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The correlation between transcutaneous oxygen tension and microvascular complications in type 2 diabetic patients

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ABSTRACT

Aims: This study aimed to assess whether transcutaneous oxygen tension ($TcPO_2$) was associated with the presence of microvascular complications in type 2 diabetic (T2D) patients and whether $TcPO_2$ could act as an independent risk factor for predicting the occurrence of microvascular events in these patients.
Methods: We recruited 436 patients with T2D. Based on the presence of diabetic kidney disease, diabetic retinopathy, and/or diabetic peripheral neuropathy, the patients were divided into groups with and without microvascular complications. The differences between these 2 groups were examined using the chi-square test and the t test. The influencing factors of diabetic microangiopathy were studied using a logistic regression analysis.
Results: The results showed that sex, diabetes duration, smoking history, $TcPO_2$, and HbA1c were independent risk factors for the occurrence of diabetic microvascular events ($P < 0.05$). In particular, the risk of developing microvascular complications was 10.16 times higher in patients with low $TcPO_2$ than that in those with high $TcPO_2$ (OR = 10.157, 95% CI: 4.602–22.418).
Conclusion: This study showed that $TcPO_2$ was significantly negatively associated with the occurrence of microvascular events in type 2 diabetic patients and that $TcPO_2$ may be an independent risk factor for predicting the occurrence of microvascular complications in these patients. These results suggest that for type 2 diabetes mellitus with clinically reduced $TcPO_2$, we should pay close attention to the occurrence of microvascular complications and engage in early prevention.

1. Introduction

Diabetic microvascular complications are multifactorial pathologies resulting from diabetes that threaten human health and pose enormous economic burdens. Therefore, early screening for diabetic microvascular complications is particularly important. Diabetic microvascular complications mainly present in the retina, kidney, and nerves, and the typical pathological changes are thickening of the microvascular basement membrane and damage to the filtration barrier function of the vascular wall.

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD),[1] and its incidence in China is rapidly increasing. In particular, between 2009 and 2012, the prevalence of DKD in type 2 diabetic patients in China was 30%–50% in community patients and approximately 40% in hospitalized patients.[2] The major pathological changes in DKD are glomerular hypertrophy, glomerular and tubular basement membrane thickening, and the accumulation of extracellular matrix, which all result in diffuse or nodular glomerulosclerosis and renal failure. The pathogenic mechanism is very complex and has not been completely confirmed. Meanwhile, diabetic retinopathy (DR) is the main cause of blindness among working-aged adults worldwide.[3] The major pathological changes are the selective reduction of retinal capillary pericytes, the proliferation of endothelial cells, and thickening of the basement membrane, which result in retinal vascular stenosis and abnormal hemodynamics due to the long-term high-glucose environment and which can lead to capillary blockage. Blocked capillaries specifically cause capillary occlusion, reducing perfusion, which further aggravates the ischemia and hypoxia of local retinal tissues, in turn causing retinal vascular injury and the formation of a large number of new vessels.[4] Finally, diabetic peripheral neuropathy (DPN) is one of the most common chronic complications in diabetic patients. Diabetic microvascular complications are an important factor affecting the occurrence and

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development of DPN.[5] The pathogenic mechanism of DPN is not yet clear but is currently known to include hyperglycemia-mediated activation of several major biochemical pathways, including the polyol pathway, changes in the activation of protein kinase C (PKC), and Schwann cell apoptosis, which are all significant contributors to the occurrence and development of DPN.[6] Once the neuropathy develops, it is difficult to reverse this process; therefore, early diagnosis and treatment are particularly important.

Transcutaneous oxygen tension ($TcPO_2$) measurement is a non-invasive and accurate detection method. This method can also be highly reusable and can accurately reflect the metabolic state of the lower limbs.[7] In 1951, Horwitz et al.[8] discovered oxygen exchange between the skin and the surrounding air and experimentally quantified the amount of this oxygen exchange. In 1967, Evans and Naylor[9] first reported the application of a platinum wire electrode system to measure the oxygen tension of the skin and showed that the oxygen tension on the surface of the skin was 45 ± 7 mm Hg. This system was later gradually developed for prediction of the amputation level needed, the healing of diabetic foot ulcers, the effect of hyperbaric oxygen therapy, and the occurrence of cardiovascular events.[10–13] However, few studies have examined $TcPO_2$ in the context of diabetic microvascular complications.

The aims of our study were to investigate the correlation between $TcPO_2$ and microvascular complications in type 2 diabetic patients and to evaluate whether $TcPO_2$ could be an independent risk factor for predicting the occurrence of microvascular complications.

2. Methods

2.1. Study subjects

We recruited 436 type 2 diabetic patients who were admitted to and treated in the Department of Endocrinology of the First Affiliated Hospital of Henan University of Science and Technology between January 2015 and January 2016. We collected basic information on the patients as well as hematological indicator and complication screening data. The patients were diagnosed with diabetes according to the American Diabetes Association[14] criteria. The exclusion criteria were as follows: (1) type 1 diabetes mellitus; (2) acute complications of diabetes mellitus, such as diabetic ketoacidosis (DKA), a hyperosmolar hyperglycemic state (HHS), or lactic acidosis; (3) severe heart, liver, and/or kidney dysfunction; (4) malignant tumors; (5) malignant or secondary kidney diseases and/or kidney stones; (6) any type of acute or chronic infection; (7) recent trauma and/or surgery (within six months); and (8) Gestational diabetes. The study was approved by the ethics committee.

DKD was defined as present when urine samples collected after blood glucose levels stabilized exhibited an albumin excretion rate (AER) ≥30 mg/24 h. Other factors, such as exercise, heart failure, urinary tract infection, and uncontrolled hypertension (>180/100 mm Hg) were excluded.[15] DR was diagnosed using non-mydriatic ocular fundus photography performed by professional personnel using an optical fundus camera (CR-2 1-0.4A, Canon, Japan), followed by image review by specially assigned individuals. The diagnostic criteria conformed to the DR staging criteria adopted by the 2002 American Academy of Ophthalmology unified international clinical DR severity grading standards. Additionally, DPN was defined based on abnormal temperature and vibration perception; disappearance of the ankle jerk reflex, abnormal pressure perception; reduced nerve transduction velocity, as confirmed by neurophysiology; and the exclusion of neuropathy by other causes.[16] Smoking was defined as present if patients were current smokers or former ones, and drinking was defined as present if patients had a drinking history or were current drinkers. Hypertension was defined based on the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) guidelines.[17] Microvascular complications in type 2 diabetic patients were defined as the presence of DKD, DR, and/or DPN (either alone or in combination).

2.2. Methods

The $TcPO_2$ measurements were performed by specially assigned individuals using a TCM400 Radiometer device (Medical Aps, Bronshoj, Denmark). Before measurement, all of the patients avoided smoking and caffeine intake and tried to maintain stable emotions, and the participants also rested for 20 minutes in a room with a temperature between 22 °C and 24 °C. The patients assumed a supine position; the measurement site was the dorsum of the foot, which was carefully cleaned using saline solution. An electrochemical transducer was fastened to the skin using double-sized adhesive rings and contact fluid. The electrode was first calibrated, after which it was placed on the skin of the first metatarsophalangeal joint. The electrode temperature was 44 °C. After 15–20 minutes, when the $TcPO_2$ value was stable (no more than 2 mm Hg fluctuation within five minutes), measurement began. After 30 minutes, the $TcPO_2$ value was recorded. The toe arterial pressure and the brachial arterial pressure (systolic pressure) were measured using a Doppler ultrasonic blood flow detector. The ratio of these two indicators was considered as the lower-extremity toe–brachial index (TBI) of the present side. The above steps were repeated on the other side as well. $TcPO_2$ and the TBI were thus measured in both legs. For both $TcPO_2$ and the TBI, the lowest value is reported as the result of the analyses.

2.3. Collection of clinical and laboratory data

The following information was collected for each patient: age; sex; diabetes duration; smoking history; drinking history; family history of diabetes; hypertension; $TcPO_2$ value; related biochemical indicators, including glycated hemoglobin (HbA1c), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c); fasting blood glucose (FBG); the TBI; and diabetic complications. Indicator assessment required blood samples (following a minimum of an 8-hour fast). HbA1c levels were detected by using high-performance liquid chromatography. TC, TG, HDL-c, and LDL-c were detected with a Hitachi 7600 automatic biochemistry analyzer.

2.4. Statistical analysis

Statistical analysis was performed using SPSS software (version 17.0 for Windows). Measurement data are expressed as the mean ± standard deviation ($x \pm SD$). Comparisons between groups were performed using the t test. Comparisons of count data were performed using the chi-square test to determine whether the distributions of all clinical characteristics between the groups with and without microvascular complications groups differed. The presence of microvascular complications was used as a dependent variable, and relevant factors were used as independent variables for unconditional logistic regression analysis to identify independent risk factors for the occurrence of microvascular complications. The best threshold value of $TcPO_2$ for the development of microvascular complications was determined based on a receiver operating characteristic (ROC) curve. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Incidence of microvascular complications

$TcPO_2$ was used as the observation indicator in the ROC curve analysis. The diagnostic area under the curve (AUC) value for the entire population was 0.799 (95% CI: 0.746–0.852), and the best threshold value was 50 mm Hg (sensitivity 0.766, specificity 0.702,

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