

*Medical Data Mining***A study of medication rules of traditional Chinese medicine in the treatment of pre diabetes based on data mining**

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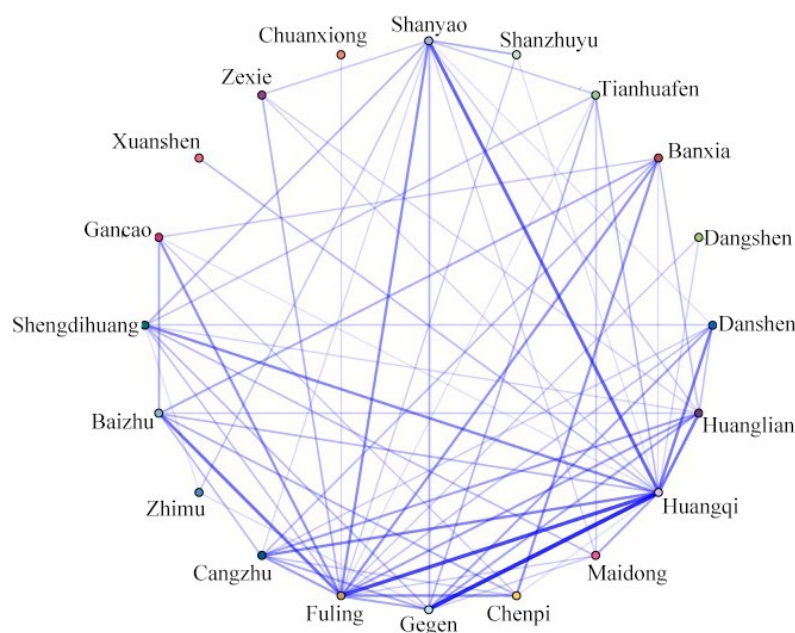
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Highlights

1. All the prescriptions used in this paper are from the published effective clinical research on the treatment of pre-diabetes. Most of the prescriptions are based on the experience of clinicians, and the curative effect is reliable.
2. In this paper, 153 prescriptions were analyzed by data mining method. The results showed that Huangqi (*Astragali radix*), Fuling (*Poria*), Huanglian (*Coptidis rhizoma*), Shanyao (*Dioscoreae rhizoma*) and Gegen (*Puerariae lobatae radix*) were high-frequency drugs for the clinical treatment of pre-diabetes. The drug compatibility and prescription rules were summarized. It was concluded that the disease nature of pre-diabetes was deficiency, the disease location was in the spleen and stomach, the pathological factor was phlegm dampness, and the key link of clinical treatment was “Yiqijianpi”, which has a guiding role in clinical practice.



Abstract

Background: To summarize the concerted application and prescription rules of traditional Chinese medicine in the treatment of pre diabetes. **Methods:** Microsoft Excel 2010 was used to summarize the categories, nature, flavour and channel tropism of drugs. The cluster analysis of high-frequency drugs was carried out by SPSS 22.0, and the association rules of high-frequency drugs were analyzed by Apriori algorithm provided by SPSS modeler 14.0. **Results:** One hundred and forty-six references were included, including 153 prescriptions and 131 drugs. Their frequency of use is listed in the following order. The top 3 categories of drugs were “Tonifying, Heat-Clearing”, diuresis and “Diffusing Dampness” drugs. The top 5 drugs were Huangqi (*Astragali radix*), Fuling (*Poria*), Huanglian (*Coptidis rhizoma*), Shanyao (*Dioscoreae rhizoma*), Gegen (*Puerariae lobatae radix*). The top 3 channel tropism of drugs were spleen, stomach and lung. The top 3 nature of drugs were cold, warm and calm. The top 3 flavour of drugs were sweet, bitter and pungent. The cluster analysis of high-frequency drugs showed that it could be classified into 4 categories: “Benefiting Qi” for promoting production of fluid, “Clearing Heat” and “Eliminating Dampness”, “Nourishing Yin” and “Clearing Heat”, and “Invigorating Spleen” for “Diffusing Dampness”. The results of association rule analysis showed that the combination with the highest degree of confidence and support was *Poria*-Chenpi (*Citri reticulatae pericarpium*)-Banxia (*Pinelliae rhizoma*)-Baizhu (*Atractylodis macrocephalae rhizoma*) and the combination with the highest frequency was *Astragali radix*-*Puerariae lobatae radix*. **Conclusion:** The pre diabetes is due to deficiency. The disease location is spleen and stomach and the pathological factor is phlegm-damp, that is why benefiting qi and invigorating spleen is regarded as the key link of clinical treatment.

Key words: Pre diabetes, Traditional Chinese medicine, Medication rules, Data mining

Abbreviations:

IGR, impaired glucose regulation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Competing interests:

The authors declare that they have no conflict of interest.

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Background

Pre diabetes refers to the development from normal glucose regulation to impaired glucose regulation (IGR), with elevated blood glucose but not yet up to the diagnostic criteria for diabetes, including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). The 2 can occur alone or in combination. The clinical symptoms are not typical generally, feeling sweet in the mouth, thirst, strong appetite, abdominal distension and enlargement and fatigue are the main symptoms [1]. Studies have shown that: it is estimated that by 2030, there will be 470 million people with pre diabetes worldwide, and 70% of them will develop diabetes in different time periods [2–4]. In 2013, the International Diabetes Federation pointed out that the intervention treatment of impaired glucose regulation is an important means to prevent and delay the occurrence and development of diabetes [5]. With the deepening of relevant studies, the clinical efficacy and advantages of traditional Chinese medicine in the treatment of pre diabetes are becoming more and more obvious. Modern medical practitioners often use methods of “Qingrequshi” (“Clearing Heat” and “Eliminating Dampness”) [6, 7], “Kusuantongtiao” (treat with mainly bitter and sour drugs) [8] and “Jianpishugan” (“Invigorating Spleen” and “Dispersing Stagnated Liver Qi”) [9, 10]. Based on modern clinical research literature, this paper analyzes the medication rules and characteristics of traditional Chinese medicine in the treatment of pre diabetes, in order to provide reference for clinical application and scientific research design.

Materials and methods

Literature retrieval

With the subject words “pre diabetes”, “impaired glucose tolerance”, “abnormal glucose tolerance”, “impaired glucose regulation”, “impaired fasting glucose”, “Pidan” (a heat syndrome of the “Spleen”), “traditional Chinese medicine”, “Chinese patent medicine”, “herbal medicine” and “clinical observation”, the related literature of China National Knowledge Infrastructure, VIP and Wanfang Data were retrieved from the built of database to December 31, 2019.

Inclusion criteria for literature

(1) Journal papers have been published. (2) The literature types include randomized controlled trials, case-control trials and case reports. (3) The research objects meet the diagnostic criteria of “pre-diabetes” in traditional Chinese medicine and western medicine: traditional Chinese medicine diagnostic criteria: obesity, abnormally high waist-hip ratio and body mass index, strong appetite, strong bodywithpoor endurance; 168 | no. 4 | vol. 3 | December 2020 | MDM

Western medicine diagnostic criteria: $6.1 \text{ mmol/L} \leq \text{fasting plasma glucose} \leq 7.0 \text{ mmol/L}$ with impaired glucose tolerance, $7.8 \text{ mmol/L} \leq 2 \text{ h plasma glucose} < 11.1 \text{ mmol/L}$ [11–12]. (4) The intervention measures are mainly traditional Chinese medicine prescriptions with definite drug composition. (5) Traditional Chinese medicine is effective in clinical treatment in their studies, excluding exercise, diet, acupuncture and other factors.

Exclusion criteria for literature

(1) The research object is a pregnant women. (2) The same studies have been published repeatedly and the different studies with the same prescription should be included only once with the latest publication year. (3) The full-text literature cannot be obtained.

Data entry and standardization

Microsoft Excel 2010 was used to extract the key information of the included literature, such as article title, year of publication, author, prescription medication, etc., and the data was extracted and collated by 2 personnel respectively. Referring to the 2015 edition of *Chinese Pharmacopoeia*, the names of Chinese medicine the original database were standardized, such as Shenghuangqi (*Astragali radix*) was unified as Huangqi (*Astragali radix*), and Xianlingpi (*Epimedii folium*) was unified as Yinyanghuo (*Epimedii folium*).

Statistical analysis

In this study, descriptive statistics, cluster analysis and association rule analysis were used. (1) Descriptive statistics: Microsoft Excel 2010 was used to conduct frequency statistics on categories, nature, flavour and channel tropism of drugs. (2) Cluster analysis: the system cluster analysis method in SPSS22.0 was used. (3) Association rules method: the Apriori algorithm provided by SPSS modeler 14.0 was used to analyze the association rules of high-frequency drugs in prescriptions.

Results

Literature retrieval results

In this study, a total of 906 related literatures were retrieved and 178 repetitive literatures were deleted by Noteexpress 3.2.0 document management software. According to the inclusion and exclusion criteria of literature, the title and abstract were read for initial screening, and the remaining was downloaded and read for rescreening. Finally, 146 literatures and 153 prescriptions were included.

Categories and frequency of traditional Chinese medicine in the treatment of pre diabetes

Among the 153 prescriptions included, there were 16 categories of drugs involving 131 drugs, which were

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used 1,337 times in total. The top 3 categories were “Tonifying, Heat-Clearing, Regulating Qi”-flowing drugs according to the literature analysis. The cumulative frequency of use from high to low showed that tonifying drugs ranked first, with 419 times, accounting for 31.3%. It was followed by heat-clearing

drugs, which were used 243 times, accounting for 18.2%. The top 5 drugs were *Astragali radix* (80 times), *Fuling (Poria)* (67 times), *Huanglian (Coptidis rhizoma)* (52 times), *Shanyao (Dioscoreae rhizoma)* (51 times) and *Gegen (Puerariae lobatae radix)*. Details of the top 10 drugs were listed in Table 1.

Table 1 Categories and frequency of traditional Chinese medicine in the treatment of pre diabetes

Category	Category number	Frequency (time)	Frequency (%)	Medicine (frequency)
“Tonifying”	34	419	31.3	Huangqi (<i>Astragali radix</i> , 80), Shanyao (<i>Dioscoreae rhizoma</i> , 51), Baizhu (<i>Atractylodis macrocephalae rhizoma</i> , 39), Gancan (<i>Glycyrrhizae radix et rhizoma</i> , 37), Maidong (<i>Ophiopogonis radix</i> , 28), Dangshen (<i>Codonopsis radix</i> , 22), Renshen (<i>Ginseng radix et rhizoma</i> , 19), Huangjing (<i>Polygonati rhizoma</i> , 19), Gouqizi (<i>Lycii fructus</i> , 17), Shudihuang (<i>Rehmanniae radix praeparata</i> , 13), Danggui (<i>Angelicae sinensis radix</i> , 13), Baishao (<i>Paeoniae radix alba</i> , 11), Heshouwu (<i>Polygoni multiflori radix</i> , 8), Yuzhu (<i>Polygonati odorati rhizoma</i> , 8), Nvzhenzi (<i>Ligustri lucidi fructus</i> , 8), Dazao (<i>Fructus jujubae</i> , 5), Xiyangshen (<i>Panax quinquefolii radix</i> , 5), Yinyanghuo (<i>Epimedii folium</i> , 5), Taizishen (<i>Pseudostellariae radix</i> , 4), Baibian dou (<i>LABLAB semen album</i> , 4), Shihu (<i>Dendrobii caulis</i> , 4), Beishashen (<i>Glehniae radix</i> , 3), Jiaogulan (<i>Herba gynostemmatis</i> , 2), Mohanlian (<i>Ecliptae herba</i> , 2), Sangshen (<i>Mori fructus</i> , 2), Tiandong (<i>Asparagi radix</i> , 2), Ciwujia (<i>Acanthopanax senticosi radix et rhizoma seu caulis</i> , 1), Duzhong (<i>Eucommiae cortex</i> , 1), Lujiao jiao (<i>Cervi cornuscolla</i> , 1), Bajitian (<i>Morindae officinalis radix</i> , 1), Roucongrong (<i>Cistanches herba</i> , 1), Baihe (<i>Lilii bulbis</i> , 1), Biejia (<i>Trionycis carapax</i> , 1), Buguzhi (<i>Psoraleae fructus</i> , 1), Huanglian (<i>Coptidis rhizoma</i> , 5), Shengdihuang (<i>Radix rehmanniae</i> , 39), Tianhuafen (<i>Trichosanthis radix</i> , 27), Zhimu (<i>Anemarrhenae rhizoma</i> , 24), Xuanshen (<i>Scrophulariae radix</i> , 22), Mudanpi (<i>Moutan cortex</i> , 16), Huangqin (<i>Scutellariae radix</i> , 12), Zhizi (<i>Gardeniae fructus</i> , 9), Huangbo (<i>Phellodendri Chinensis cortex</i> , 8), Juemingzi (<i>Cassiae semen</i> , 8), Chishao (<i>Paeoniae radix rubra</i> , 7), Xiakucao (<i>Prunellae spica</i> , 4), Digupi (<i>Lycii cortex</i> , 4), JinYinhua (<i>Lonicerae japonicae flos</i> , 3), Shigao (<i>Gypsum fibrosum</i> , 2), Kushen (<i>Sophorae flavescens radix</i> , 2), Lugen (<i>Phragmitis rhizoma</i> , 1), Chuanxinlian (<i>Andrographis herba</i> , 1), Pugongying (<i>Taraxaci herba</i> , 1), Tufuling (<i>Smilacis glabrae rhizoma</i> , 1), Fuling (<i>Poria</i> , 67), Zexie (<i>Alismatis rhizoma</i> , 31), Yiyiren (<i>coicis semen</i> , 16), Yumixu (<i>Stigma maydis</i> , 3), Yinchen (<i>Artemisiae scopariae herba</i> , 3), Huzhang (<i>Polygoni cuspidati rhizoma et radix</i> , 3), Dongguapi (<i>Benincasae exocarpium</i> , 1)
“Clearing Heat”	20	243	18.2	
“Diuresis and Diffusing Dampness”	7	124	9.3	

Table 1 Categories and frequency of traditional Chinese medicine in the treatment of pre diabetes (continued)

Category	Category number	Frequency (time)	Frequency (%)	Medicine (frequency)
“Activating Blood and Resolving Stasis”	11	112	8.4	Danshen (<i>Salviae miltiorrhizae radix et rhizoma</i> , 40), Chuanxiong (<i>Chuanxiong rhizoma</i> , 27), Guijianyu (<i>Ramuli euonymi</i> , 10), Taoren (<i>Persicae semen</i> , 9), Yujin (<i>Curcuma radix</i> , 7), Niuxi (<i>Achyranthis bidentatae radix</i> , 7), Yimucao (<i>Leonuri herba</i> , 6), Honghua (<i>Carthami flos</i> , 4), Shuizhi (<i>Hirudo</i> , 4), Tubiechong (<i>Eupolyphaga steleophaga</i> , 1), Gusuibu (<i>Drynariae rhizoma</i> , 1) Gegen (<i>Puerariae lobatae radix</i> , 50), Chaihu (<i>Bupleuri radix</i> , 22), Shengjiang (<i>Zingiberis rhizoma recens</i> , 7), Sangye (<i>Mori folium</i> , 6), Guizhi (<i>Cinnamomi ramulus</i> , 3), Shengma (<i>Cimicifugae rhizoma</i> , 1), Niubangzi (<i>Arctii fructus</i> , 1)
Relieving superficies	7	90	6.7	<i>Citri reticulatae pericarpium</i> (32), Zhishi (<i>Aurantii fructus immaturus</i> , 13), Xiangfu (<i>Cyperii rhizoma</i> , 12), Lizhihe (<i>Litchi semen</i> , 8), Muxiang (<i>Aucklandiae radix</i> , 2), Zhiqiao (<i>Aurantii fructus</i> , 2), Huajuhong (<i>Citri grandis exocarpium</i> , 1), Chuanlianzi (<i>Toosendan fructus</i> , 1), Foshou (<i>Citri sarcodactylis fructus</i> , 1), Meiguihua (<i>Rosae rugosae flos</i> , 1), Xiebai (<i>Allii macrostemonis bulb</i> , 1), Gansong (<i>Nardostachyos radix et rhizoma</i> , 1), Dafupi (<i>Arecae pericarpium</i> , 1) Cangzhu (<i>Atractylodis rhizoma</i> , 45), Peilan (<i>Eupatorii herba</i> , 18), Houpo (<i>Magnoliae officinalis cortex</i> , 3), Huoxiang (<i>Herba agastaches</i> , 3), Baidoukou (<i>Fructus amomi rotundus</i> , 2), Sharen (<i>Amomi fructus</i> , 1), Caoguo (<i>Tsaoko fructus</i> , 1)
“Regulating Qi-Flowing”	13	76	5.7	Shanzhuyu (<i>Corniffructus</i> , 24), Wuweizi (<i>Schisandrae chinensis fructus</i> , 14), Heye (<i>Nelumbinis folium</i> , 12), Wumei (<i>Mume fructus</i> , 6), Wubeizi (<i>Galla chinensis</i> , 2), Fupenzi (<i>Rubi fructus</i> , 1), Lianzi (<i>Nelumbinis semen</i> , 1)
“Eliminating Dampness”	7	73	5.5	Banxia (<i>Pinelliae rhizoma</i> , 40), Gualou (<i>Trichosanthis fructus</i> , 8), Zhuru (<i>Bambusae caulis in taenias</i> , 3), Sangbaipi (<i>Mori cortex</i> , 3), Jiegeng (<i>Platycodonis radix</i> , 2), Dannanxing (<i>Arisaema cum bile</i> , 1), Chuanbeimu (<i>Fritillariae cirrhosae bulb</i> , 1)
Astringing for hemostasis	7	60	4.5	Shanzha (<i>Crataegi fructus</i> , 13), Shenqu (<i>Massa MEDICATA FERMENTATA</i> , 8), Jtneijin (<i>Gallii gigerii endothelium corneum</i> , 6), Laifuzi (<i>Raphani semen</i> , 5), Maiya (<i>Hordei fructus germinatus</i> , 3)
“Eliminating Phlegm”	7	58	4.3	
“Resolving Food Stagnation”	5	35	2.6	

The channel tropism, nature and flavour of traditional Chinese medicine in the treatment of pre diabetes

In order to facilitate the analysis, when recording the nature and flavour of drugs, the “cold”, “great cold” and “slight cold” ones should be uniformly recorded as “cold” and the “bitter” and “slight bitter” ones should be classified as “bitter” for statistics. The results

showed that the top 3 channel tropism of drugs were spleen (792), stomach (576) and lung (557). The top 3 nature of drugs were cold, warm and calm. The top 3 flavour of drugs were sweet, bitter and pungent, as shown in Figure 1.

Cluster analysis of high frequency traditional Chinese medicine in the treatment of pre diabetes

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Drugs with frequency ≥ 20 were selected as high-frequency drugs [13]. The results of drug frequency analysis showed that there were 21 high-frequency drugs, with 795 times in total, accounting for 59.5%. Microsoft Excel 2010 was used to establish a high-frequency drug database for these 21 drugs. Drugs appearing in various literature were

counted as “1” and drugs not appearing as “0”. SPSS 22.0 was used for cluster analysis, with the clustering method as intergroup link and distance type as Euclidean distance, as shown in Figure 2. Based on the analysis of clinical practice, it was concluded that the clustering results (Table 2) showed well when the clustering reached four categories.

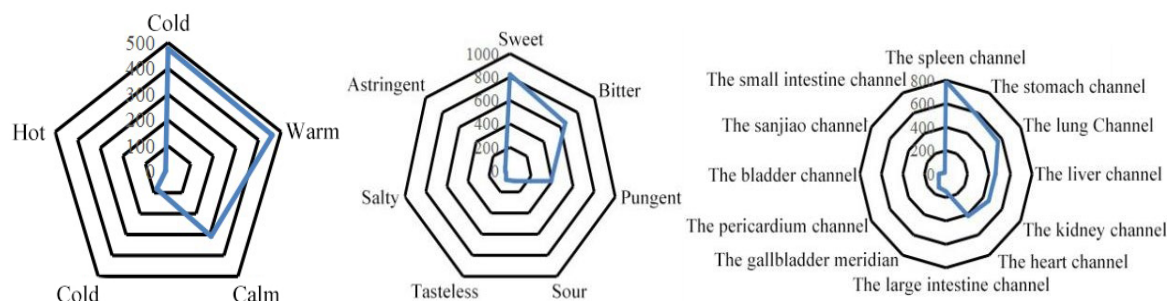


Figure 1 Frequency of the channel tropism, nature and flavour of traditional Chinese medicine in the treatment of pre diabetes

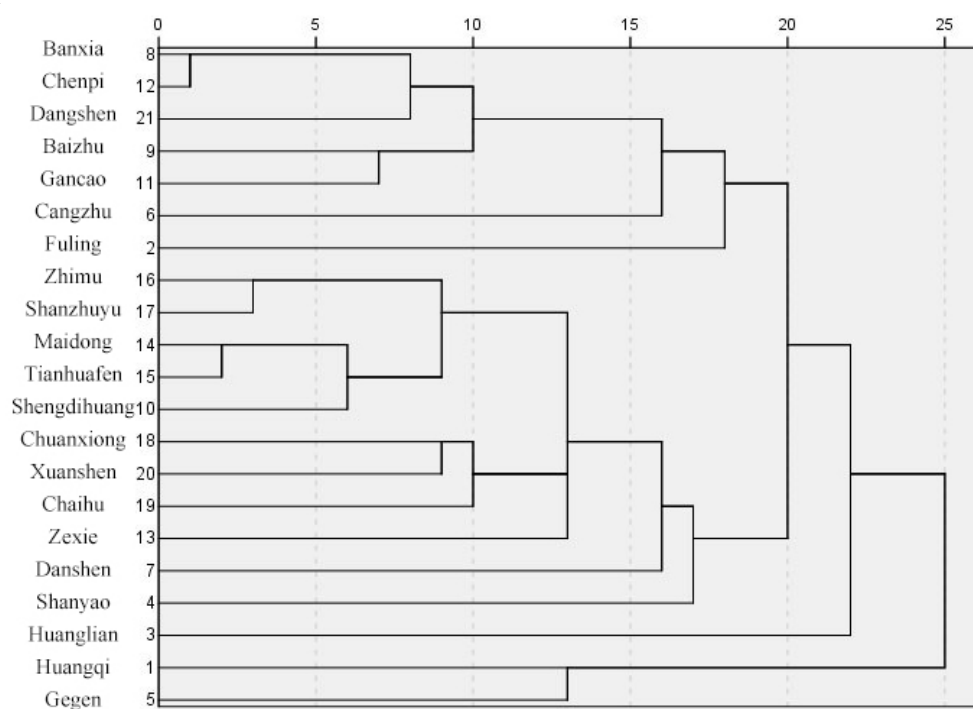


Figure 2 Cluster analysis of high frequency traditional Chinese medicine (frequency ≥ 20) in the treatment of pre diabetes. Note: the abscissa represents the relative distance.

Association rule analysis of high frequency traditional Chinese medicine in the treatment of pre diabetes

Apriori algorithm by SPSS modeler 14.0 was used to analyze the association rules of the high-frequency drugs with frequency ≥ 20 . The minimum support degree was set as 6%, the minimum confidence degree was set as 100%, and the maximum number of the preceding items was 5 to obtain 11 association rules of drugs (Table 3). Among them, the support degree refers to the frequency of the concerted application in all prescriptions, the confidence degree reflects the

possibility of the occurrence of the latter item if the former item appears, and the promotion degree > 1 indicates that all combinations are statistically effective [14]. The drug combinations with frequency > 25 is shown in Table 4. The association network diagram constructed by high-frequency drugs is shown in Figure 3, which can intuitively reflect the degree of association between drugs. The thicker the line in the figure is, the higher the degree of association is. Combined with Table 4, it can be seen that *Astragali radix-Puerariae lobatae radix* has the highest correlation degree.

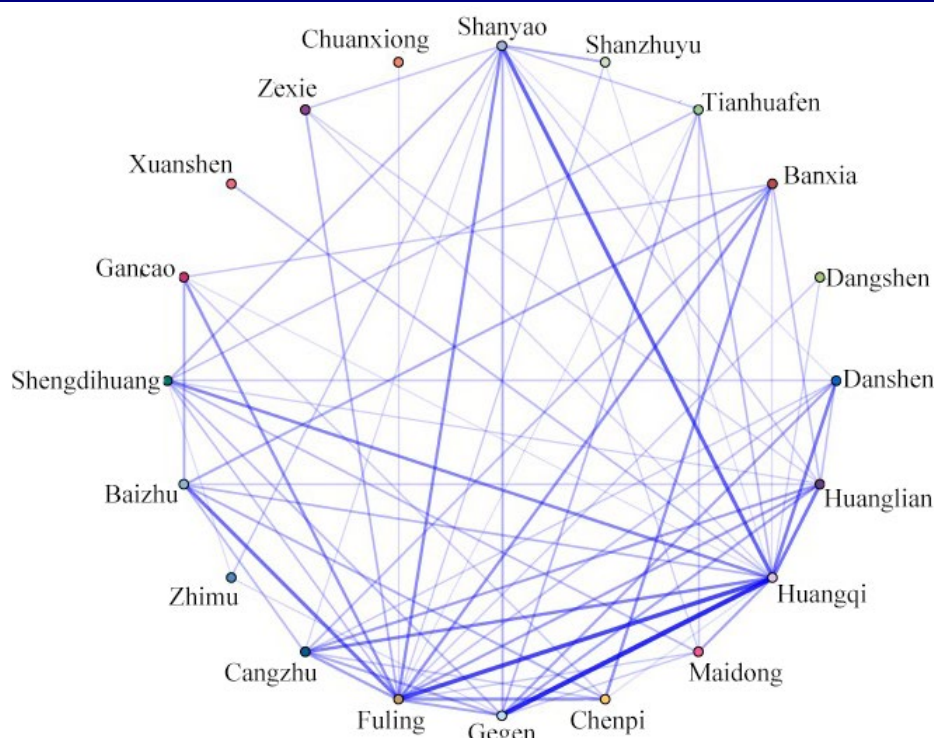


Figure 3 Association network diagram of high-frequency traditional Chinese medicine in the treatment of pre diabetes

Table 2 Cluster analysis of high frequency traditional Chinese medicine in the treatment of pre diabetes

No.	Members number	Medicine	Effect
C1	2	Huangqi (<i>Astragali radix</i>), Gegen (<i>Puerariae lobatae radix</i>)	“Benefiting Qi” for promoting production of fluid
C2	1	Huanglian (<i>Coptidis rhizoma</i>)	“Clearing Heat” and “Eliminating Dampness”
C3	11	Shanyao (<i>Dioscoreae rhizoma</i>), Danshen (<i>Salviae miltiorrhizae radix et rhizoma</i>), Zexie (<i>Alismatis rhizoma</i>), Chaihu (<i>Bupleuri radix</i>), Xuanshen (<i>Scrophulariae radix</i>), Chuanxiong (<i>Chuanxiong rhizoma</i>), Shengdihuang (<i>Radix rehmanniae</i>), Tianhuafen (<i>Trichosanthis radix</i>), Maidong (<i>Ophiopogonis radix</i>), Shanzhuyu (<i>Cornifrutus</i>), Zhimu (<i>Anemarrhenae rhizoma</i>)	“Nourishing Yin” and “Clearing Heat”
C4	7	Fuling (<i>Poria</i>), Cangzhu (<i>Atractylodis rhizoma</i>), Baizhu (<i>Atractylodis macrocephalae rhizoma</i>), Dangshen (<i>Codonopsis radix</i>), Chenpi (<i>Citri reticulatae pericarpium</i>), Banxia (<i>Pinelliae rhizoma</i>)	“Invigorating Spleen” for “Diffusing Dampness”

Table 3 Association rules of high frequency traditional Chinese medicine in the treatment of pre diabetes

No.	Consequent	Antecedent	Support degree (%)	Upgrade degree
1		Chenpi (<i>Citri reticulatae pericarpium</i>) + Banxia (<i>Pinelliae rhizoma</i>) + Baizhu (<i>Atractylodis macrocephalae rhizoma</i>)	10.959	2.179
2	Fuling (<i>Poria</i>)	Ganciao (<i>Glycyrrhizae radix et rhizoma</i>) + <i>Pinelliae rhizoma</i> + <i>Atractylodis macrocephalae rhizoma</i>	8.904	2.179
3		<i>Citri reticulatae pericarpium</i> + <i>Glycyrrhizae radix et rhizoma</i> + <i>Pinelliae rhizoma</i>	8.219	2.179

Table 3 Association rules of high frequency traditional Chinese medicine in the treatment of pre diabetes (continued)

No.	Consequent	Antecedent	Support degree (%)	Upgrade degree
4		<i>Citri reticulatae pericarpium</i> + <i>Glycyrrhizae radix et rhizoma</i> + <i>Atractylodis macrocephalae rhizoma</i>	8.219	2.179
5		Dangshen (<i>Codonopsis radix</i>) + <i>Citri reticulatae pericarpium</i>	7.534	2.179
6	Fuling (<i>Poria</i>)	<i>Citri reticulatae pericarpium</i> + <i>Atractylodis macrocephalae rhizoma</i> + Cangzhu (<i>Atractylodis rhizoma</i>)	6.849	2.179
7		<i>Citri reticulatae pericarpium</i> + <i>Glycyrrhizae radix et rhizoma</i> + <i>Pinelliae rhizoma</i> + <i>Atractylodis macrocephalae rhizoma</i>	6.849	2.179
8	<i>Citri reticulatae pericarpium</i>	Chuanxiong (<i>Chuanxiong rhizoma</i>) + <i>Pinelliae rhizoma</i>	6.849	4.562
9	Huangqi (<i>Astragali radix</i>)	Xuanshen (<i>Scrophulariae radix</i>) + Shanyao (<i>Dioscoreae rhizoma</i>)	6.849	1.825
10		<i>Scrophulariae radix</i> + Gegen (<i>Puerariae lobatae radix</i>)	6.849	1.825
11	<i>Dioscoreae rhizoma</i>	Shanzhuyu (<i>Cornifrutus</i>) + Zexie (<i>Alismatis rhizoma</i>)	6.164	2.863

Note: the confidence is 100%.

Table 4 Combinations of drugs with frequency > 25 in the prescription of traditional Chinese medicine in the treatment of pre diabetes

No.	Combination	Frequency (time)	No.	Combination	Frequency (time)
1	Huangqi (<i>Astragali radix</i>)-Gegen (<i>Puerariae lobatae radix</i>)	43	6	<i>Astragali radix</i> -Dangshen (<i>Codonopsis radix</i>)	29
2	<i>Astragali radix</i> -Fuling (<i>Poria</i>)	38	7	<i>Astragali radix</i> -Cangzhu (<i>Atractylodis rhizoma</i>)	28
3	<i>Astragali radix</i> - Shanyao (<i>Dioscoreae rhizoma</i>)	33	8	<i>Astragali radix</i> -Shengdihuang (<i>Radix rehmanniae</i>)	27
4	<i>Poria</i> -Baizhu (<i>Atractylodis macrocephalae rhizoma</i>)	31	9	<i>Poria</i> -Chenpi (<i>Citri reticulatae pericarpium</i>)	26
5	<i>Astragali radix</i> -Huanglian (<i>Coptidis rhizoma</i>)	30	10	<i>Poria</i> - <i>Dioscoreae rhizoma</i>	26

Discussion

Basic Questions (a book on the basic theory of traditional Chinese medicine, written by many medical practitioners in the Warring States period to the Western Han Dynasty) says: “What is the problem if one feels sweet in his mouth and how it causes? This is because the essence of food is overflowing from the mouth. This disease is called Pidan. It is considered that pre diabetes belongs to the category of “Pidan” in traditional Chinese medicine combined with relevant clinical symptoms [15]. *General Records of Holy*

Universal Relief (a book of traditional Chinese medicine prescriptions written under the auspices of the government by Zhao Jie and others in the Song Dynasty) says: “Food through the spleen’s transportation and transformation, can promote “Yang Qi”. So eating too much greasy, sweet and highly-flavored food which causes “Endogenous Heat” and flatulence will lead to excessive “Yang Qi” in the body, and this excess “Yang” is called “Dan”. It overflows and makes you feel sweet in your mouth. The above process is called “Pidan”. If not treated for a long time, the disease will develop into “Xiaoke” (a

syndrome with thirst as the main symptom)", which records the etiology, pathogenesis, main symptom and deteriorated case of "Pidan". Combined with the research results, the clinical medication rules for modern treatment of pre diabetes are analyzed as follows.

Analysis of the medication rules

Combined with the statistical results of drug categories, it was found that among the prescriptions for the treatment of pre diabetes, tonifying drugs were used most (31.3%), which contained the most drugs, indicating that the pre diabetes is due to deficiency. Professor Wei Zixiao also believed that pre diabetes was the syndrome of intermingled deficiency and excess, including the vital "Qi" deficiency and the pathogenic "Qi" excess. Vital "Qi" deficiency includes "Spleen Deficiency", "Qi Deficiency" and "Yin Deficiency", and pathogenic "Qi" includes "Blood Stasis", "Phlegm-Turbidity" and "Stomach Heat" [16]. The above data shows that *Astragali radix* is most frequently used of all drugs, and as a kind of benefiting qi drug, it can expell pus, relieve pain and strengthen body, used for the treatment of the carbuncle and deep-rooted carbuncle for a long time with chronic ulcer, hemorrhoid and fistula, and also many diseases of children, as *The Classic of Herbal Medicine and Shen-nung Pen-tsao Ching* (written by Shennong between about 200 and 250 CE.) says. Modern pharmacological studies suggest that *Astragali radix* mainly contains astragalus polysaccharide, flavonoids and triterpenes, among which astragalus polysaccharide, as a macromolecular compound, has relatively strong biological activity and may be the main component of lowering blood glucose [17]. Geng Ying observed the intervention effect of point injection with *Astragali radix* on pre diabetes, and the results showed that it could improve the patients' blood glucose level [18]. As a characteristic of traditional Chinese medicine, channel tropism is a localization and orientation theory of drugs acting on a "Zang-Fu" viscera, meridian or specific part. In the treatment of pre diabetes, the results showed that the spleen meridian and stomach meridian drugs were used most. At the same time, combined with the nature and flavour analysis, it was found that the drugs nature for the treatment of pre diabetes was mainly sweet, bitter and pungent, and the flavour was mainly cold and warm, which were both used. Therefore, the concerted application of drugs conforms to the characteristics of "Xinkaikujiang" (using pungent and bitter medicine to regulate "Qi" movement) and "Hanrepingtiao" (using cold and warm medicine to mildly regulate cold and heat), which can restore the function of spleen and stomach. As Wu Jutong advocated, the focus of the treatment of "Middle Jiao" disease" is to let "Spleen Qi" ascend and "Stomach Qi" descend. Therefore, the

location of pre diabetes is spleen and stomach, which is also made clear in *Intergrating Chinese and Western Medicine* (written by Zhang Xichun in the Qing dynasty). Modern medical practitioners have also made achievements in treating patients with pre diabetes from spleen [19–21]. Therefore, "Dysfunction of Spleen" in transportation because of deficiency is an important link in the pathogenesis of "Pidan".

Analysis of cluster results

Cluster analysis is a statistical method to study "birds of a feather flock together", which is classified according to the quantity of drugs and the similarity between them [22]. According to the cluster analysis, 4 clustering prescriptions for the treatment of pre diabetes were obtained. Prescription 1: *Astragali radix*, *Puerariae lobatae radix*. *Astragali radix*, as an important drug for "Invigorating Spleen-Stomach" and "Replenishing Qi", it is also conducive to the essence transportation from spleen up to lung by promoting an upward movement of "Spleen Qi". *Puerariae lobatae radix*, with white inner and sweet flavour, acts on the stomach and lung meridian. It can also promote an upward movement of "Spleen Qi", and "Benefit Qi" for promoting production of fluid together with *Astragali radix*. Prescription 2: *Coptidis rhizoma*, with yellow flower, fruit and root, it has cold nature and bitter flavour. The channel tropism of it is "Spleen Meridian", "Stomach Meridian" and "Large Intestine Meridian". *Coptidis rhizoma*, is good at "Clearing Heat" in the heart and stomach, and it is regarded as an important medicine to "Clear Heat" and "Eliminate Dampness", which is also the prescription 2's function. Prescription 3: *Dioscoreae rhizoma*, Danshen (*Salviae miltiorrhizae radix et rhizoma*), Zexie (*Alismatis rhizoma*), Chaihu (*Bupleuri radix*), Xuanshen (*Scrophulariae radix*), Chuanxiong (*Chuanxiong rhizome*), Shengdihuang (*Radix rehmanniae*), Tianhuafen (*Trichosanthis radix*), Maidong (*Ophiopogonis radix*), Shanzhuyu (*Cornifrutus*), Zhimu (*Anemarrhenae rhizoma*). Among these drugs, *Radix rehmanniae*, *Anemarrhenae rhizoma*, *Scrophulariae radix* together with *Trichosanthis radix* which is good at "Clearing Accumulated Heat" in lung and stomach, can relieve thirst caused by "Xiaoke" by "Clearing Heat", "Promoting Fluid Production" and "Nourishing Yin". There is also *Ophiopogonis radix*, which is good at "Nourishing Lung and Stomach Yin", compatible with *Ophiopogonis radix* for "Nourishing Liver and Kidney Yin", to strengthen the effect of "Nourishing Yin" and "Clearing Heat". Prescription 4: *Poria*, Cangzhu (*Atractylodis rhizoma*), Gancao (*Glycyrrhizae radix et rhizoma*), *Atractylodis macrocephalae rhizoma*, Dangshen (*Codonopsis radix*), Chenpi (*Citri reticulatae pericarpium*), Banxia (*Pinelliae rhizoma*). It is to add *Atractylodis rhizoma*, Baizhu (*Atractylodis macrocephalae rhizoma*) and *Codonopsis radix* on the basis of the Classic ancient

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prescription Erchen decoction, which is about getting recovery of spleen's function of governing transportation and transformation to transport essence all over the body, especially lung and stomach. Combined with the above analysis of pre diabetes disease location, the spleen, as a “Zang”-viscera in “Middle Jiao”, works better under the action of aromatic and warm-natured drugs which can “Eliminate Dampness”. Food, through “the Receiving by Stomach and the Transportation by Spleen”, can be transformed into essence and then transported to the whole body, meeting its metabolic needs. If the spleen and stomach function is impaired, especially if the spleen can not transport essence, food and essence will stagnate and turn into phlegm-damp, which accumulates for a long time will generate heat and consume “Qi” and “Yin”. This is also the meaning expressed in *Basic Questions*. Some experts [23] believe that most patients with pre diabetes have phlegm-damp diathesis. So regulating the biased diathesis can not only prevent the occurrence of impaired glucose regulation, but also prevent the further development of impaired sugar regulation into type 2 diabetes. Therefore, it can be considered that the main pathological factor of pre diabetes is phlegm-damp. The treatment should be based on the recovery of the spleen's function to let “Spleen Qi” ascend and “Stomach Qi” descend normally. The core is to eliminate dampness and phlegm. At the same time, according to the specific situation of patients, “Clearing Heat”, “Benefiting Qi” and “Nourishing Yin” drugs should be used.

Analysis of association results

According to the association rule analysis, the combination of commonly used drugs often mutually promote and enhance [24]. The results of association analysis of drugs in the treatment of pre diabetes showed that, under the condition of 100% confidence, the combination of high-frequency drugs mostly contained the drugs of “Benefiting Qi”, “Nourishing Yin” and “Clearing Heat”, which suggested that these kinds of drugs should be taken seriously in the treatment of pre diabetes. In addition, the most supportive drug combination *Poria-Citri reticulatae pericarpium-Pinelliae rhizoma-Atractylodis macrocephalae rhizoma*, also contains drugs that “Benefit Qi” and “Invigorate Spleen”, and “Eliminate Phlegm-Damp”, which is exactly in line with the above results about the pathogenesis, disease location and pathological factor of pre diabetes. Further analysis of high-frequency drug combinations showed that the combinations of *Astragali radix* and other drugs were most common, and the most common combination was *Astragali radix-Puerariae lobatae radix*, which was consistent with the prescription in the above cluster analysis. In this combination, *Puerariae lobatae radix* can help *Astragali radix* to

“Invigorate Spleen-Stomach” and “Replenish Qi” and promote an upward movement of it. It can be seen that “Benefiting Qi” and “Invigorating Spleen” is an important link in the treatment of pre diabetes.

To sum up, it can be considered that the pathogenesis is mainly the syndrome of “Phlegm-Dampness” due to “Spleen Deficiency”, and “Phlegm-Dampness” is the pathological basis, on which some pathological factors such as “Damp-Heat”, “Qi Stagnation”, “Stasis Blood” and “Intermingled Phlegm” are produced, forming a state of intermingled deficiency and excess [25]. Therefore, the clinical treatment should focus on the recovery of spleen and stomach function, through “Benefiting Qi” and “Invigorating Spleen”, “Eliminating Dampness and Phlegm”, “Nourishing Yin” and “Clearing Heat”, so as to make the essence transportation normally. This is similar to promoting insulin secretion and making it better involved in glucose metabolism to regulate blood glucose [26]. In order to achieve the purpose of “Invigorating Spleen-Stomach”, “Clearing Heat” and “Eliminating Dampness”, we should take tonifying medicine as the basis, using cold and warm nature drugs together, and satisfying the spleen's appetite with bitter and sweet flavour drugs. At the same time, drugs in the prescription should be added and deleted according to different pathogenesis. For example, in order to “Clear Heat” and “Eliminate Dampness”, “Nourish Yin” and “Produce Fluid”, the drugs with bitter cold and sweet cold flavor should be used more. If the course of disease is too long to affect blood vessels and cause blood stasis, the drugs for “Activating Blood and Resolving Stasis” should be properly added to eliminate blood stasis, so that blood vessels are unobstructed. However, “Benefiting Qi” and “Invigorating Spleen” is still the key treatment.

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