Changes of renal function impairment, extracellular matrix regulation, renal fibrosis and inflammation in patients with chronic glomerulonephritis

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Objective: To investigate the changes and clinical significance of renal function impairment, extracellular matrix regulation, renal fibrosis and inflammation in patients with chronic glomerulonephritis. Methods: A total of 50 patients with chronic glomerulonephritis admitted to our hospital from May 2016 to February 2018 were selected as observation group and 50 healthy people as control group. The expression levels and related inflammatory markers of renal dysfunction [including uric acid (UA), retinol binding protein (RBP) and type IV collagen (Col-IV)], extracellular matrix modulation [including tissue inhibitor of metalloproteinase -1 (TIMP-1) and matrix metalloproteinase-9 (MMP-9)], renal fibrosis [including transforming growth factor β1 (TGF-β1), laminin (LN) and hyaluronic acid (HA)], and degree of inflammation [including leukocyte stimulating hormone-1 (Lkn-1) and tumor necrosis factor α (TNF-α)] were observed and compared between the two groups. Results: The changes of renal function impairment, extracellular matrix regulation, renal fibrosis and inflammation were significant in both groups. Compared with healthy controls in the control group, UA [(352.49±26.57) μmol/L], RBP [(98.75±26.91) mg/L], Col-IV [(224.77±72.32) ng/L], TIMP-1 [(145.79±49.67) ng/mL], MMP-9 [(177.71±52.35) ng/mL], TGF-β1 [(15.23±7.61) ng/mL], LN [(153.82±23.01) μg/L], HA [(366.80±77.98) μg/L], Lkn-1 [(82.71±20.64) pmol/L] and TNF-α [(138.01±45.26) pg/mL] levels were significantly elevated. The differences were statistically significant. Conclusions: Chronic glomerulonephritis patients with renal dysfunction and abnormal regulation of extracellular matrix, and severe renal fibrosis, the body is at a higher level of inflammation, clinical indicators should be strengthened to detect the early diagnosis of the disease and treatment basis.

1. Introduction

Chronic glomerulonephritis (CGN) is a common chronic kidney disease[1], which can cause bilateral glomerular inflammatory changes[2], the main symptoms are edema, hematuria, etc., the incidence is concealed, the recurrence and aggravation of the disease is caused by a variety of causes, and often causes chronic renal failure[3,4]. The study found that 21.2% of end-stage renal diseases are caused by CGN[5], and its incidence rate increases along with work stress increases[6], so timely treatment is needed. Renal fibrosis is prone to occur during CGN disease, resulting in loss of renal function[5], and excessive expression of various inflammation-related factors can also damage the kidney. Therefore, this article analyzes the factors related to renal dysfunction, extracellular matrix regulation, renal fibrosis and inflammation in CGN patients, in order to understand its clinical significance for CGN guidance diagnosis, assessment of disease and prognosis.
2. Materials and methods

2.1 Clinical data

A total of 50 patients with chronic glomerulonephritis who were treated in our hospital from May 2016 to February 2018 were selected as observation group, including 32 males and 18 females, aged 19-60 years old, with a course of 3 months - 5 years; 50 healthy subjects were selected as the control group, including 30 males and 20 females, aged 20-62 years old. There was no differences in general data such as gender and age of subjects in both groups ($P>0.05$), which could be compared and analyzed.

Inclusion criteria: 1 patients were consistent with the relevant diagnostic criteria for chronic glomerulonephritis[7]; 2 diagnosed by histopathology after renal biopsy. Exclusion criteria: 1 exclude primary hypertensive nephritis, hepatitis-associated nephritis, diabetic nephritis and other secondary nephropathy, no co-infection or other immune diseases; 2 exclude patients who are unwilling to cooperate with the study.

2.2 Methods

Sample collection: 5 mL of fasting venous blood at the time of admission in the observation group and in the control group when health examination, centrifuged for 10 min, and serum was collected. Observation indicators: UA level was detected by automatic biochemical analyzer (Japanese Hitachi 7170); RBP was detected by latex immunoturbidimetry; Col-IV, TIMP-1, MMP-9, TGF-β, Lkn-1 and TNF-α were detected by double antibody sandwich enzyme-linked immunosorbent assay (ELISA); LN and HA were detected by radioimmunoassay.

2.3 Statistical methods

The data were analyzed by SPSS 13.0 statistical software. The measurement data were expressed by mean ± standard deviation. The two groups were compared by independent sample t test. When $P<0.05$, the difference was considered statistically significant.

3. Results

3.1 Renal damage factors level in both groups

After testing the two groups of subjects, the levels of UA, RBP and Col-IV in the observation group were (352.49±26.57) μmol/L, (98.75±26.91) mg/L and (224.77±72.32) ng/L respectively, which were significantly higher than the control group, and the difference was statistically significant ($P<0.05$), as shown in Table 1.

### Table 1.
Comparison of renal damage factor levels in the two groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>UA (μmol/L)</th>
<th>RBP (mg/L)</th>
<th>Col-IV (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>50</td>
<td>352.49±26.57</td>
<td>98.75±26.91</td>
<td>224.77±72.32</td>
</tr>
<tr>
<td>Control group</td>
<td>50</td>
<td>301.55±29.45</td>
<td>46.90±7.94</td>
<td>101.60±17.54</td>
</tr>
<tr>
<td>$t$</td>
<td></td>
<td>9.082</td>
<td>13.068</td>
<td>11.704</td>
</tr>
<tr>
<td>$P$</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

3.2 Extracellular matrix regulatory factors levels in both groups

After testing the two groups of subjects, the levels of TIMP-1 and MMP-9 in the observation group were (145.79±49.67) ng/mL and (177.71±52.35) ng/mL respectively, which were significantly higher than the control group, the difference was statistically significant ($P<0.05$) as shown in Table 2.

### Table 2.
Comparison of extracellular mechanism regulatory factors level between the two groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>TIMP-1 (ng/mL)</th>
<th>MMP-9 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>50</td>
<td>145.79±49.67</td>
<td>177.71±52.35</td>
</tr>
<tr>
<td>Control group</td>
<td>50</td>
<td>50.88±21.18</td>
<td>91.07±24.55</td>
</tr>
<tr>
<td>$t$</td>
<td></td>
<td>12.431</td>
<td>10.596</td>
</tr>
<tr>
<td>$P$</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

3.3 Renal fibrosis diagnostic factor levels in both groups

After testing the two groups of subjects, the levels of TGF-β, LN and HA in the observation group were (15.23±7.61) ng/mL, (153.82±23.01) μg/L and (366.80±77.98) μg/L, respectively. Compared with the control group, the difference was statistically significant ($P<0.05$), as shown in Table 3.

### Table 3.
Comparison of the levels of renal fibrosis diagnostic factors in both groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>TGF-β (ng/mL)</th>
<th>LN (μg/L)</th>
<th>HA (μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>50</td>
<td>15.23±7.61</td>
<td>153.82±23.01</td>
<td>366.80±77.98</td>
</tr>
<tr>
<td>Control group</td>
<td>50</td>
<td>8.97±2.35</td>
<td>90.16±16.69</td>
<td>115.21±46.10</td>
</tr>
<tr>
<td>$t$</td>
<td></td>
<td>5.562</td>
<td>15.838</td>
<td>19.639</td>
</tr>
<tr>
<td>$P$</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

3.4 Renal inflammation degree factor levels in both groups

After testing the two groups of subjects, the levels of Lkn-1 and TNF-α in the observation group were (82.71±20.64) pmol/L and (138.01±45.26) pg/mL, respectively, which were significantly higher than the control group. All were statistically significant ($P<0.05$), see Table 4.

### Table 4.
Comparison of renal inflammatory factors levels between the two groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Lkn-1 (pmol/L)</th>
<th>TNF-α (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>50</td>
<td>82.71±20.64</td>
<td>138.01±45.26</td>
</tr>
<tr>
<td>Control group</td>
<td>50</td>
<td>30.83±17.44</td>
<td>99.26±31.03</td>
</tr>
<tr>
<td>$t$</td>
<td></td>
<td>13.577</td>
<td>4.994</td>
</tr>
<tr>
<td>$P$</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
4. Discussion

CGN is a chronic persistent disease of the kidney, which is composed of various etiology and pathological types. The etiology and related pathogenesis are not fully understood, and it is presumed to be related to hypersensitivity caused by bacteria, viruses and other exogenous substances[8]. Before the appearance of obvious clinical symptoms, CGN patients have a long-term asymptomatic stage, and early damage to renal function is concealed, and the development of the disease course will show a progressive damage, when the glomerular filtration function continued decline, the condition of the disease course will show a progressive damage, when the early damage to renal function is concealed, and the development symptoms, CGN patients have a long-term asymptomatic stage, and have suggested that the increase in UA levels is closely related to renal dysfunction in patients with CGN in the early and middle stages and to take timely treatment measures.

Because renal function of patients in early and middle stage of renal dysfunction is in a compensatory stage, active treatment can restore renal function, and when the kidney enters the late terminal stage, renal failure will be irreversible, and the treatment prognosis is poor[1,9]. At present, renal function damage is mainly evaluated by detecting renal tubular reabsorption and excretion function, glomerular filtration function, etc. Commonly used indicators include urinary β2-microglobulin, creatinine, microalbumin, etc., detected mainly in the compensation period of renal dysfunction, but because there are more influential factors, it does not accurately reflect the extent of kidney damage, especially in the early stage of kidney damage. In view of this, in order to treat and prevent renal dysfunction in patients with CGN, it is necessary to screen early evaluation indicators of renal damage[10]. Serum UA levels are associated with abnormal body metabolism[11]. Some studies have suggested that the increase in UA levels is closely related to the occurrence of renal disease and renal dysfunction[8,12,13]. RBP is a low molecular weight carrier protein that transports retinoids. Under normal conditions, it is difficult to filter out from the glomerulus[14]. With the gradual decline in glomerular filtration, RBP will continuously accumulate in the blood and the level is significantly higher than the normal value. Therefore, some studies have suggested that serum RBP can be used to judge the glomerular filtration function and the degree of renal proximal convoluted tubule damage, resulting in renal damage[10,15]. The content of Col-IV can objectively reflect the metabolic state of the body collagen and the changes of the basement membrane and is closely related to the severity of CGN disease, and participate in the process of renal fibrosis and damage[5,16]. In this study, the levels of UA, RBP and Col-IV in the observation group, ie CGN, were significantly higher than those in the control group (P<0.05), suggesting that UA, RBP and Col-IV levels are closely related to renal dysfunction, to a certain extent, can be used to assess renal impairment in patients with CGN.

During the development of CGN, the degradation of extracellular matrix is reduced, and the synthesis increases into renal fibrosis. Matrix metalloproteinases (MMPs) are the most important enzymes regulating extracellular matrix (ECM)[13,14,17,18], which regulates kidney development, physiological metabolic processes, and rebuild ECM in disease states. MMP-9 is a specific enzyme capable of degrading type IV collagen[14,19]. TIMPs are specific endogenous inhibitors of MMPs that inactivate MMPs, inhibit ECM degradation, and promote fiber formation. TIMP-1 mainly inhibits MMP-9 and plays an important role in ECM metabolism and renal fibrosis[20,21]. In this study, the levels of TIMP-1 and MMP-9 in CGN patients were significantly higher than those in the control group (P<0.05), suggesting that they are closely related to the inhibition of ECM degradation, which may reflect the degree of renal fibrosis in a certain degree.

Disorder of ECM synthesis and degradation can squeeze and occlude capillaries, reduce the filtration range, affect kidney metabolism, cause renal interstitial fibrosis and glomerular sclerosis. TGF-β1 is a renal fibrosis factor that stimulates the synthesis of ECM and inhibits the expression of MMPs[3,22]. LN and HA are important components of ECM[23,24], and the detection of elevated levels is an important indicator of renal fibrosis diagnosis[25,26]. In this study, TGF-β1, LN and HA levels were significantly elevated in CGN patients compared with healthy subjects (P<0.05), indicating that TGF-β1, LN and HA levels can be used for the diagnosis of renal fibrosis and for guiding clinical work.

Inflammatory cells are closely related to the development of kidney disease. For example, activated mesangial cells can produce inflammatory mediators such as TNF-α and IL-6, synthesize mesangial cells, and degrade collagen and basement membrane neutral proteases, thereby destroying and aggravating the degree of glomerular damage[17,27]. Macrophages can promote the formation of renal interstitial fibrosis by secreting TGF-β1. Other non-immune-mediated factors such as hyperglycemia, hypertension and massive proteinuria can aggravate glomerular sclerosis and renal parenchymal ischemia injury[29]. Both interaction, forming a vicious circle, can cause kidney fibrosis[3]. Lkn-1 belongs to the chemokine CC subgroup and is a new member of this subgroup. It is involved in the local inflammatory response of atherosclerotic vascular wall and also plays a role in the inflammation of chronic renal disease, which can promote the development of inflammatory cells[30]. TNF-α is a pro-inflammatory cytokine with a wide range of biological activities. It can induce macrophage production of chemokines, thereby promoting the accumulation of inflammatory cells in glomeruli, hyperplasia as fibroblasts and promoting the development of renal fibrosis. And some studies have suggested that the abnormal increase of TNF-α is related to the occurrence of CGN[13]. In this study, Lkn-1 and TNF-α levels were significantly elevated in CGN patients compared with healthy subjects (P<0.05), suggesting that Lkn-1 and TNF-α levels may lead to renal function degradation by enhancing inflammatory response, is beneficial for judging the degree of renal fibrosis in patients with CGN.

In summary, UA, RBP and Col-IV in patients with CGN are closely related to renal dysfunction. The regulation of extracellular matrix of TIMP-1 and MMP-9 is related to renal interstitial fibrosis. TGF-β1, LN and HA are available for the diagnosis of renal
fibrosis, the levels of Lkn-1 and TNF-α are related to the degree of inflammatory reaction. Detection of these indicators has important guiding significance for evaluating prognosis and judging disease progression.

References


