone two kidney transplantations. Altogether ESRD had developed in 10/174 patients (6%) by the

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**Table 1. Clinical renal findings at the first and second visits**

<table>
<thead>
<tr>
<th>Finding</th>
<th>1st visit (%)</th>
<th>2nd visit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macroscopic haematuria in history</td>
<td>29</td>
<td>42</td>
</tr>
<tr>
<td>Microscopic haematuria and proteinuria</td>
<td>75</td>
<td>40</td>
</tr>
<tr>
<td>(≥0.08 g/24 h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopic haematuria alone</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Proteinuria alone (≥0.08 g/24 h)</td>
<td>24</td>
<td>52</td>
</tr>
<tr>
<td>Proteinuria (≥1.0 g/24 h)</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Proteinuria (≥3.0 g/24 h)</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Impaired renal function</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>ESRD</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Transplantation once</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Transplantation twice</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

The number of patients varies (n = 123–174).

**Table 2. The use of antihypertensive and lipid-lowering medication during the visits; proportion of patients (%)**

<table>
<thead>
<tr>
<th>Medication</th>
<th>1st visit</th>
<th>2nd visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid-lowering agents</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>Statin</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Fibrate</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>49</td>
<td>60</td>
</tr>
<tr>
<td>β-blockers</td>
<td>31</td>
<td>36</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>AT1-receptor antagonists</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Diuretics</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Ca²⁺ entry blockers</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

The number of patients varies (n = 153–174).

Glomerular filtration rate (GFR) was determined using serum cystatin-C, which was either measured at the time of each visit or obtained from the patient files. Serum cystatin-C values were considered normal if they were <1.2 mg/l when the age was ≤50 years, or <1.4 mg/l when the age was >50 years. A six variable modification of diet in renal disease (MDRD) estimate of GFR was also calculated. Progressive IgAGN during the follow-up was defined as an elevation of the serum cystatin-C above the normal level and over 20% elevation from the value of the first visit, or if the patient had had a kidney transplantation or was on dialysis. No pre-emptive transplantations were carried out.

**Laboratory determinations**

Serum insulin concentrations were determined from overnight fasting samples, which were originally frozen at −70°C. The analyses were simultaneously carried out for both visits using a human insulin specific radioimmunoassay kit (Linco Research, Inc, St Charles, MO, USA). The lowest detection level by the kit was 2 μU/ml in a 100 μl sample size, the specificity for human insulin 100% and for human proinsulin <0.2%, the means for within and between assay variations being 3.2 and 3.88%, respectively, and normal insulin concentrations 5–15 μU/ml (all values as reported by the manufacturer). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated according to the formula [plasma fasting insulin (μU/ml) × plasma fasting glucose (mmol/l)/22.5]. All other laboratory variables were
time of the first visit, and in 13/174 patients (7%) by
the time of the second visit. All the transplanted
patients were on dialysis before the procedure, and
they were included in the analyses unless indicated
otherwise.

At the second visit, IgAGN was classified as
progressive in 23/118 (19.5%) patients (Table 3),
based on the definition presented earlier (see
Methods). The progressive group was characterized
by higher age, higher prevalence of hypertension,
increased concentrations of serum insulin, higher
HOMA-IR and urate values and higher level of
proteinuria, when compared to the stable group.
There was no statistical difference in BMI, waist
circumference, gender distribution, smoking habits
or plasma lipid profiles between the groups.

**Table 3.** The comparison of continuous clinical and laboratory variables of the first visit between the patients with progressive and stable
disease (n = 118)

<table>
<thead>
<tr>
<th>1st visit</th>
<th>Stable disease (n = 95)</th>
<th>Progressive disease (n = 23)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47 (44–49)</td>
<td>55 (50–60)</td>
<td>0.007</td>
</tr>
<tr>
<td>Hypertension (% of patients)</td>
<td>61%</td>
<td>96%</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 (26–27)</td>
<td>28 (25–30)</td>
<td>0.364</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>89 (86–92)</td>
<td>94 (88–100)</td>
<td>0.154</td>
</tr>
<tr>
<td>Male sex (% of patients)</td>
<td>64%</td>
<td>65%</td>
<td>1.0</td>
</tr>
<tr>
<td>Smoking (% of patients)</td>
<td>50%</td>
<td>52%</td>
<td>0.317</td>
</tr>
<tr>
<td>Never</td>
<td>16%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>34%</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>Insulin (µU/ml)</td>
<td>14 (11;19)</td>
<td>19 (14;33)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cystatin-C (mg/l)</td>
<td>0.7 (0.6;0.8)</td>
<td>1.12 (0.9;1.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>MDRD (ml/min)</td>
<td>90 (85–95)</td>
<td>50 (40–59)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Urate (mmol/l)</td>
<td>0.38 (0.36–0.40)</td>
<td>0.47 (0.43–0.51)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Proteinuria (g/24 h)</td>
<td>0.3 (0.2;0.6)</td>
<td>0.9 (0.2;2.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.3 (5.2–5.5)</td>
<td>5.7 (5.1–6.3)</td>
<td>0.187</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.24 (1.16–1.32)</td>
<td>1.16 (1.02–1.29)</td>
<td>0.329</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.3 (1.0;1.8)</td>
<td>1.5 (1.1;2.3)</td>
<td>0.308</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.79 (2.13;4.14)</td>
<td>4.43 (2.88;6.79)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Normally distributed variables are expressed as mean and the 95% confidence intervals, and non-normally distributed variables as median
and the 25th and 75th percentiles.

**Fig. 2.** Plasma insulin concentration (panel A) and Homa-IR
(panel B) of the first visit and the progression of IgA glomerulonephritis. Progression was defined as an elevation of the serum
cystatin-C above the normal level and over 20% elevation from the
value of the first visit, requirement for dialysis treatment, or if the
patient had had a kidney transplantation. Results are depicted as
median (line inside the box), 25th and 75th percentile (box), and
range (whiskers).

**Associations and correlations of serum insulin levels
and HOMA-IR with the progression of IgAGN**

The continuous serum insulin concentrations,
measured at the first visit, showed a significant
association with the progression of IgAGN during
the follow-up (Figure 2). The patients in the progress-
ive IgAGN group had higher insulin concentrations
than the stable patients. Also the HOMA-IR of
the first visit showed a significant association to
the progression, and analogously the progressive
patients had a higher index when compared to the
stable group. If kidney function was estimated by
the use of the six variable MDRD formula, the
continuous serum insulin concentration did not
have a significant correlation with kidney function
(r = −0.166, P = 0.067), but HOMA-IR showed a
significant inverse correlation (r = −0.217, P = 0.016).
Discussion

Our results suggest for the first time that increased plasma insulin and HOMA-IR levels are associated with the progression of IgAGN. The patient population described here represents a typical clinical spectrum of IgAGN, with the majority of patients having either normal renal function or mild renal dysfunction [13], and being slightly overweight. It should be noted that, hitherto, our study provides one of the longest follow-ups concerning the prognostic significance of elevated insulin levels in patients with IgAGN.

Various techniques have been previously utilized to assess insulin resistance and glucose tolerance in renal disease, including euglycaemic insulin clamp, HOMA-IR, oral or i.v. glucose tolerance test and fasting insulin concentrations. There is considerable variation regarding the cut-off point for patients who are defined as either insulin resistant or insulin sensitive using the HOMA-IR, whereby it was examined as a continuous variable in the present investigation. Since oral or i.v. glucose tolerance test or clamp were not feasible in the present study design, we chose to use the fasting insulin values and HOMA-IR to assess insulin resistance. Most of the earlier studies on insulin resistance in mild to moderate renal insufficiency have included patients with a variety of kidney diseases, and the number of IgAGN patients in many of those reports has been rather low [6–10,15]. None of the previous studies have provided several years of follow-up information concerning the progression of IgAGN in relation to insulin levels. In one of the latest reports, renal function did not correlate with insulin resistance, as assessed using the HOMA-IR [16]. However, this particular study included patients with mild-to-moderate renal dysfunction due to various kidney diseases, while only less than half of the study population (97 patients) consisted of patients with glomerulonephritis of unreported origin.

Serum cystatin-C is considered to be a more reliable indicator of kidney function than serum creatinine and the estimates of glomerular filtration derived thereupon [17]. Therefore, the present definition of disease progression was based on the observed changes in serum cystatin-C levels. Progressive IgAGN was defined as cystatin-C elevation above the normal level and >20% elevation during the follow-up, in order to avoid the misclassification of those patients with elevated cystatin-C values but nevertheless a stable disease. GFR was also estimated using the six variable MDRD formula. The results differed slightly when compared to those obtained using cystatin-C as a marker of GFR. Serum insulin was not significantly associated with progression any more, but with HOMA-IR the association remained significant. The inconsistency might be due to the fact that cystatin-C is nevertheless a measured marker and MDRD a calculated marker of GFR. The progressive group was characterized by higher serum insulin, HOMA-IR and urate values, increased proteinuria, higher age and higher prevalence of hypertension when compared with the stable group. The observed difference in insulin values could not be explained by differences in body weight, since the BMIs of the progressive and stable groups were similar. Altogether, the observed rate of disease progression in our cohort corresponds to previous findings in IgAGN patients [13].

A recent Japanese report did not find a relationship between insulin resistance and renal dysfunction (measured using creatinine clearance and serum creatinine) [15], but rather an association between insulin resistance and hypertension in IgAGN-patients. In that study, insulin resistance was assessed using HOMA-IR, and insulin values were also reported as continuous variables. However, the study design was not a follow-up but a cross-sectional approach, which can well explain the discrepancy when compared to our results. It is possible that the influence of hyperinsulinaemia and insulin resistance on the progression of IgAGN only becomes evident in the course of time, and is covered underneath other stronger variables (hyperuricaemia, hypertension, proteinuria and age) when assessed in a cross-sectional design.

We previously reported that hypertriglyceridaemia and hyperuricaemia at the time of the diagnosis were both risk factors for the progression of IgAGN [14]. In contrast, hypertriglyceridaemia in the present study was not significantly associated with the progression of IgAGN. The difference with our earlier report may be explained by the more frequent use of lipid-lowering agents on the second visit when compared to the first visit (19 vs 4% of patients, respectively). It seems likely that the use of statins and fibrates during the follow-up period has mitigated the putative harmful influence of hypertriglyceridaemia on renal function. BMI was not associated with the progression of IgAGN in the present study. We and a French group previously reported that BMI at the time of the diagnosis was significantly higher in the progressive group [14,18]. The differences in the results may be explained by the different time scales as the patients in the present study were assessed on average 11 years after the renal biopsy.

Hyperinsulinaemia is one of the features of the metabolic syndrome, which is a cluster of metabolic derangements consisting of insulin resistance, hyperuricaemia, elevated blood pressure, dyslipidaemia and abdominal obesity. The characteristic components of the metabolic syndrome correlated significantly with insulin values also in the present IgAGN-patient cohort. Insulin might be used as an additive tool when evaluating the metabolic profile in these patients. It is probable that our findings are not limited to patients with IgAGN, but more likely can be applied to a variety of proteinuric kidney diseases. The risk of atherosclerosis is known to be increased in both patients with the metabolic syndrome and patients with impaired kidney function, while hyperinsulinaemia itself has been implicated as an independent risk factor for cardiovascular disease [19]. It has also been
postulated that similar mechanisms lie beneath the development of atherosclerosis and glomerulosclerosis, thus linking these two phenomena together [20]. As we have shown a significant association between elevated insulin as well as HOMA-IR values and the progression of IgAGN, one possible mechanism could be the analogous underlying pathophysiology in atherosclerosis and glomerulosclerosis.

In conclusion, our results show that in addition to the known risk factors age, hypertension, proteinuria and hyperuricaemia, increased serum insulin and HOMA-IR levels may be associated with the progression of IgAGN. However, more studies are needed to confirm whether a direct relationship exists between insulin concentrations and progression of IgAGN.

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Conflict of interest statement. None declared.

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