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. 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.

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.
Microscopic haematuria and proteinuria

Macroscopic haematuria in history 29 42

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

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>Macroscopic 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>

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, based on 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

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 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.
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.

**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 progressive 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 in 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.

Acknowledgements. This work was supported by a grant from the Finnish Kidney Foundation, Research Foundation of Orion Corporation and Medical Research Fund of Tampere University Hospital. The authors also like to thank Mrs Heidi Hälstöm, Mrs Kati Yli-Nikkilä and Mrs Mirja Ikonen for their skilful technical assistance.

Conflict of interest statement. None declared.

References

19. Stout R. Overview of the association between insulin and atherosclerosis. Metabolism 1983; 34 [Suppl 1]: 7–12

Received for publication: 21.5.06
Accepted in revised form: 31.10.06