EVALUATION OF THE RELATIONSHIP BETWEEN DIABETES AND LARGE BLOOD VESSEL DISEASE

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ABSTRACT
We analyzed the characteristics of diabetes-related macrovascular complications with the objective of more effectively preventing later lethal complications involving cerebral infarction. The associated diseases of approximately 8,000 diabetic patients and >50,000 non-diabetic individuals were evaluated. The distribution characteristics of the four major vascular complications, hypertension, hyperlipemia, coronary heart disease and cerebral infarction in different gender and age groups, together with the relationship among these complications, were investigated. Statistical analysis entailing >600 clinical detection indices in the two major populations (diabetic patients with or without the four major complications listed above) were performed. It is found that in southern Zhejiang Province, China, macroangiopathy is the major complication of diabetes. The most relevant four vascular diseases are hypertension, hyperlipemia, coronary heart disease and cerebral infarction. There is a clear peak prevalence of these four complications in women with diabetes around the age of 65-70 years. There were significant differences in uric acid, triglyceride, creatinine, total cholesterol, serum sodium and other indices (P < 0.05) between the diabetic populations with and without the four complications.

KEY WORDS
diabetes, large blood vessel disease, cerebral infarction, peak prevalence, uric acid

1. Introduction
Diabetes, which is characterized by high blood sugar, is a metabolic disease caused by the hyposecretion of insulin or dysfunction concerning the use of insulin. The global population with diabetes, especially patients with type 2 diabetes has increased rapidly in recent years. According to the seventh edition of the diabetes atlas newly published by the International Diabetes Federation (IDF), there are currently 415 million adult patients with diabetes worldwide; that is, on average 1 in every 11 people has diabetes. Global expenditure on preventing and curing diabetes and its complications reached 673 billion U.S. dollars in 2015. The cost of treatments for diabetes and its complications has become a heavy economic burden for patients, their families and governments worldwide. The numerous complications of the disease can seriously lower patient quality of life; for example, diabetic nephropathy can develop into uremia in the later stages, diabetic retinopathy may lead to insomnia, and diabetic foot ulcers may lead to amputation. Even worse, the complications can be life-threatening; for example, diabetic ketoacidosis can cause coma, and diabetic cerebral blood vessel embolism can cause stroke. According to the latest statistics released by the IDF on World Diabetes Day in 2015, one diabetic patient dies every 6 seconds. The mortality rate for diabetes has surpassed the total mortality rate for AIDS, tuberculosis and malaria. Diabetes has become a serious public health problem worldwide. There have been many studies on various essential clinical examination indices for diabetes and its complications; however, the sample numbers in some current research studies are limited and the conclusions may lack universality. In addition, few existing studies critically compare complications associated with diabetes regarding all of the related essential medical examination indices using statistical sequencing. There have also been few studies concerning the distribution characteristics of these complications in different gender and age groups. However, elucidation of these characteristics is vital for understanding, preventing and curing diabetes; consequently, for this disease, which has numerous complications, study of its prevalence in different gender and age groups, and determining the important medical examination indices based on large sample sizes number using statistical methods is of great significance.

2. Materials And Methods
2.1 Determination the major complications of diabetes
Statistical analysis of the accompanying diseases which have the highest incidence among approximately 8,000 patients with diabetes, who were mainly distributed in the
The prevalence ratio of these diseases in the populations with and without diabetes was compared. The population with no diabetes consisted of >50,000 individuals; the disease prevalence ratio which had the greatest difference between the two populations was considered as a complication of diabetes.

2.2 Distribution characteristics of major vascular complications

The four complications evaluated were hypertension, hyperlipemia, coronary heart disease and cerebral infarction; the prevalence of these diseases in patients who had at least one of the diseases was presented in intuitionistic graphic form, to reveal a strong correlation between these major vascular complications. The total number of males and females with these four diseases at each 5-year age interval were counted separately; graphs were plotted to show the distribution characteristics of these four diseases in different gender and age groups.

2.3 Differences in the clinical indices between the diabetic populations with and without macroangiopathy

The clinical detection data for approximately 8,000 diabetes patients was divided into two parts according to whether the patients had hyperlipemia, hypertension, coronary heart disease or cerebral infarction. After removing the non-digital testing records, there remained >600 medical test indices in the two datasets; they were each statistically analyzed using Wilcoxon rank sum test to verify whether there were significant differences in these indices between the two populations. The objective was to identify the test indices with the most obvious changes when the diabetic patient began to develop large vascular lesions.

3. Results

3.1 Statistical analysis of complications in patients with diabetes

This study was based on two clinical datasets, namely DATA0 and DATA1. DATA0 was the main dataset for the study, and contained the clinical data of 7,823 patients who were diagnosed with diabetes in the Department of Endocrinology, First Affiliated Hospital of Wenzhou Medical University from October 22, 2010, to November 25, 2013. DATA1 covered the clinical data for general individuals who underwent physical examinations in the same hospital from October 2010 to August 2014.

Many patients included in dataset DATA0 had one or more diseases in addition to the basic disease (diabetes), such as hyperlipemia, renal insufficiency, coronary disease, lower extremity arterial stenosis, and others. We carried out statistical analysis of the prevalence of all the diabetic patients in the DATA0 dataset and found a total of 2,168 diseases in which the International Classification of Diseases coding differed. For statistical analysis, we selected the 10 diseases which had the highest prevalence in the population (Figure 1A).

It was evident that hypertension and hyperlipemia were the most common diseases in the patients with diabetes from evaluation of data set DATA0. Nearly 40% of the patients were suffering from hypertension at the same time, and almost a quarter of the patients had hyperlipemia. This was followed by gastritis and coronary disease, and the number of cases were all >500. Next was cerebral infarction (495 cases). And the subsequent five diseases with the largest numbers in turn were urinary tract infection, diabetic nephropathy, upper respiratory tract infection, diabetic peripheral neuritis and diabetic retinopathy.

To further verify whether the other diseases were mainly caused by the basic disease (diabetes), we removed the information of patients with diabetes from dataset DATA1 and obtained the medical datasets of non-diabetic individuals form dataset DATA2. We undertook statistical analysis regarding the proportional distribution of the top 10 diseases accompanying diabetes described above in the non-diabetic dataset DATA2. In addition, we compared the proportional distribution of these 10 diseases in diabetic dataset DATA0. The results are shown in Figure 1B.

The DATA1 dataset had a total of 56,399 individuals, including 2,157 patients with diabetes. After removing the records of patients with diabetes, we obtained dataset DATA2, which included the medical information of 54,242 non-diabetic individuals. Diabetic nephropathy, diabetic peripheral neuropathy and diabetic retinopathy are very definite complications associated with diabetes; the prevalence ratio of these three diseases in DATA2 was zero (Figure 1B).

In comparing Figure 1A and Figure 1B, it can be seen that the incidence ratio for gastritis, urinary infection and upper respiratory tract infection in the general population is even higher than that in the population with diabetes; therefore, the correlation between these three diseases and diabetes is not strong. The incidence ratio for hypertension, hyperlipemia, coronary disease and cerebral infarction in the population with diabetes is considerably higher than that in the general population. Diabetic nephropathy, diabetic peripheral neuropathy and diabetic retinopathy are also very definite complications of diabetes; in southern Zhejiang Province, according to the data from the DATA0 dataset, diabetic macroangiopathy, such as hypertension, hyperlipemia, coronary disease and cerebral infarction is more common than diabetic microvascular disease such as diabetic nephropathy, diabetic peripheral neuritis and diabetic retinopathy.
Among them, hypertension is the most common complication of diabetes.

![Top 10 diseases accompanying diabetes (A)](image)

**Name of the accompaniment diseases**

![The proportional distribution of the top 10 diseases in the diabetic and non-diabetic populations (B)](image)

**Prevalence rate**

Figure 1 — Top 10 diseases accompanying diabetes (A). The proportional distribution of the top 10 diseases in the diabetic and non-diabetic populations (B).

### 3.2 Correlation between the four types of major vascular complications and the distribution characteristics in different age and gender groups

The most important top four complications were extremely relevant to each other. The patients with hyperlipemia were more likely to have higher blood pressure than ordinary individuals. The incidence of cerebral infarction in patients with high blood pressure and coronary heart disease is several times higher than in ordinary individuals. In Figure 2 the distribution of the top four complications of patients with diabetes in the DATA0 dataset is shown. There are 4,007 patients who had at least one of the four major types of vascular disease out of the 7,823 patients with diabetes.
As can be seen in Figure 2 approximately 1/3 of the hypertension patients had hyperlipemia. The vast majority of patients with coronary heart disease were simultaneously suffering from hypertension; >2/3 of the cerebral infarction patients had hypertension, and >1/3 of the cerebral infarction patients had hyperlipemia. The incidence rate of cerebral infarction was 1.5% in the 54,242 individuals in the non-diabetic population (DATA2), and the rate was 6.3% in the 7,823 patients in the diabetic population (DATA0).

According to whether or not the diabetes patient had one or more of the diseases—hypertension, hyperlipemia and coronary heart disease, the DATA0 dataset involving patients with diabetes was further subdivided into the DATA0 I and DATA0 II datasets. The total number of patients in the DATA0 I dataset was 3,908, of which 399 had cerebral infarction. The total number of patients in the DATA0 II dataset was 3,915; among them, 99 had cerebral infarction. In patients with diabetes who did not have hypertension, hyperlipemia and coronary heart disease (single diabetic patient), the incidence rate of cerebral infarction was 2.5%, slightly higher than that in the general population without diabetes. If the diabetic patient was suffering from one or more of hypertension, hyperlipemia and coronary heart disease, the incidence rate for cerebral infarction in the population was 10.2%; this was much higher than the incidence rate for cerebral infarction in non-diabetic and single diabetic patients without macroangiopathy. If the population is further subdivided the following was found: in the diabetic patients who had the hypertension complication the probability of occurrence of cerebral infarction was 11.6%; in the diabetic patients who had the hyperlipemia complication the probability of occurrence of cerebral infarction was 9.8%; and in the diabetes patients who had the coronary disease complication the probability of occurrence of cerebral infarction was 8.1%.

In Figure 3, the distribution of the four kinds of diseases in the different age and gender groups is shown. In the DATA0 diabetic patient dataset, there were a total of 4,113 male patients and 3,710 female patients; the ratio of male to female patients was approximately 1.1:1. Among these patients, 1,563 males had hypertension and 1,477 females had hypertension; the proportion of male diabetic patients who had hypertension was 38%, and the proportion of female diabetic patients who had hypertension was 39.8%.

The number of patients who had hyperlipemia, coronary heart disease or cerebral infarction in the male diabetic population was 948 (23.0%), 371 (9.0%) and 284 (6.9%), respectively; in the female diabetic population it was 789 (21.2%), 278 (7.4%) and 214 (5.7%), respectively.

The proportion of patients with diabetes who had hypertension was slightly higher in women than in men; the proportion of patients who had hyperlipemia, coronary heart disease and cerebral infarction was slightly lower in women than in men. Before the age of 60 years, the prevalence of these four types of disease in men with diabetes was generally lower than in women. However, after the age of 65 years, the number of female diabetic patients suffering from the four diseases began to increase dramatically, and at the age of 65–70 years there was a significant peak incidence. In the situation where the overall number of women was slightly lower than the number of men, there were even more female diabetic patients aged 65–70 years suffering from hypertension, hyperlipemia or cerebral infarction than male diabetic patients.
3.3 Analysis of differences in the indices between diabetic patients with and without large vascular disease

Stroke is a group of diseases that have brain ischemia or hemorrhage injury as the main clinical manifestations; they have a very high morbidity and mortality and are among the most lethal diseases in the world. Cerebral infarction, one of the important complications of diabetes, is associated with ischemic cerebral apoplexy. In diabetic patients with accompanying diseases such as hypertension, hyperlipemia, or coronary disease, the incidence of cerebral infarction would be much higher than in patients without vascular pathological changes. Hypertension, hyperlipemia, coronary heart disease, and cerebral infarction are a group of strongly correlated diseases. 2,3 It is easy for diabetic patients in the continuous progression of the disease to experience a cerebrovascular accident in the late stage. 4 Because of the lack of effective treatment, prevention is considered to be the best measure at present. It is necessary to analyze the differences in the clinical indices between diabetic patients with these four types of major vascular lesions and diabetic patients without them.

In the DATA0 dataset, diabetic patients participated in a total of 1270 different clinical tests. After removing all of the non-digital records in the dataset, a total of 6722 person, involving a total of 615 digital test items and 311437 test results remained. Among the 6722 person, 3588 person with the four major vascular complications, and 3134 without the vascular complications. According to whether the patients had hyperlipemia, hypertension, coronary heart disease, or cerebral infarction the DATA0 dataset was divided into the DATA0A and DATA0B datasets.

Non-parametric statistical tests were performed involving 615 test indices in two types of diabetic patients in the DATA0A and DATA0B datasets; here Rank Sum Test method was used when comparing the data. Test indices were deleted from the statistical calculation when the number of patients who participated in the test was <50. Eventually we obtained the top 10 indices with the greatest differences between diabetic patients with and without macroangiopathies (Table 1); these 10 indices were sorted from top to bottom by means of the significance level of the differences from large to small (i.e., P-values from small to large). Some of our findings regarding the different indices are supported by the conclusions of some previous studies. However, there has not been much focus on the relationship concerning serum sodium and total protein between these two groups of diabetic patients with and without the four major complications. In the present study, triglyceride and cholesterol levels were found to be significant risk factors for vascular diseases. The statistical findings indicated that the differences in the distribution of triglyceride in the two groups of patients were greater than was the case for total cholesterol. An increasing number of studies are reporting that uric acid and creatinine are important independent risk factors for vascular diseases; however, results have shown that the influence of uric acid and creatinine on the process of development of vascular diseases might be more important than previously thought. 5,6 The differences in uric acid and creatinine levels in the two groups of diabetic patients were very large, and both are greater than those for total cholesterol level. The differences for uric acid were even larger than those for triglycerides, which was the most significantly different index in the two groups of diabetic patients.
According to the results of the comparisons, the top five medical indices with the greatest difference between the two groups of diabetic patients were uric acid, triglyceride, creatinine, total cholesterol and serum sodium. In diabetic patients with macroangiopathy, uric acid, triglyceride, creatinine and total cholesterol indices are prone to have high values; the serum sodium index is prone to have a low value.

Table 1 — The top ten most different clinical indexes between two different diabetic populations

<table>
<thead>
<tr>
<th>Order</th>
<th>Measurements</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Uric Acid</td>
<td>9.24962E-33</td>
</tr>
<tr>
<td>2</td>
<td>Triglyceride</td>
<td>1.5164E-30</td>
</tr>
<tr>
<td>3</td>
<td>Creatinine (Enzymatic Method)</td>
<td>2.21377E-29</td>
</tr>
<tr>
<td>4</td>
<td>Total Cholesterol</td>
<td>2.60234E-19</td>
</tr>
<tr>
<td>5</td>
<td>Serum Sodium</td>
<td>1.59952E-18</td>
</tr>
<tr>
<td>6</td>
<td>Urea Nitrogen</td>
<td>1.62313E-18</td>
</tr>
<tr>
<td>7</td>
<td>Gamma Glutamyltransferase</td>
<td>8.28588E-18</td>
</tr>
<tr>
<td>8</td>
<td>Total Protein</td>
<td>3.4222E-15</td>
</tr>
<tr>
<td>9</td>
<td>Absolute Value Of Acid</td>
<td>2.41875E-13</td>
</tr>
<tr>
<td>10</td>
<td>Lymph Absolute Value</td>
<td>6.37925E-13</td>
</tr>
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</table>

4. Discussion

Diabetes is a chronic disease with many complications in the late stages. The patient has a high blood glucose level for an extended period; the blood vessels and the microvasculature of the patient would therefore be damaged, and the heart, brain, kidney, eyes, feet and other organs may well be involved gradually. The prevalence of approximately 8,000 patients with diabetes and >50,000 patients without diabetes were analyzed. The top 10 accompanying diseases that were associated with the largest number of patients in the diabetic population were determined, and the prevalence of these 10 diseases was compared in the diabetic and non-diabetic populations; the prevalence of diabetic complications was greatly increased because of the basic disease (diabetes). Statistical results showed that in southern Zhejiang Province, China, macroangiopathy is the major complication of diabetes, and occurs much more frequently than small vascular lesions. Among them, hypertension is the most important complication of diabetes, and approximately 40% of diabetic patients have hypertension. Through study regarding the distribution characteristics of the four major vascular complications in different gender and age groups, it was found that the number of women with diabetes who suffered from these four types of complications before the age of 60 years was generally lower than the number of men; however, after the age of 65 years the number of women suffering from diabetic macrovascular disease began to increase sharply, basically at the same or a higher rate than in men, especially for hypertension and hyperlipemia. The statistical analysis was performed on >600 clinical detection indices in the two diabetic population groups with and without the four major complications. It was found that there were significant differences in uric acid, triglyceride, creatinine, total cholesterol, serum sodium and other indices (P < 0.05) between these two diabetic populations.

The basic data used in the present study included thousands of individuals and involved analysis of the test results using hundreds of clinical indices; it was one of the most comprehensive studies in this field. However, if the original dataset had been larger, for example involving tens of thousands or hundreds of thousands of patients, and had included almost all of their test results, the sorting conclusions might have been slightly different.

5. Conclusion

The most relevant four vascular diseases of diabetes are as follows: hypertension, hyperlipemia, coronary heart disease and cerebral infarction. There was an obvious peak prevalence of macroangiopathy in female patients
with diabetes around the age of 65-75 years. There were significant differences in uric acid between diabetic populations with and without vascular complications. In the present study, the probability of patients with single diabetes suffering from cerebral infarction was 2.5%. However, if the patient had large vascular complications associated with diabetes, the probability of suffering a cerebral infarction reached approximately 10%. According to our findings, in women with diabetes the prevalence of large vascular complications is not low, but they generally appear late relative to male diabetics. Before reaching the age of 65 years, women with diabetes should control their diet and undertake strengthening exercises to actively prevent hypertension, hyperlipemia and coronary heart disease. Besides common vascular disease indices such as triglyceride and cholesterol levels, attention should also be focused on uric acid, creatinine, serum sodium and other indices in patients with diabetes; this will facilitate a better understanding of the disease, and help prevent or reduce the incidence of cerebral infarction.

References