

A Study of Syndrome Characteristic of Diabetic Nephropathy Stage 3 and 4 Based on Traditional Chinese Medicine

Charupan Phosat^{1*}, Chanchira Phosat²

¹Faculty of Chinese Medicine, Huachiew Chalermprakiet University

²Faculty of Tropical Medicine, Mahidol University, Thailand

*E-mail: charupan.pho@outlook.com

Abstract

Diabetic nephropathy (DN) is the leading causes of death among diabetic patients. Early detection is needed in order to decrease its severity and its progression. However, DN diagnostic guideline base on Traditional Chinese Medicine (TCM) is limited. Therefore, this study aimed to determine the difference of syndrome characteristics between DN stage 3 and DN stage 4 based on TCM principle. A Retrospective study was conducted. People who went to Endocrinology department of the first affiliated hospital of Guangxi University of Chinese Medicine during April 2014 and December 2015 and were diagnosed to DN were recruited. A total number of subjects was 186. Secondary data were collected including anthropometric data, blood glucose levels, liver & kidney function indicators, and clinical symptoms. These data were subsequently statistical analysis. The noteworthy differences found between the subjects with DN stage 3 versus those with DN stage 4 were qi deficiency (57.9% vs. 41.5%, $P=0.034$) and yang deficiency (19.0% vs. 43.1%, $P<0.001$). In conclusion, this study suggested that qi deficiency was the outstanding syndrome of DN stage 3 and yang deficiency was a remarkable syndrome for DN stage 4.

Keywords: Diabetic nephropathy, Traditional Chinese Medicine

บทคัดย่อ

โรคไตที่เกิดจากเบาหวานเป็นสาเหตุสำคัญอย่างหนึ่งของการเสียชีวิตในผู้ป่วยเบาหวาน การวิเคราะห์อาการ ที่ถูกต้องตั้งแต่เริ่มแรกจะช่วยลดความรุนแรงและยับยั้งการพัฒนาของโรคได้ อย่างไรก็ตาม ข้อมูลแนวทางการ วินิจฉัยโรคโดยใช้ศาสตร์การแพทย์แผนจีนยังมีจำกัด การศึกษาจึงนี้มีวัตถุประสงค์เพื่อวิเคราะห์ความแตกต่างของ กลุ่มอาการของโรคในระยะที่ 3 และ 4 โดยใช้หลักการแพทย์แผนจีน การศึกษาผลย้อนหลังนี้ได้รวบรวมกลุ่ม ตัวอย่างจากผู้ป่วยเบาหวานที่มีโรคไตแทรกซ้อนที่เข้ารับการรักษา ณ โรงพยาบาลสังกัดลำดับที่ 1 ของ มหาวิทยาลัยแพทย์จีนกว่างซี ระหว่างเดือนมกราคม พ.ศ. 2557 ถึง เดือนธันวาคม พ.ศ. 2558 รวมทั้งสิ้น 186 ราย ผู้เข้าร่วมวิจัยได้ถูกเก็บรวบรวมข้อมูลเกี่ยวกับสัดส่วนร่างกาย ระดับน้ำตาล ตัวชี้วัดประสิทธิภาพการทำงานของตับและไต และ อาการทางคลินิก ผลการวิจัยพบว่ากลุ่มอาการที่เด่นชัดของผู้ป่วยโรคไตจากเบาหวานระยะที่ 3 คือ กลุ่มอาการลมปราณพร่อง และกลุ่มอาการที่เด่นชัดของผู้ป่วยโรคไตจากเบาหวานระยะที่ 4 คือ กลุ่มอาการ หยางพร่อง

คำสำคัญ: โรคไตจากเบาหวาน, แพทย์แผนจีน

* Lecturer at Faculty of Chinese Medicine, Huachiew Chalermprakiet University. 18/18 Bangna-Trad Road Bang Chalong, Bang Phli, Samutprakan 10540. Email: charupan.pho@outlook.com Tel. 02-312-6300 ext. 1108, 02-3126479

** Ph.D. student at Faculty of Tropical Medicine, Mahidol University

Introduction

Diabetic Nephropathy (DN) is often reported as the consequence of blood vessels damage in the kidneys due to chronic increased blood sugar. In Thailand, approximately 40 percent of diabetic patient developed DN^[1]. The progression of DN can be divided into 5 stages^[2]. Its clinical symptoms usually present when the disease is progressed to stage 3. At the final stage, known as end stage renal disease (ESRD), the kidneys are unable to function. The only way for treating the patient at this stage is dialysis or transplantation which is health-harm and costly. Thus, early detection of DN stage 3 and stage 4 is necessary in order to relieve the severity of DN and to prevent the progression of ESRD.

Based on Traditional Chinese Medicine (TCM), the disease diagnosis is performed through 4 examination methods, without using any apparatus, including looking, listening & smelling, questioning, and touching^[3]. Previously, there was no specific name for DN^[4]. It was suspected to be Xiaodan (消瘵) syndrome because its characteristics were analogous to those of Xiaodan (消瘵) syndrome as stated in the Yellow Emperor's Inner Classic. Likewise, the General Treatise of Causes and Manifestations of All Disease published in Sui dynasty (580-618) reported that DN was a syndrome which was typically occurred at the end stage of dispersion thirst (消渴) syndrome. Recently, TCM stated the concepts regarding DN development. DN could results from poor dietary intake and alcohol consumption. With poor eating behavior, stomach, kidney as well as spleen are affected. These subsequently cause damp-heat, blood stasis, and phlegm & dampness^[5]. In addition, deficiency of yin for a long time could results in yang deficiency and blood stasis which can also progresses to DN^[6]. Ye Hui^[7] performed a study among the subjects with DN stage 3 (N=50). They found that almost half were qi & yin deficiency (48.0%) and had blood stasis (46.0%). Similarly, the study conducted by Sun Fei^[8] revealed that qi & yin deficiency and blood stasis were detected among two third of the subjects with DN stage 3 (69.6% and 66.1%, respectively). In 2011, Dai Danxia^[9] also reported that yin and qi deficiency were commonly found in DN stage 3 group (81.8% and 81.8%, respectively). In addition, they studied the syndrome characteristics among the subjects with DN stage 4 and found that half of this group were deficient in yin (56.5%), qi (55.2%), and yang (51.7%)^[9].

However, TCM guideline for DN diagnosis is not yet standardized and the diagnostic guidelines for each DN stage is hardly found. Therefore, this retrospective study aimed to investigate the difference of syndrome characteristics of DN stage 3 and 4 in order to providing DN diagnostic guideline based on TCM. With early detection, the patient could reduce severity as well as prevent the progression of the disease.

Methods

1. Subjects

People who went to endocrinology department of the first affiliated hospital of Guangxi University of Chinese Medicine, Guangxi, China during April 2014 and December 2015 and were diagnosed to DN stage 3 and 4 were recruited into the study. Those who had other chronic diseases, cystitis, urinary tract infection, diabetic ketoacidosis, tumors, tuberculosis, or were pregnant or in lactation period were excluded. A total number of subject was 186.

2. Data collection

Secondary data were collected. The data including anthropometry; weight and height, laboratory parameters; fasting blood glucose (FBG), 2 hours blood glucose (2hBG), glycated hemoglobin (HbA_{1c}), serum creatinine concentration (Scr), blood urea nitrogen (BUN), alanine transaminase (ALT), and aspartate aminotransferase (AST), and clinical symptoms based on traditional Chinese Medicine (TCM) principle^[10]. The subjects' symptoms were classified into 2 main type of syndrome including deficient type and excessive type, with 4 and 3 subtypes, respectively.

Deficient type

1. Qi deficiency: fatigue, unable to deeply breathe, bored of communication, sweating easily, having thready pulse, and having swollen tongue with tooth print. If at least 2 symptoms were detected, the subjects were classified into this group.

2. Blood deficiency: having pale face, cadaverous lips and nails, and swollen tongue. If at least 2 symptoms were detected, the subjects were classified into this group.

3. Yin deficiency: discomfort in hot weather, sweating a lot or sweating at night, having dry mouth and throat, having red thin tongue with a deep groove, having thready rapid pulse, having dysphoria in chest palm soles, and being in a fret. If at least 2 symptoms were detected, the subjects were classified into this group.

4. Yang deficiency: feeling of shivery, lack of warmth in the limbs, having facial edema and edema of legs, soreness and weakness of waist and knees, night frequent micturition, having corpulent tongue with white coating, and having deep and moderate pulse. If at least 2 symptoms are detected, it would be classified into this group.

Excessive type

1. Phlegm and dampness: fullness and distention of the chest and abdomen, lose appetite, being nausea and vomiting, having overweight, being dull ache, distention and pain in the head. If at least 2 symptoms were detected, the subjects were classified into this group.

2. Damp heat: having abdominal pain, lose appetite, being nausea and vomiting, feeling of sliminess in the mouth, being smell breathe, being ungratifying defecation, having yellowish or reddish urine, having reddish tongue, having slimy yellow fur, having rolling and rapid pulse or having wiry and rolling pulse. If at least 3 symptoms were detected, the subjects were classified into this group.

3. Blood stasis: The patient may feel of stabbing pain at the specific area, having purple lips, having dry scaly/bloody skin, having tongue with ecchymosis, dilation of sublingual duct. If at least one symptoms were detected, the subjects were classified into this group.

3. Statistical analysis

The data was statistically analyzed using Statistical Package for the Social Sciences (SPSS version 20.0). The differences between subjects with DN stage 3 versus those with DN stage 4 were evaluated by chi-square test and t-test. The results were presented as mean and standard deviation (SD). *P* value less than 0.05 was statistically significant.

Results

1. Baseline characteristics and biochemical indices of the subjects

The present study recruited 186 subjects; 103 men and 83 Women. Total number of DN stage 3 and 4 groups were 121 subjects (62 men and 59 women) and 65 subjects (41 men and 24 women), respectively. Most of the subjects aged between 60 and 74 (table1). Anthropometric data including weight and height were not differ ($P>0.05$ for all). Both of DN stage 3 and DN stage 4 groups showed high level of blood pressure. Blood glucose parameters; 2hBG and HbA1c were more likely to increase in accordance with the progression of DN. Regarding indicators of liver and kidney function, the subjects with DN stage 4 had significantly higher Scr ($P=0.000$) and BUN ($P=0.000$) than those with DN stage 3 (table 2). In addition, the subjects with DN stage 4 also showed greater trend of ALT and AST, even without statistical significance.

2. Syndrome characteristics of the subjects with DN stage 3 and 4

Comparison of symptoms characteristics based on TCM principle between the subject with DN stage 3 and 4 are shown in table 2. The three most common syndrome found in the subject with DN stage 3 were yin deficiency (84.3%) followed by blood deficiency (64.5%) and qi deficiency (57.9%). Likewise, the subjects with DN stage 4 commonly presented yin deficiency (73.9%) and blood deficiency (70.8%). Interestingly, there were significant differences were observed in qi deficiency and yang deficiency. Qi deficiency was more frequently found in the subject with DN stage 3 ($P=0.034$) while yang deficiency was more frequently detected in those with DN stage 4 ($P<0.001$).

Table 1 Baseline characteristics and biochemical indices of the study subjects

| | DN stage 3 (n=121) | DN stage 4 (n=65) | <i>P</i> value |
|------------|-----------------------|----------------------|--------------------|
| n (%) | | | 0.122 ^a |
| Men | 62 (51.2%) | 41 (63.1%) | |
| Women | 59 (48.8%) | 24 (36.9%) | |
| Age, n (%) | | | 0.250 ^a |
| ≤ 44 years | 12 (9.9%) | 3 (4.6%) | |

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|---------------------------------|-------------|--------------|--------------------|
| 45-59 years | 27 (22.3%) | 20 (30.8%) | |
| 60-74 years | 54 (44.6%) | 32 (49.2%) | |
| ≥ 75 years | 28 (23.1%) | 10 (15.4%) | |
| Weight (kg) | 66.12±14.14 | 64.31±10.13 | 0.314 ^b |
| Height (m) | 1.61±0.09 | 1.63±0.07 | 0.252 ^b |
| Systolic blood pressure (mmHg) | 137.59±21.6 | 146.32±24.18 | 0.013 ^b |
| Diastolic blood pressure (mmHg) | 75.86±12.41 | 75.63±14.67 | 0.910 ^b |
| Fasting blood glucose (mmol/L) | 9.13±2.74 | 8.3±2.47 | 0.043 ^b |
| 2-hour blood glucose (mmol/L) | 8.13±3.65 | 9.25±4.58 | 0.092 ^b |
| Glycated hemoglobin (%) | 13.65±5.13 | 15.01±5.78 | 0.101 ^b |

^a *P* value were tested by chi-square test

^b *P* value were tested by t-test

Table 2 Characteristics of kidney and liver function indicators the study subjects

| | DN stage 3 (n=121) | DN stage 4 (n=65) | <i>P</i> value |
|---|-----------------------|----------------------|----------------|
| Serum creatinine concentration (μmol/L) | 79.25±32.94 | 120.8±48.59 | 0.000** |
| Blood urea nitrogen (mmol/L) | 6.66±1.97 | 8.68±4.17 | 0.000** |
| Alanine transaminase | 27.5±5.71 | 28.32±5.32 | 0.340 |
| Aspartate Aminotransferase | 32.6±8.3 | 34.73±6.56 | 0.057 |

**P* value were tested by t-test

Table 3 Syndrome characteristics of the subjects with DN stage 3 and 4

| Syndromes | DN stage 3 (n=121) | | DN stage 4 (n=65) | | <i>P</i> value |
|---------------------|--------------------|-------|-------------------|-------|----------------|
| | n | (%) | n | (%) | |
| Qi deficiency | 70 | 57.9% | 27 | 41.5% | 0.034* |
| Blood deficiency | 78 | 64.5% | 46 | 70.8% | 0.384 |
| Yin deficiency | 102 | 84.3% | 48 | 73.9% | 0.085 |
| Yang deficiency | 23 | 19.0% | 28 | 43.1% | <0.001** |
| Phlegm and dampness | 20 | 16.5% | 16 | 24.6% | 0.183 |
| Damp heat | 11 | 9.1% | 6 | 9.2% | 0.975 |
| Blood stasis | 12 | 9.9% | 12 | 18.5% | 0.097 |

**P* value were tested by t-test

Discussion

This present study determined the difference of syndrome characteristics between DN stage 3 and DN stage 4. This would be beneficial for providing effective diagnostic guideline. DN was commonly found when increasing age, with the subject aged between 60 and 74 constituted the highest proportion. There were a tendency of increased blood glucose; 2hBG and HbA1c when the disease was progressed from stage 3 to stage 4. Compared to the group of

DN stage 3, the kidney function indicators; Scr and BUN were dramatically elevated higher in the subjects with DN stage 4. Consistently, the indicators of liver function; ALT and AST also increased along with increased disease severity.

Based on TCM, illness is occurred due to two main type of syndrome; deficiency type and excessive type. Each of these types consist of 4 subtypes (qi deficiency, blood deficiency, yin deficiency, and yang deficiency) and 3 subtypes (phlegm & dampness, damp heat, and blood stasis), respectively^[11]. There were studies reported that qi & yin deficiency and blood stasis were the most common syndromes found in the subjects with DN stage 3^[7,8,12]. This was also partially consistent to the study of Dai Danxia^[9]. The author revealed that DN stage 3 patients frequently presented qi (81.8%) and yin (81.8%) deficiency. Additionally, qi, yin, and yang deficiency were often reported among DN stage 4 patients^[9]. In 2007, Gao Hongjie^[13] studied the syndrome characteristics of DN stage 3 and DN stage 4 patients. The results showed that most of DN stage 3 patients were qi and yang deficiency while most of DN stage 4 patients were yin and yang deficiency. In 2013, Wang Ying^[14] revealed the two most common syndromes found in the subjects with DN stage 3 and DN stage 4. These were qi and yin deficiency. On the other hand, Sun Xin^[15] believed that the progression of DN resulted from blood stasis syndrome. In this study, yin deficiency and blood deficiency were commonly detected in both DN stage 3 and DN stage 4 groups. Remarkably, the significant differences were found in yin deficiency and blood deficiency. The subjects with DN stage 3 tended to have qi deficiency more than those with DN stage 4 (57.9% vs. 41.5%, $P=0.034$). On contrary, yang deficiency was more frequently detected among the subjects with DN stage 4 than those with DN stage 3 (19.0% vs. 43.1%, $P<0.001$). These results were corresponded to those of previous studies. Therefore, it could be suggested that qi deficiency was a remarkable syndrome for the subjects with DN stage 3 and yang deficiency was a remarkable syndrome for those with DN stage 4.

Conclusion

In summary, this study suggested the remarkable syndrome for each of DN stage 3 and DN stage 4. During DN stage 3, the subjects often presented qi deficiency. When the disease was progressed to stage 4, yang deficiency was frequently detected. However, there was a limitation in this study. The number of DN patient who came to the hospital as well as the study time was limited. Therefore, further study of larger amount of subjects might be required to confirm the results obtained from this study.

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