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**Study of the Correlation between the Level of CRP and Chemerin of Serum and the Occurrence and Development of DN**

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**Abstract:** The aim of the study was to find the correlation between CRP and chemerin in development of DN. We choose 90 type-2 diabetic patients between February 2010 and February 2013, who were then divided into DN group and healthy control group. The results of BP showed that there is no difference in SBP and DBP of patients in the three groups. HDL-C of patients in diabetic group and DN group is lower compared with control. CRP in diabetic group and DN group is higher than that of patients in control group. Comparing the patients in DN group with that in diabetic group, CRP was significantly higher. Chemerin level in the diabetic group and DN group is higher than control group. When comparing the patients in DN group with those in diabetic group, serum level of chemerin was significantly higher. Serum level of chemerin is negatively correlated with HDL-C and positively correlated with FPG, HbA1c, LDL-C, BUN and Scr. Serum CRP is negatively correlated with HDL-C and positively correlated with FPG, HbA1c, LDL-C, BUN and Scr. Serum level of chemerin is positively correlated with CRP (r=0.701, P<0.05). CRP and chemerin of the DN patients rose significantly, and may participate in the occurrence and development of DN.

**Keywords:** CRP, chemerin, DN

**1 Introduction**

Diabetes brings serious economic burden and ranks only second to tumor and CVD (cardiovascular disease) at present. There are more than 90,000,000 diabetic patients in China [1-2]. Macroangiopathy and microangiopathy are the main pernicious vascular complications, while microangiopathy mainly lies in cardiac muscle tissue, nerves, retina and kidney. DN is the main cause of clinical renal transplantation [3]. Adipocytokines chemerin is a kind of new adipocytokines only discovered in recent years (Ref) that is found in the lipid metabolism proces of adipocyte, playing an important role in the initiation of diabetes and DN thus increasingly drawing attention of medical workers [4-5]. CRP is a type of non-specific marker of vascular inflammation reaction, which will cause a compensatory mutual resistance between the hyperinsulinemia and insulin. This study is designed to test the C-reactive protein (CRP) of serum and the level of chemerin of diabetic patients so as to study the correlation between it and the occurrence and development of DN.

**2 Data and methods**

**2.1 Basic data**

Choose the 90 type-2 diabetic patients treated by our hospital during February 2010 – February 2013 as study objects, and all the patients meet the diagnostic criteria and classification standard for diabetes prepared by the Diabetes Expert Committee of WHO. The following cases are excluded: (1) endocrine diseases such as thyroid carcinoma; (2) malignant tumor, connective tissue diseases or hematological system diseases; (3) such kidney diseases and serious infections as primary nephritic syndrome; (4) no diabetic ketoacidosis and other severe complications in recent period; (5) the patient who did not take medicine harmful to kidney in recent three months; and (6) the patient who did not take glucocorticoid and thiazolidinediones medicines. Respectively we classified 45 patients in diabetes group and DN group on the basis
whether the patients suffer or not from DN. The patients in diabetes group included 23 males and 22 females who were 66.3±6.1 years old, with a disease course of 7.3±3.2 years. The patients in DN group included 24 males and 21 females who were 66.5±6.3 years old, with a disease course of 7.5±3.4 years. In addition, we chose 45 healthy patients as the control group comprising 23 males and 22 females who were 66.4±6.2 years old. There was not a statistical difference between the gender and the age of all three groups (P>0.05). The direct relatives of all the study objects had no medical history of endocrine metabolic diseases and diabetes.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors’ institutional review board or equivalent committee.

Informed consent: Informed consent has been obtained from all individuals included in this study.

2.2 Inclusion criteria

Inclusion criteria for patients in diabetes group: Have diabetic symptoms, VPG at any time ≥11.1mmol/L, or OGTT2hPG≥11.1mmol/L, or FBG ≥7.0mmol/L. Inclusion criteria for patients in DN group: UAER ≥30mg/24h. Inclusion criteria for patients in control group: healthy cases without dyslipidemia, heart disease, nephropathy and diabetes.

2.3 Test method

After 12 hours of overnight fasting, we collected the limosis vein blood of 2~3ml from all study objects, conducted centrifugation for 5 minutes at the speed of 3000r/min, and then divided the serum into two parts, the one for testing the content of FPG, HbA1c, HDL-C, LDL-C, BUN and Cr and the other for keeping in the refrigerator at -80°C for testing after being marked. We used a fully automatic biochemical analyzer to test HbA1c, HDL-C, LDL-C, BUN and Cr and we used glucose oxidase method to test FPG. We tested serum levels of Chemerin by ELISA method. The Human Chemerin ELISA test kit was provided by Nanjing Biological Technology Co., Ltd. The test was conducted in strict line with the Instructions of Kit.

2.4 Statistical method

Conducted statistical analysis of the measured data via the software SPSS17.0, showed measurement data with ±s. Conducted pairwise comparison via q test and comparison among several groups through variance analysis. Determined P<0.05 as that the difference is of statistical significance. Used simple linear correlation analysis to determine the correlation between relevant measured indicators.

3 Results

3.1 Comparison between basic clinical data and observation indicators

SBP and DBP of patients in three groups are of no statistical difference (P>0.05). HDL-C of patients in diabetes group and DN group is lower than that of the patients in control group (P<0.05), while FPG, HbA1c, LDL-C, BUN and Scr are higher than that of patients in control group. HDL-C patients in DN group is lower than that of patients in diabetes group (P<0.05), while FPG, HbA1c, LDL-C, BUN and Scr are higher than that of patients in diabetes group (P<0.05). See details in Table 1.

3.2 Serum CRP and the level of chemerin between the patients in three groups

CRP of the patients in diabetes group and DN group is higher than that of the patients in the control group (P<0.05). We compared the patients in the DN group with that in diabetes group, CRP significantly rose (P<0.05). Serum level of chemerin of patients in the diabetes group and DN group is obviously higher than that of patients in control group. Compared the patients in DN group and diabetes group, serum level of chemerin is significantly rose (P<0.05). See details in Table 1.

3.3. Correlation analysis

3.3.1 Correlation between the level of chemerin of serum and basic indicators

The level of chemerin of serum is negatively correlated with HDL-C and positively correlated with FPG, HbA1c, LDL-C, BUN and Scr. See details in Table 3.
3.2 Correlation between the serum CRP and the basic indicators

Serum CRP is negatively correlated with HDL-C and positively correlated with FPG, HbA1c, LDL-C, BUN and Scr. See details in Table 4.

3.3.2 Analysis of the correlation between the level of chemerin and CRP of serum

The level of CRP of serum is negatively correlated with CRP (r=0.701, P<0.05).

4 Discussions

Type-2 diabetes is caused by complicated factors together such as environmental factor, genetic factor, absence of B cells functions, insulin resistance and lipotoxicity [6]. A large number of studies have verified that [7-9], it is a nonspecific chronic inflammation process for the mutual resistance between type-2 diabetes and insulin, for the long-term low inflammation state can lead to insulin resistance and finally type-2 diabetes. However, diabetic microangiopathy, which is the major reason for the death of patients, is commonly seen in DN [10]. And besides, the occurrence and development of diabetic microangiopathy is also an interactive result of various factors such as dyslipidemia, genetic factor, oxidative stress, endocrine disorder of fat cells and insulin resistance.

Some researchers have pointed out [11] that inflammatory factors may play an essential role in the pathogenetic process of DN. CRP is a sensitive non-specific inflammatory marker while the body has an inflammatory reaction, which can activate the complement system and possess immune regulation and recognition function. The mechanism for CRP to get involved in the diabetic microangiopathy is that [12]: (1) through insulin resistance process, CRP participates in the development of diabetic microangiopathy; (2) produce stimulus via complement and cause damage to endothelial cells; (3) prompt more activator inhibitor and protein expressions of endothelial cells plasma plasminogen and therefore enhance their activities; (4) suppress the expressions and release of NO synthase. This group of study rules out the effects of other inflammatory reactions on CRP and finds that CRP level of type-2 diabetes patients is obviously higher than that in control group and the rising level is positively correlated with renal injury degree. So the mechanism might be that in the normal case insulin shall suppress liver synthetic CRP and type-2 diabetes patients shall also be less sensitive to insulin, which decreases the suppression function of liver for CRP synthesis and then leads to the increase of CRP concentration [13]. In addition, in the process of insulin resistance, cytokine levels like TNF-α, IL-6, shall also increase, which can further increase the function of liver and therefore lead to the increase of CRP. And oxidative stress induced by CRP that has appeared inflammatory reaction shall cause direct damage to the glomerular endothelial cells. The study result shows that CRP of DN patients is higher than that in the control group and diabetes group, and CRP is positively correlated with

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Table 1: Comparison of basic indicators between the patients in three groups.

| Indicator       | Control group | Diabetes group | DN group | F value | P value |
|-----------------|---------------|----------------|----------|---------|---------|
| SBP(mmHg)       | 142±12        | 143±14         | 149±12   | 4.786   | <0.05   |
| DBP(mmHg)       | 75±6          | 78±8           | 79±8     | 1.095   | >0.05   |
| FPG(mmol/L)     | 4.95±0.57     | 7.75±0.82      | 9.31±2.04| 32.098  | <0.05   |
| HbA1c (%)       | 4.88±0.46     | 8.57±1.45      | 9.56±2.04| 54.076  | <0.05   |
| LDL-C(mmol/L)   | 2.26±0.23     | 3.45±0.87      | 4.78±0.93| 11.986  | <0.05   |
| HDL-C(mmol/L)   | 2.46±0.51     | 1.37±0.29      | 1.01±0.32| 19.234  | <0.05   |
| BUN(mmol/L)     | 3.21±0.36     | 5.31±1.26      | 8.63±5.73| 13.754  | <0.05   |
| Scr (umol/L)    | 74.49±27.56   | 75.62±13.47    | 137.96±87.32| 20.652  | <0.05   |

Table 2: Comparison of serum CRP and the level of chemerin between the patients in three groups.

| Group        | Cases | CRP (mg/L) | Chemerin (mg/L) |
|--------------|-------|------------|-----------------|
| Control group| 45    | 4.9±1.4    | 2.12±0.31       |
| Diabetes group| 45    | 8.5±1.7    | 2.48±0.43       |
| DN group     | 45    | 9.3±2.6    | 5.03±0.76       |
| F            | 44.387| 98.209     |
| P            | <0.05 | <0.05      |
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The indexes of FPG, HbA1c, LDL-C, BUN, and Scr, which means that the inflammatory state of DN patients is much more serious than that of diabetes patients. One of the important links in the process of type-2 diabetes onset is insulin resistance, in which the insulin decreases the liver synthetic CRO and fibrinogen. And insulin sensitivity decrease or insulin resistance is the primary reason for the insulin physiological action weakness, which makes CRP synthesis increase and further illustrates that inflammatory factor CRP gets involved in the DN development via inflammatory reaction.

Being a new type of adipocytokine found in recent years, chemerin participates in the lipid metabolism regulation process of the body [16], with functions to regulate differentiation of preadipocyte, to increase intakes of insulin dependence glucose sugar and to strengthen signal transduction between adipocytes and insulin. Adipocytokine chemerin anomaly plays a significant role in the development of type-2 diabetes and DN, for the adipocytes together with myocyte, islet tissues and internal secretion nerve center constitute a feedback network by releasing factors like chemerin, maintains glucolipid metabolism of the body, and then give essential play to adipocyte genes expressions correlated with the glucolipid metabolism and normal adipocyte proliferation and differentiation. If type-2 diabetes patients are in the low inflammatory state, adipocyte factor concentration also varies in this case. And adipocyte factor has great significance in low inflammation, for it can activate immune reactions, regulate genetic expressions, promote adipocyte differentiation, and get involved in insulin resistance, metabolic syndrome and inflammation of fat cells. Chemerin is released in the form of precursor protein prochemerin, and activated by hydrolyzing serine protease after activation. And the activated chemerin shall make the inflammatory cells the express G protein-coupled receptor aggregate in the inflammatory sites. The study result shows that a large number of chemerins are expressed in the human’s inflammatory fluid [15]. Some scholars have discovered that [16], chemerin also possesses physiological function of angiogenesis and plays a key role in the diabetes-induced microangiopathy like DN. The study result in this group shows that, compared with the diabetes group and control group, chemerin in DN group is remarkably higher, positively correlated with FPG, HbA1c, LDL-C, BUN and Scr, which illustrates that chemerin expression and DN development is closely correlated with each other.

In recent years, some studies have also pointed out that chemerin also has a certain relation with inflammatory reaction. Chemerin shows its anti-inflammatory effect primarily via mediation of its receptor chemR23. In the initial stage of inflammation, polymorph nuclear leukocytes infiltration of the inflamed tissue is

Table 3: Effects of treatments on pylorus ligation induced gastric ulcers in rats.

| Treatments                              | Ulcer index (mm) | I (%) | Volume of gastric secretion (ml) | I (%) | Mucus weight/stomach weight ratio | THP (mol/mg of tissue protein) | I (%) |
|-----------------------------------------|------------------|-------|---------------------------------|-------|---------------------------------|-------------------------------|-------|
| Vehicle+no pylorus-ligation (sham)      | 00*              |       | 0.10.03*                        |       | 92.95.8                         | 10.30.6*                       |       |
| Pylorus ligation +                      |                  |       |                                 |       |                                 |                               |       |
| Vehicle (positive control)              | 19.73.2          |       | 10.41.5                         | 86.72.1 | 29.22.3                        |                               |       |
| D-002 50 mg/kg                          | 8.61.0*          | 56    | 8.6 0.6                         | 92.88.3 | 20.91.0*                       | 44                            |       |
| D-002 200 mg/kg                         | 7.31.0*          | 63    | 6.90.7*                         | 107.55.2* | 18.06.4*                       | 59                            |       |
| D-002 400 mg/kg                         | 7.20.9*          | 63    | 6.40.8**                        | 106.77.0* | 17.21.2*                       | 63                            |       |
| Lyprinol 50 mg/kg                       | 9.53.1*          | 52    | 8.61.6                         | 88.43.5 | 25.0 1.0**                     | 22                            |       |
| Lyprinol 200 mg/kg                      | 8.72.7*          | 56    | 8.60.5                         | 85.93.3 | 22.80.6**                      | 34                            |       |
| Lyprinol 400 mg/kg                      | 7.01.3*          | 64    | 9.00.8                         | 96.22.6* | 21.60.6**                      | 40                            |       |
| Omeprazole 10 mg/kg                     | 7.92.6*          | 60    | 5.10.8*                         | 86.0 4.8 | 11.61.6*                       | 93                            |       |

I % percent inhibition, THP total hydroxyperoxides; *p<0.05; comparison with the positive control; +p<0.05; comparison with D-002 (Mann Whitney U test)

Table 4: Analysis of the correlation between the level of chemerin of serum and basic indicators.

| Indicators | CRP r | P   |
|------------|-------|-----|
| FPG        | 0.398 | <0.05 |
| HbA1c      | 0.243 | <0.05 |
| LDL-C      | 0.138 | <0.05 |
| HDL-C      | -0.572 | <0.05 |
| BUN        | 0.409 | <0.05 |
| Scr        | 0.621 | <0.05 |
prior to antigen-presenting cells, and protease released by polymorph nuclear leukocytes can activate the receptor prochemerin of chemerin, which can be seen that adipocyte factor chemerin in the initial stage of inflammation has been already produced. The study result in this group shows that chemerin content is positively correlated with CRP, too, which illustrates that there might be synergistic effects between chemerin and CRP and chemerin is also a type of inflammation factor that participates in the inflammatory reaction as well as possibly gives play to the DN development.

To sum up, CRP and chemerin levels of DN patients has been obviously increased, and is correlated with FPG, HbA1c, renal function and blood lipid, and so on. CRP and chemerin might participate in the occurrence and development of DN by regulating insulin resistance, inflammation reaction, adipocyte differentiation and metabolism and endothelium damage, and other mechanisms.

Conflict of interest statement: Authors state no conflict of interest.

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