SUMMARY

Introduction/Objective This study aimed to assess the changes of adiponectin (APN), IL-1β, adiponectin receptor 1 (Adipo R1), and NLRP3 expression of patients with idiopathic membranous nephropathy (IMN) complicated with hyperuricemia (HUA) and analyze the relationship between the APN pathway and the NLRP3 pathway.

Methods A group of 48 patients with IMN + HUA, a group of 49 patients with IMN, 30 healthy controls, and 24 samples of healthy renal tissue were evaluated. APN and IL-1β of each group were detected by the ELISA method. AdipoR1 and NLRP3 in kidney tissue were detected by immunohistochemistry. The clinical data of each group were collected, and the relationship between APN, IL-1β, AdipoR1, NLRP3, and other indexes was analyzed.

Results (1) The concentration of UA, APN, IL-1β, and NLRP3 in the IMN + HUA group were significantly higher than those in the IMN group, but the AdipoR1 was lower. (2) With the severity of chronic kidney disease stage, APN, IL-1β, and NLRP3 gradually increased in the IMN + HUA group, but AdipoR1 gradually decreased. However, the aforementioned indicators did not change significantly in the IMN stages.

Conclusion The AdipoR1–AMPK and NLRP3–caspase-1–IL-1β signaling pathway may play an essential role in IMN + HUA patients. An intervention on these two pathways may have significant impact on the disease occurrence and progression in IMN + HUA patients.

Keywords: adiponectin; AdipoR1; NLRP3; idiopathic membrane nephropathy; hyperuricemia

INTRODUCTION

The idiopathic membranous nephropathy (IMN) is a kind of kidney-specific autoimmune glomerular disease, which is a common pathological type of adult nephrotic syndrome [1, 2]. It is well known that hyperuricemia (HUA) in chronic kidney disease (CKD) may aggravate the inflammatory reaction, cause oxidative stress injury, and aggravate the deterioration of renal function.

Adiponectin (APN) is a unique protein secreted by adipocytes, which is involved in glucose, lipid metabolism, and inflammatory reaction. APN has the effects of insulin-sensitizing, anti-inflammation, and anti-atherosclerosis. Some scholars have found that the AdipoR1-AMP-activated protein kinase (AMPK) pathway can maintain the normal physiological homeostasis of the kidney [3]. Serum uric acid (UA) is an independent predictor of the development, progress, and prognosis of primary nephrotic syndrome (PNS) [4–8]. It can induce the overexpression of the nod-like receptor protein 3 (NLRP3) signaling pathway and cause kidney inflammation [9]. Recent studies have shown that UA may first activate the NLRP3 inflammatory pathway, which then triggers APN–AdipoR1 signal transduction to reduce local inflammation in renal proximal tubule epithelial cells (PTECs) [10]. The purpose of this study was to examine the expression of ANP, IL-1β, and AdipoR1, NLRP3 in patients with IMN + HUA and IMN, and to assess the relationship between APN–AdipoR1 pathway and NLRP3–caspase-1–IL-1β pathway. We speculate that high-level UA would initially activate the NLRP3 pathway, followed by the APN pathway, thus triggering renal self-protection in IMN + HUA. A certain degree of UA elevation may be beneficial to renal self-compensation.

METHODS

Participants

The study involved 97 patients with histologically proven IMN who were hospitalized in the period from January 2018 to November 2018 in the Nephrology Department of the Shanxi
Provincial People's Hospital. This group was divided into two subgroups: IMN + HUA (48 patients) and IMN (49 patients). These subgroups were compared clinically with 30 healthy individuals (plasma and urine) from the medical examination center and histologically with 24 samples (after traumatic nephrectomy) of healthy kidney tissue from the urology department, which represented the control group. The age and sex of the enrolled population may be comparable. All participants in this study signed an informed consent form and were approved by the ethics committee.

Inclusion criteria were as follows: according to the light microscope, there were more than 15 glomeruli in the histological specimens of the patients; estimated glomerular filtration rate (eGFR) > 30 ml/min/1.73 m²; except glucocorticoid, immunosuppressive, and other drug treatments before the first diagnosis; blood pressure, urine and blood biochemistry were normal in the control group.

Exclusion criteria were as follows: pregnancy, tumor, diabetes, hyperlipidemia, obesity, secondary glomerulonephritis.

**General clinical data**

The general clinical data of the enrolled group were collected. IMN + HUA and IMN were classified into CKD1–3 according to the K/DOQI stage.

**Collection of plasma, urine, and renal tissue**

Venous blood and clean morning mid-stream of urine were collected. The samples were centrifuged at 3000 rotations per minute and 15 minutes at an average temperature using a high-speed centrifuge.

After ultrasound-guided renal puncture, kidney tissue specimens were stained and sectioned. The renal tissue wax blocks were classified into 1–3 pathological stages according to Ehrenreich and Churg classification [11].

**Determination of APN and IL-1β in plasma and urine by ELISA**

Plasma and urine APN and IL-1β were assayed with a commercially available kit (Boster Biological Technology, Ltd). According to the manufacturer, the assay has a measurement range of 1.56–100 ng/ml, a sensitivity of < 60 pg/ml, an intra-assay precision was coefficient of variation (CV) < 5.8%, and inter-assay precision was CV < 6.9%.

**AdipoR1, NLRP3 detection with immunohistochemical analysis of kidney tissue**

The wax block to be tested was sliced and baked. Then the wax block was processed by immunohistochemistry. Using a high-power microscope (×400), each slice was selected for five fields of view for preservation. Image analysis was performed using Image J software, and five different areas of view of each slice were determined. The average optical density (AOD) was calculated separately, and the average value was taken as the absorbance value of the index measured for each slice.

**Statistical analysis**

All the data obtained in the study were processed and analyzed by IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA). The mean ± standard deviation or median (interquartile range) was used to describe the econometric data, and the frequency and percentage of the counting data were defined. The comparison of econometric data in two groups was carried by LSD-t-test, a non-parametric test was used to compare the homogeneity of normal variance between the two groups, the χ² test was used to compare the qualitative data between different groups, and Spearman analysis was used to analyze the correlation between the two groups.

**RESULTS**

**Patients and controls**

Basic data on the studied subjects are presented in Table 1. There were 48 patients with IMN + HUA, and the average age was 47.9 ± 11.6 years old, including 62.5% males and 37.5% females. CKD stage 1 patients accounted for 72.9%, 2–3 stage accounted for 27.1% (CKD4, 5 patients basically no renal biopsy); IMN patients accounted for 64.6% of stage 1, and stage 2–3 accounted for 35.4%. Normal plasma and urine samples were 30 cases, and the average age was 46.7 ± 7.6 years old, including 56.7% for males and 43.3% for females. Basic data on the examined patients grouped according to histological stages of IMN, and controls were shown in Table 2. There were 24 normal renal tissue specimens with an average age of 49.7 ± 11.7 years, of which 66.7% were males, and 33.3% were females. There was no difference in age and sex between groups.

**Table 1. Basic data of clinical grouping of plasma and urine samples x ± s**

| Parameter | Control n = 30 | IMN + HUA n = 48 | IMN n = 49 |
|-----------|---------------|----------------|-----------|
| Number    | 30            | 35 (72.9%)     | 29 (59.2%) |
| Age, years| 46.7 ± 7.6    | 46.9 ± 10.7    | 52.3 ± 9.6 |
| Sex, m/f  | 17/13         | 22/13          | 18/11     |

| Number    | 24            | 31 (64.6%)     | 29 (59.2%) |
| Age, years| 49.7 ± 11.7   | 47.7 ± 12.8    | 48.1 ± 9.6 |
| Sex, m/f  | 16/8          | 19/12          | 19/10     |

CKD – chronic kidney disease; IMN + HUA – idiopathic membranous nephropathy + hyperuricemia; m – male; f – female

**Table 2. Basic data of clinical grouping of renal tissue samples x ± s**

| Parameter | Control n = 24 | IMN + HUA n = 48 | IMN n = 49 |
|-----------|---------------|----------------|-----------|
| Number    | 24            | 31 (64.6%)     | 29 (59.2%) |
| Age, years| 49.7 ± 11.7   | 47.7 ± 12.8    | 48.1 ± 9.6 |
| Sex, m/f  | 16/8          | 19/12          | 19/10     |

| Number    | 24            | 31 (64.6%)     | 29 (59.2%) |
| Age, years| 49.7 ± 11.7   | 47.7 ± 12.8    | 48.1 ± 9.6 |
| Sex, m/f  | 16/8          | 19/12          | 19/10     |

IMN – idiopathic membranous nephropathy; HUA – hyperuricemia; m – male; f – female
Laboratory data in the studied groups

Basal laboratory analyses are shown in Table 3 and Figures 1 and 2. In comparison to the control group of patients, blood urea nitrogen, uric acid (UA), serum creatinine, Cystatin C, 24 h urine protein test (UPT), APN, and IL-1β were significantly higher in the IMN + HUA group (p = 0.039–0.001), while eGFR was lower (p = 0.01). In comparison to the IMN group, the IMN + HUA group of patients had UA, APN, and IL-1β higher (p < 0.001).

NLRP3 and AdipoR1 in renal tissue specimens with immunohistochemical analysis in three studied groups of patients

In comparison to the IMN and the control group, NLRP3 was significantly higher, and AdipoR1 was significantly lower in the IMN + HUA group of patients (p < 0.001) (Figures 3A, 3B). Semi-quantitative analysis by immunohistochemical staining showed that both AdipoR1 and NLRP3 were expressed in PTECs. The disease state reduced the expression of AdipoR1, but increased the expression of NLRP3 (Figure 3C).

Idiopathic membranous nephropathy and hyperuricemia: renal function, histological stages, and adiponectin and IL-1β analyses

Comparison of CKD and histological stages of IMN + HUA are presented in Table 4. As the stage of histological lesions worsens, renal function decreases, as well as 24hUPT. A comparison of APN and IL-1β analyses in blood and urine in patients with different stages of CKD and histological changes in IMN + HUA is shown in Figures 4 and 5. No significant differences were observed among these analyses, except for urinary APN, which was the highest in patients with stage 2–3 CKD and histological stage I of IMN + HUA.

Correlation among examined laboratory analyses (Table 5) showed that APN and IL-1β of IMN + HUA patients were positively correlated with serum creatinine, blood urea nitrogen, UA, and 24hUPT.
The role of adiponectin and its receptor in patients with idiopathic membranous nephropathy complicated with hyperuricemia

In recent years, researchers have shown an increased interest in HUA and PNS. UA is considered a marker of renal dysfunction. More and more studies show that HUA is identified as an independent risk factor for the occurrence and progression of PNS. Therefore, IMN + HUA patients were selected as the subjects.

APN is identified as an adipose-specific protein and primarily secreted by adipocytes.

APN, beyond its actions in metabolic responses such as energy metabolism regulation and insulin-sensitivity, has pleiotropic effects in many diseases. Studies reported expression of AdipoR1 in glomerular endothelial cells, mesangial cells, PTECs, podocytes, while renal expression of AdipoR2 was much lower than that of AdipoR1 [12, 13]. Recent findings revealed that APN involves in protective effects in renal diseases, which can be filtered through the kidney barrier, binding to AdipoR1. Activation of the AMPK pathway after the binding of APN to AdipoR1 inhibits its downstream pathway, significantly resisting stress, inhibiting protein synthesis, and preventing fibrosis [14, 15]. Therefore, the AdipoR1–AMPK pathway plays an important role in maintaining the normal physiological homeostasis of the kidney [3].

**DISCUSSION**

In the present study, we evaluated the expression of AdipoR1 and NLRP3 in renal tissue specimens with immunohistochemical analysis in IMN + HUA group. Immunohistochemical analysis revealed that progression of CKD was accompanied by a decrease in AdipoR1, while NLRP3 increased gradually (Table 6). There was no significant difference in the progression of CKD in AdipoR1 and NLRP3 expression related to the severity of pathological changes in different histological stages of membranous nephropathy (p > 0.05).

In addition, the expression of AdipoR1 in PTECs of IMN + HUA was negatively correlated with UA, 24hUPT, NLRP3, APN, and IL-1β (Table 7). NLRP3 was positively correlated with UA, 24hUPT, APN, and IL-1β (p < 0.05), and negatively correlated with AdipoR1 (p < 0.05) (Figures 6 and 7).

**Figure 3.** Median values of AdipoR1 (A), NLRP3 (B) and immunostaining (C) in studied patients; AdipoR1 values (A) were the lowest in idiopathic membranous nephropathy + hyperuricemia (IMN+HUA) group of studied patients in comparison to others (p = 0.001), while NLRP3 (B) was the opposite; immunostaining (C) of renal tissue in normal, IMN + HUA, and IMN (×400) (brown and yellow granules are corresponding indexes for immunostaining, respectively); NLRP3 stained most obviously in IMN + HUA, while for AdipoR1 the opposite was true.

**Figure 4.** Median values of blood (A) and urinary (B) adiponectin in studied patients; blood and urine adiponectin values were the highest in patients with stage 2–3 CKD and histological stage I of idiopathic membranous nephropathy + hyperuricemia in comparison to others (p = 0.001)
The study confirmed that the APN decreased in patients with coronary artery disease and metabolic syndrome [16, 17]; still, the APN was at a high level in different stages of CKD [18, 19, 20]. This phenomenon of reverse epidemiology may be related to an inflammatory reaction, vascular injury, body consumption, and insulin resistance [4].

UA has recently been certified as a risk factor for the development, prognosis, and progression of IMN [5, 6, 7, 9, 21, 22], which also leads to kidney inflammation in a lens-dependent and -independent manner [23]. The research showed that UA may firstly activate the NLRP3 inflammatory pathway. After that, APN–AdipoR1 signal transduction triggers to reduce inflammation in the PTECs, which is related to toll-like receptor 4 [10]. We designed this study to determine whether UA affects the development of the IMN + HUA in the same way.

In conclusion, current studies suggested that UA significantly increased APN, AdipoR1 expression, and AMPK phosphorylation in PTECs. Thus, we considered that AdipoR1–AMPK pathway may become a potential therapeutic target for IMN + HUA.

The findings of the present study showed that APN, IL-1β, NLRP3 was higher, and AdipoR1 was lower in the IMN + HUA group in comparison to the IMN group, increasing with the progress of kidney disease, suggesting that the inflammatory state gradually worsened. Hence, we found that UA is a critical activating factor between the AdipoR1–AMPK pathway and NLRP3–caspase-1–IL-1β pathway. Regrettably, there was no apparent difference in the above indicators in the IMN stage. The reason is that IMN stage is based on the stage of kidney pathology under a light microscope. Some pathological changes are between stages 1 and 2, which is difficult to define. To investigate whether this change is specific to IMN, detecting of the anti-PLA2R antibody is helpful. We affirmed that there was no significant correlation between a-PLA2R and all indexes. Thus, we guess that this change is widespread in CKD.

The correlation analysis showed that UA and 24hUPT are the main factors, affecting the expression of NLRP3, AdipoR1, APN, and IL-1β. Our results are similar to a previous study confirming 24hUPT as an independent factor affecting APN [24]. Our study also confirms that UA correlate to APN, IL-1β, NLRP3, AdipoR1. We speculate that UA may also first activate the NLRP3–IL-1β pathway, induce an inflammatory response, and promote the downstream signaling factors of the NLRP3 pathway to activate the AdipoR1–AMPK pathway, thus producing the body’s defense response in IMN + HUA.

Combined with the results of Yang et al. [10], UA can improve the expression of APN and AdipoR1 in mice PTECs. The promotion effect is stronger with the increase of UA concentration. However, what is different from them is that we discovered that the expression of AdipoR1 decreases gradually with the deterioration of renal function in IMN + HUA. APN is negatively correlated with AdipoR1, considering that it is affected by underlying kidney disease, or renal tubular damage leads to a decrease in AdipoR1, or other factors affect AdipoR1 expression. Receptor–ligand activation disorder may be a compensatory process for kidney disease, which can predict disease progression.

In this study, we also found that the APN pathway was closely related to the NLRP3 pathway in IMN + HUA.
The role of adiponectin and its receptor in patients with idiopathic membranous nephropathy complicated with hyperuricemia

CONCLUSION

The AdipoR1–AMPK pathway is significantly increased in IMN + HUA, and the prediction of the AdipoR1–AMPK signaling pathway may play an essential role in IMN + HUA, but it is non-specific.

It is speculated that UA may induce self-protection by activating the NLRP3–caspase-1–IL-1β pathway and the AdipoR1–AMPK pathway, but it is essential to improve the expression of AdipoR1 in IMN + HUA.

Conflict of interest: None declared.

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Table 5. Correlation analysis between APN, IL-1β, and clinical indexes in IMN + HUA

| Parameter | Normal renal tissue control | IMN + HUA |
|-----------|----------------------------|-----------|
|           | SCR | BUN | UA | eGFR | Cys-C | 24hUPT | Blood APN | Urine APN | PLA2R |
| Blood IL-1β | r   | 0.357 | 0.569 | 0.315 | -0.458 | 0.124 | 0.712 | 0.827 | 0.317 | 0.033 |
| p         | p   | <0.001** | <0.001** | 0.009*  | 0.001*  | 0.400 | <0.001** | <0.001** | 0.011*  | 0.38 |
| Urine IL-1β | r   | 0.293 | 0.580 | 0.417 | -0.413 | 0.145 | 0.712 | 0.873 | 0.326 | 0.017 |
| p         | p   | <0.001** | 0.006*  | <0.001** | 0.004*  | 0.327 | <0.001** | <0.001** | 0.015*  | 0.324 |
| Blood APN | r   | 0.190 | 0.395 | 0.691 | -0.537 | 0.015 | 0.947 | -    | -    | 0.110 |
| p         | p   | 0.005*  | 0.003*  | 0.006*  | 0.005*  | 0.919 | <0.001** | 0.001** | 0.459 |    |
| Urine APN | r   | 0.333 | 0.437 | 0.370 | -0.340 | 0.046 | 0.836 | -    | -    | 0.047 |
| p         | p   | 0.021*  | 0.002*  | 0.047*  | 0.018*  | 0.756 | <0.001** | -    | -    | 0.331 |

Table 6. Difference analysis of renal tissue indexes in patients with different CKD stages and IMN stages IMN + HUA

| Staging | Normal renal tissue control | IMN + HUA |
|---------|----------------------------|-----------|
|         | AdipoR1 (AOD value) | 1.6 ± 0.4 | 0.7 ± 0.1* | 0.5 ± 0.2** | <0.001** | 0.6 ± 0.2* | <0.001** |
|         | NLRP3 (AOD value)   | 0.8 ± 0.1 | 1.1 ± 0.2* | 1.4 ± 0.3** | <0.001** | 1.2 ± 0.2* | <0.001** |

Table 7. Analysis of the correlation between AdipoR1 and clinical indexes in renal tissue of IMN + HUA

| Parameter | SCR | BUN | UA | eGFR | Cys-C | 24hUPT | Blood APN | Urine APN | PLA2R |
|-----------|-----|-----|----|------|-------|--------|------------|-----------|-------|
| AdipoR1   | r   | -0.151 | -0.317 | -0.487 | 0.494 | -0.124 | -0.438 | -0.855 | -0.338 | -0.892 | -0.839 | 0.092 |
| p         | p   | 0.307 | 0.028*  | 0.004*  | 0.007*  | 0.402 | 0.005*  | 0.009*  | 0.019*  | 0.008*  | 0.006*  | 0.007*  | 0.17 |
| NLRP3     | r   | 0.378 | 0.265 | 0.705 | -0.333 | 0.205 | 0.522 | 0.760 | 0.471 | 0.771 | 0.874 | -    | 0.142 |
| p         | p   | 0.008*  | 0.069 | 0.002*  | 0.021*  | 0.161 | 0.003*  | 0.002*  | 0.018*  | 0.006*  | 0.005*  | 0.007*  | 0.273 |

BUN – blood urea nitrogen; UA – uric acid; SCR – serum creatinine; eGFR – glomerular filtration rate; Cys-C – cystatin C; 24hUPT – 24-hour urine protein test; APN – adiponectin; IMN + HUA – idiopathic membranous nephropathy + hyperuricemia

Considering that UA should mainly stimulate the production of APN through the NLRP3 pathway, but there are not enough receptors. The body’s self-regulation was unbalanced. It is well known that IMN belongs to refractory kidney diseases, and the treatment plan of IMN is only limited to treating with hormone combination immunosuppressants debilitating effect, high recurrence rate, and, if possible, increase in the expression of AdipoR1, or it can be one of the new treatment routes of the IMN + HUA. As for the mechanism that affects AdipoR1 expression, we need to further explore in vitro basic experiments.
Улога адипонектина и његовог рецептора код болесника са идиопатском мембранозном нефропатијом компликованом хиперурицемијом

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САЖЕТАК
Увод/Циљ
Ова студија имала је за циљ да процени про мена адипонектина (APN), IL-1β, рецептора за адипонектин 1 (AdipoR1) и NLRP3 у групи болесника са идиопатском мембранозном нефропатијом (IMN) компликованом хиперурицемијом (HUA) и анализира однос између стаза APN и стaza NLRP3.

Методе
Изабрано је 48 болесника са IMN + HUA, 49 болесника са IMN, 30 здравих болника и анализирано су 24 случа ја здравог бубрежног ткива. APN и IL-1β сваке групе су утврдени методом ELSA. AdipoR1 и NLRP3 у бубрежном ткиву су утврђени имунохистохемијом. Прикупљени су клинички подаци сваке групе и анализирана је веза између APN, IL-1β, AdipoR1, NLRP3 и других индекса.

Резултати
(1) Ниво експресије IMN + HUA на уровне IMN + HUA били су значајно виши од оних у групи IMN, али ниво експресије AdipoR1 је био нижи. (2) У различитим фазама CKD и IMN, с порастом фазе CKD, ниво експресије APN, IL-1β и NLRP3 из групе IMN + HUA постепено су се покренули, али експресије AdipoR1 постепено се значајно смањио. Методе
Изабрано је 48 болесника са IMN + HUA, 49 болесника са IMN, 30 здравих болника и анализирано су 24 случа ја здравог бубрежног ткива. APN и IL-1β сваке групе су утврдени методом ELSA. AdipoR1 и NLRP3 у бубрежном ткиву су утврђени имунохистохемијом. Прикупљени су клинички подаци сваке групе и анализирана је веза између APN, IL-1β, AdipoR1, NLRP3 и других индекса.

Кључне речи: адипонектина; AdipoR1; NLRP3; нефропатија идиопатске мембране; хиперурицемија

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