Ultra-weak photon emission as a potential tool for evaluating the therapeutic effect of traditional Chinese medicine in patients with type 2 diabetes

Meina Yang [a,b], Zhongwen Zhang [a], Jialei Fu [c], Junyan Liu [d], Jiangxiang Pang [b], Hua Fan [e], Zailin Yang [f], Yuanbin Zhang [f,**], Jinxiang Han [b,*]

[a] *Department of Endocrinology and Metabolism, The First Affiliated Hospital of Shandong First Medical University, Ji'nan, Shandong, China*
[b] *NHC Key Laboratory of Biotechnology Drugs (Shandong Academy of Medical Sciences), Biomedical Sciences College, Shandong First Medical University, Ji'nan, Shandong, China*
[c] *Shandong Academy of Traditional Chinese Medicine, Ji'nan, Shandong, China*
[d] *Shandong Cancer Hospital and Institute, Shandong First Medical University & Shandong Academy of Medical Sciences, Ji'nan, Shandong, China*
[e] *Shandong First Medical University& Shandong Academy of Medical Sciences, Ji'nan, Shandong, China*
[f] *Neck-Shoulder and Lumberjack Pain Hospital of Shandong First Medical University, Ji'nan, Shandong, China*

A R T I C L E   I N F O

A B S T R A C T

Background: Traditional Chinese medicine (TCM) has been used to prevent and treat type 2 diabetes (T2DM) for thousands of years. The holistic view of TCM and the "multitarget" characteristics of Chinese medicine have unique advantages in the prevention and treatment of T2DM. TCM syndrome differentiation and treatment are effective for T2DM; however, currently, the therapeutic effect of TCM is generally evaluated by asking for patients' subjective feelings, or by checking the changes in relevant indicators. The main problems are that the patient's descriptions are unclear and subjective, and although the self-reported symptoms may have improved significantly, the relevant indicators are sometimes not obvious, which cannot truly reflect the therapeutic effect of TCM. Therefore, it is urgent to develop a novel, sensitive, and noninvasive method to quantitatively evaluate the therapeutic effect of TCM.
Methods: In this study, ultra-weak photon emission (UPE) was measured at four sites of hands of T2DM patients with Qi-Yin deficiency before treatment and after 1 and 2 weeks of treatment with TCM. The UPE intensity and spectral distribution were calculated and analyzed using the results measured at these four sites. Spearman's correlation coefficient was used to quantify the correlation between the UPE parameters and the syndrome scores of TCM.
Results: The UPE intensity of T2DM patients with Qi-Yin deficiency decreased gradually with the course of the treatment and was significantly lower than that before the treatment. The ratio of photon counts between the wavelength ranges of 495–550 nm and 550–610 nm after the treatment was higher than that before the treatment and negatively correlated with the corresponding syndrome scores so that the degree of symptoms improvement could be characterized by the ratio (495–550 nm/550–610 nm).

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* Corresponding author.
** Corresponding author.
E-mail addresses: zhangyuanbin1977@163.com (Y. Zhang), samshjx@sina.com (J. Han).

Conclusions: The therapeutic effect of TCM in T2DM patients with Qi-Yin deficiency can be shown at the level of UPE. UPE is a potential and noninvasive tool for evaluating the therapeutic effect of TCM in patients with T2DM.

1. Introduction

Diabetes, as a major chronic disease, threatens the paysical and mental health of human over the world. According to the International Diabetes Federation(IDF), the number of diabete patients in the world have reached 537 million in 2021, and it is evaluated that there will be nearly 783 million diabetes patients in the world by 2045, 90% of them are type 2 diabetes (T2DM) [1]. Diabetes not only brings physical and mental damage and shortens the life span of the patients, but it also brings a heavy economic burden to individuals and countries. TCM has a history of preventing and curing diabetes for thousands of years, and the prevent and treatment effect is obvious. The holistic view of TCM and the "multitarget" characteristics of TCM have unique advantages in the prevention and control of complex diseases such as diabetes [2,3].

The curative effect of TCM in treating diabetes is remarkable [3]. The therapeutic effect of TCM can be evaluated by the degree of improvement in symptoms after the treatment. Currently, the efficacy of TCM is generally evaluated by asking for patients' subjective feelings, or by checking the changes in relevant indicators, such as biochemical indicators [4,5]. The main problem is that the patients' descriptions are unclear and subjective; moreover, although the self-reported symptoms have improved significantly, the examination indicators are sometimes not obvious, so the therapeutic effect of TCM cannot be truly reflected, or there are unrelated independent factors, so they cannot systematically reflect the improvement of the disease. Therefore, it is urgent to find a novel more-sensitive and noninvasive way for estimating the therapeutic effect of TCM in patients with T2DM.

All living systems, such as microorganism, plants, animals and humans, constantly emit photons outward, which was known as ultra-weak photon emission (UPE). The intensity of UPE is very low, with about a few to hundreds of photons/s/cm^2 [6,7]. The UPE origins from the transition from high to low energy state of biological macromolecules in metabolic processes [8]. It is a life phenomenon that occurs at the "molecular level," carrying information about the composition and structure of biological molecules. The UPE is a universal phenomenon of life and an essential attribute of life activities.According to the viewpoint of metabolic luminescence mechanism, UPE is produced during the electron transfer in the metabolic processes and is linked with the reactive oxygen species (ROS) [8,9]. When the body is affected by external or internal factors, resulting in abnormal physiological or pathological conditions, its metabolic state inevitably changes, and the type and number of corresponding macromolecules also change, resulting in changes in the intensity and spectral distribution of UPE [10]. Hence, there is a deviation of UPE from normal values [11–14], which can be used to evaluate the state of the body.

The UPE-detection technology has been developed in Germany, the Netherlands, Japan, and the United States to detect the UPE of life systems. Its technical characteristics are to detect and analyze the weak changes in the internal and external environment of biological systems and obtain micro-level life information. The sensitivity of the technology can reach 10 photons/s/cm^2, and it has the characteristics such as noninvasiveness, rapid measurement, good accuracy, and repeatability [15]. The broad application prospect of the UPE-detection technology makes it a hot spot for many researchers and scientific research institutions [14,16,17].

Because the integrity and dynamic characteristics of UPE coincide with the holistic view of TCM theory, researchers have tried to apply it to the field of TCM. It has been found that the intensity of UPE on the body surface of rabbits with spleen deficiency syndrome is significantly lower than that of the healthy group [18]. Yan et al. detected the UPE intensity at the meridians and acupoints on the human body surface and found that UPE carries the information of the normal physiological state and some pathological states of the human body, and different diseases carry their special pathological UPE information [19]. Zhao et al. measured the UPE intensity of both two hands from healthy male and female subjects of different ages; the results suggest that the UPE intensity varies among healthy subjects and presents an S-shaped curve with age, which could predict the physiological state of the body [20]. Sun et al. analyzed the UPE parameters of 44 prediabetic subjects to investigate the correlation between the UPE parameters and the subtypes of TCM-based syndrome. Their results suggested that measuring UPE could provide a novel way for studying the syndrome subtypes, the authors concluded that the UPE is a new non-invasive method for detecting the subtypes of syndrome in early-stage T2DM [17].

The UPE can characterize the state of the body, and the syndrome of TCM could be characterized by the UPE of the human body [21,22]. A question arises as to the change law of the human UPE in the process of symptom improvement after TCM treatment. Moreover, it would be useful to clarify whether the UPE of the human body could characterize this improvement. In this study, the UPE intensity and spectral distribution were measured at four sites of hands of T2DM patients with Qi-Yin deficiency before treatment and after treatment with TCM for 1 and 2 weeks. The UPE intensity and spectral distribution were calculated and analyzed using the results measured at the above four sites. The correlation between the UPE parameters and the syndrome scores of TCM was calculated by Spearman's correlation analysis. Thus, more-precise evidence could be provided for the use of UPE as a potential and noninvasive tool for evaluating the therapeutic effect of TCM in patients with T2DM.

2. Materials and methods

2.1. Subjects

Forty age-matched patients (age: 45–54 years; sex: 17 men and 23 women) with T2DM with Qi-Yin deficiency were recruited, and

each subject provided written informed consent. The patients with T2DM with Qi-Yin deficiency were included only if they had the same diagnosis and differentiation of symptoms and signs by three TCM doctors, who independently diagnosed the subjects in a blinded fashion.

The Western medical diagnostic criteria for T2DM refer to the diagnostic criteria for T2DM proposed by the World Health Organization (WHO) in 1999; the standard of TCM Qi-Yin deficiency syndrome differentiation refers to "Guide for Prevention and Treatment of Diabetes in TCM" [23].

2.2. TCM syndrome scores

According to "Guide for Prevention and Treatment of Diabetes in TCM" [23], Qi-Yin deficiency syndrome mainly includes the following nine symptoms: (1) thirst; (2) dry throat and mouth; (3) fatigue; (4) shortness of breath; (5) lazy speech; (6) weak waist and knees; (7) night sweat; (8) dysphoria in chest, palms, and soles; and (9) palpitation and agrypnia.

These symptoms are divided into four levels according to the severity of symptoms as follows: none (0), light (1), medium (2), and heavy (3). The higher the score, the more serious the symptoms are. Patients' symptoms were asked for and scored in a unified form before and after treatment with Chinese herbs by the researchers.

2.3. Experimental detection system

We used a two-hand UPE-detecting system, which we have described in our previous paper [12,13]. It is a tabletop model specifically designed for left and right hands. Fig. 1 and Fig. 2 displayed the components of the two-hand UPE-detection system. At the front of the dark box, there were two openings so that both left and right hands could be put inside and measured simultaneously. The core component of the detection system was photomultiplier tube (PMT) , and the two photomultiplier tubes (PMT) were directly above the left and right openings. The type of PMT we used in the experiment was Electron Tube 9235QA), and its sensitive spectral range was 290–630 nm, the diameter was 51 mm.The UPE-detecting system also included PMT high-voltage power supplies(Sens Tech PM20), photon counting unit(C9744), control box and computer with data analysis software.

Besides, a set of cutoff filters(GG395, GG455, GG495, OG550, and RG610) were used in order to obtain the UPE intensity in different spetral ranges, whose quantum efficiencies were 27%, 23%, 15%, 6%, 3%, and 2%,respectively.

2.4. UPE-measurement procedure

The UPE intensity of two hands of T2DM patients with Qi-Yin deficiency was measured before treatment and after treatment with TCM for 1 and 2 weeks. The UPE measurement was conducted between 3 p.m. and 5 p.m. to reduce the influence of diurnal rhythms. The procedures were as follows:

(a) The room temperature was adjusted to 25 °C, and the humidity was controlled between 40% and 50%. (b) The subjects washed their hands with running tap water, put on black gloves prepared in advance, and waited quietly for 20 min; during this period, we asked the patients about their body condition and filled in the TCM syndrome scores questionnaire. (c) The dark counts without and with filters in a sequence from 395 nm to 610 nm in both left and right PMT were recorded simultaneously for 2 min at intervals of 50
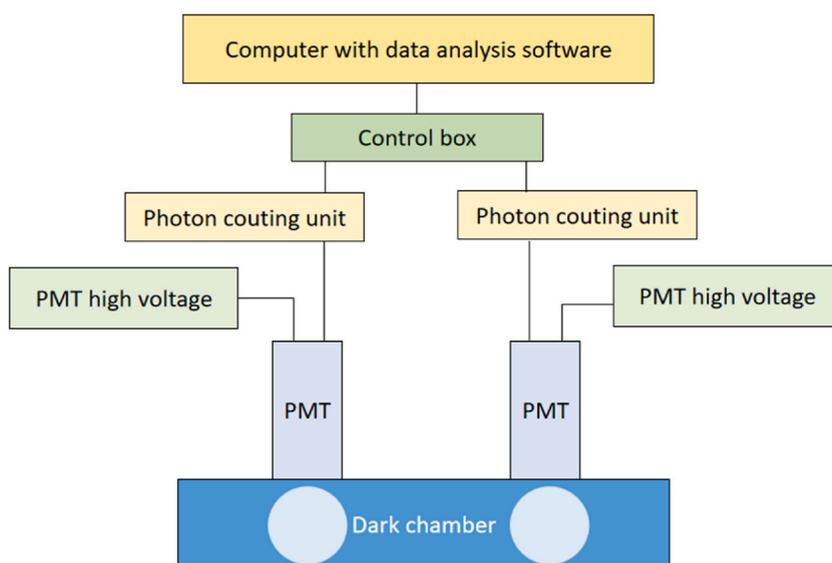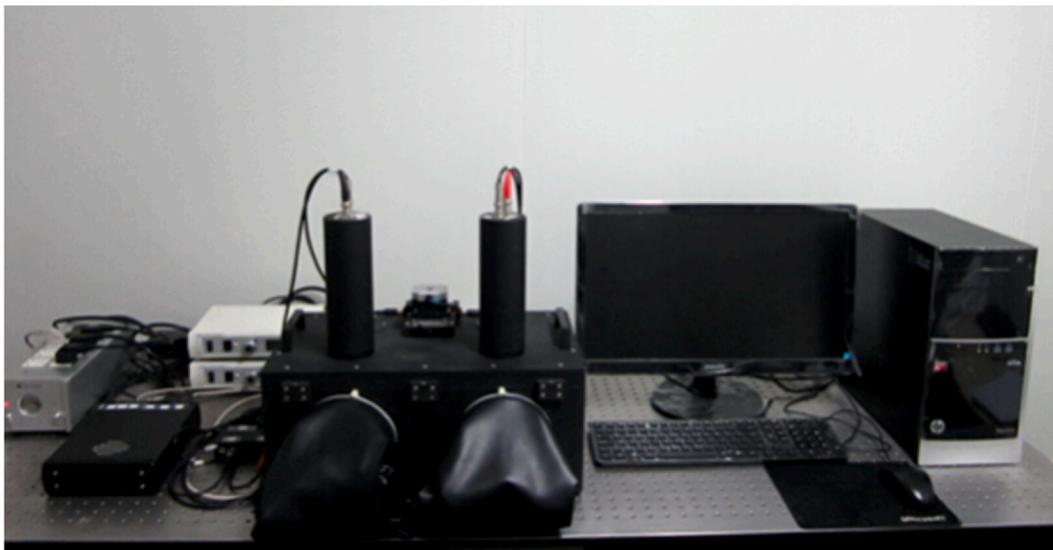

Fig. 1. Schematic representation of the two-hand photon-detecting system.

Fig. 2. The photograph of the two-hand photon-detecting system.

ms. (d) After dark adaptation of hands for 20 min, the subjects placed the left and right hands below the two photomultiplier tubes inside the dark chamber through the left and right holes. (e) The measurement time interval was set at 50 ms, the measurement time was set at 2 min, and then "measure" was clicked to start; immediately after one filter measurement, a second filter measurement identical with the first one was performed. (f) After the measurement was completed, the data were exported and analyzed.

2.5. Data analysis

The UPE intensity and spectral distribution of both hands of T2DM patients with Qi-Yin deficiency before treatment and after treatment with TCM for 1 and 2 weeks were calculated and analyzed. SPSS 16.0 (SPSS, USA) was used for statistical analysis, and a paired-sample *t*-test was used for statistical analysis. The significance tests were bilateral tests, and $p < 0.05$ was regarded as statistically significant. Origin 9.0 and GraphPad Prism 5.0 were used for data calculation and mapping. Pearson correlation analysis was used to evaluate the correlation between the UPE parameters and the syndrome scores.
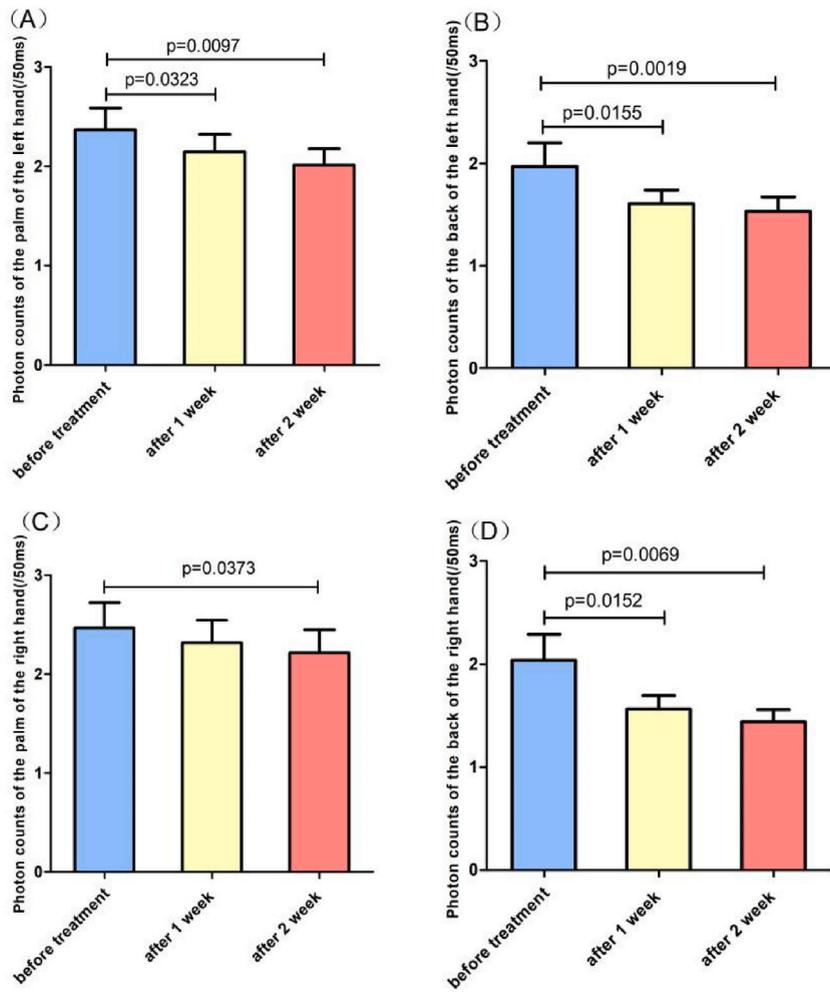
3. Results

3.1. The UPE intensity of both hands of type 2 diabetes patients with Qi-Yin deficiency before treatment and after treatment for 1 and 2 weeks

To analyze the UPE changes in T2DM patients with Qi-Yin deficiency syndrome after treatment with TCM, the UPE intensity of the palm and the back of both hands was measured before treatment and after 1 and 2 weeks of treatment. Fig. 3(A-D) displays the photon counts of the palm and the back of the left and right hands before treatment and after 1 and 2 weeks of treatment. As shown in Fig. 3(A-D), the UPE intensity decreased gradually as the course of the treatment increased at the four sites of both hands.

Specifically, the UPE intensity of the palm and the back of the left hand and the back of the right hand of T2DM patients with Qi-Yin deficiency after treatment for 1 and 2 weeks was significantly lower than that before treatment (for the left palm: $p = 0.0323$, and $p = 0.0097$; for the left back: $p = 0.0155$, and $p = 0.0019$; and for the right back: $p = 0.0152$, and $p = 0.0069$). For the palm of the right hand, there was a significant difference in the UPE intensity only between 2 weeks of treatment and before treatment ($p = 0.0373$), but there was no significant difference in the UPE intensity between 1 week of treatment and before treatment ($p > 0.05$).

3.2. The spectral distribution of UPE of both hands of type 2 diabetes patients with Qi-Yin deficiency before treatment and after 1 and 2 weeks of treatment

The calculation method of the spectral distribution of UPE has been described in our previous study [12], which was the same as that reported by Van Wijk [24]. According to the calculation, the results of the spectral distribution of the palm and back of the left and right hands of T2DM patients with Qi-Yin deficiency before treatment and after treatment for 1 and 2 weeks are shown in Fig. 4(A and B) and Fig. 5(A and B). Both Fig. 4(A and B) and Fig. 5(A and B) illustrate that photon counts of the palm and back demonstrated higher intensities in the 495–550 nm range than others for both hands. In other words, the palm and back of both hands demonstrated the maximal peak in the range of 495–550 nm. In addition, for almost the whole wavelength, the photon counts before treatment were higher than those after the treatment.

Fig. 3. The UPE intensity of both hands of type 2 diabetes patients with Qi-Yin deficiency before treatment and after 1 and 2 weeks of treatment. (A) The palm of the left hand. (B) The back of the left hand. (C) The palm of the right hand. (D) The back of the right hand.
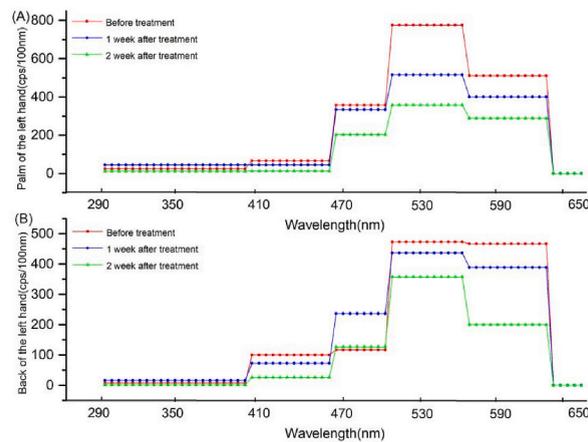
Fig. 4. The UPE spectral distribution of the left hand of T2DM patients with Qi-Yin deficiency before treatment and after treatment for 1 and 2 weeks. (A) The palm of the left hand. (B) The back of the left hand.

Importantly, in comparison with before the treatment, there was an obvious difference in the ratio of photon counts between the wavelength ranges of 495–550 nm and 550–610 nm of both hands of T2DM patients with Qi-Yin deficiency after the treatment for 1 and 2 weeks. The ratio between the wavelength ranges of 495–550 nm and 550–610 nm tended to increase as the course of the treatment increased for both hands, and this trend was not observed in other ratios. The ratio of photon counts between 495–550 nm and 550–610 nm before treatment and after treatment for 1 and 2 weeks is displayed in Fig. 6(A and B).

As shown in Fig. 6(A and B), the ratio between 495–550 nm and 550–610 nm increased gradually after treatment at the four sites of both hands. Specifically, for the left hand, the ratio between 495–550 nm and 550–610 nm after 2 weeks of treatment was significantly higher than that before treatment (for the palm: p = 0.0183, and for the back: p = 0.0091). For the right hand, the trend was more obvious, and the ratio between 495–550 nm and 550–610 nm after both 1 and 2 weeks of treatment was significantly higher than that before treatment (for the palm: p = 0.0153, and p = 0.0095; for the back: p = 0.0002, and p = 0.0076). The results also indicated that the distinguishing ability of the ratio varied among the sites of both hands.

3.3. The syndrome scores and blood glucose level of type 2 diabetes patients with Qi-Yin deficiency before treatment and after treatment for 1 and 2 weeks

The syndrome scores and blood glucose values of T2DM patients with Qi-Yin deficiency were calculated before the treatment and after 1 and 2 weeks of treatment. The results are shown in Table 1 and Fig. 7(A and B). As shown in Table 1 and Fig. 7(A and B), syndrome scores gradually decreased as the course of treatment increased. Namely, the syndrome scores after treatment for 1 and 2 weeks were significantly lower than those before treatment (p < 0.0001); moreover, there was no significant differences in the blood glucose level between before the treatment and after 1 and 2 weeks of treatment(p = 0.811, and p = 0.539, respectively).

3.4. Correlation analysis between the ratio (495–550 nm/550–610 nm) and the syndrome scores

We analyzed the correlation between the ratio (495–550/550–610 nm) and the syndrome scores of T2DM patients with Qi-Yin deficiency after treatment for 2 weeks. The results are displayed in Table 2 and depicted in Fig. 8(A-D). As shown in Table 2 and Fig. 8(A-D), the ratio between 495–550 nm and 550–610 nm for both hands negatively correlated with the syndrome scores (for the left palm: $R^2 = -0.703$, p < 0.001; for the left back: $R^2 = -0.841$, p < 0.001; for the right palm: $R^2 = -0.819$, p < 0.001; and for the right back: $R^2 = -0.906$, p < 0.001).

4. Discussion

According to the metabolic luminescence mechanism, UPE is produced during the electron transfer in the metabolic processes and is linked with the reactive oxygen species (ROS) , it was known that ROS was very important in the formation of different kinds of electronically excited species [8,9]. According to the physical and chemical principles of UPE, it can occur only when electronically excited species transition from high to low energy state. The metabolic mechanism of UPE considers that the highly active peroxides in cells generate singlet oxygen or excited carbonyl in the process of chemical recombination reaction, which was not stable and would emit photons of different wavelengths when they return to the ground state,. Experimental studies have shown that NADPH oxidase, a membrane-bound enzyme complex embedded in the cell membrane, mitochondrial membrane, chloroplast membrane, and phagosome membrane, can convert oxygen (O_2) into the superoxide anion radical ($O_2^{\bullet-}$); $O_2^{\bullet-}$ generates hydrogen peroxide (H_2O_2) via disproportionation reaction; and H_2O_2 is further converted into the hydroxyl radical ($HO^{\bullet}$) via Fenton reaction [25].

The lipids, proteins, and nucleic acids could be oxidized by $HO^{\bullet}$, during the process, triplet-excited carbonyl ($^3R\!\!=\!\!O^*$), singlet ($^1P^*$),
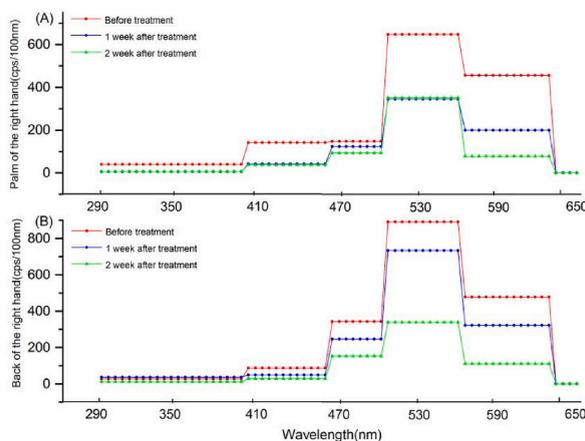
Fig. 5. The UPE spectral distribution of the right hand of type 2 diabetes patients with Qi-Yin deficiency before treatment and after treatment for 1 and 2 weeks. (A) The palm of the right hand. (B) The back of the right hand.
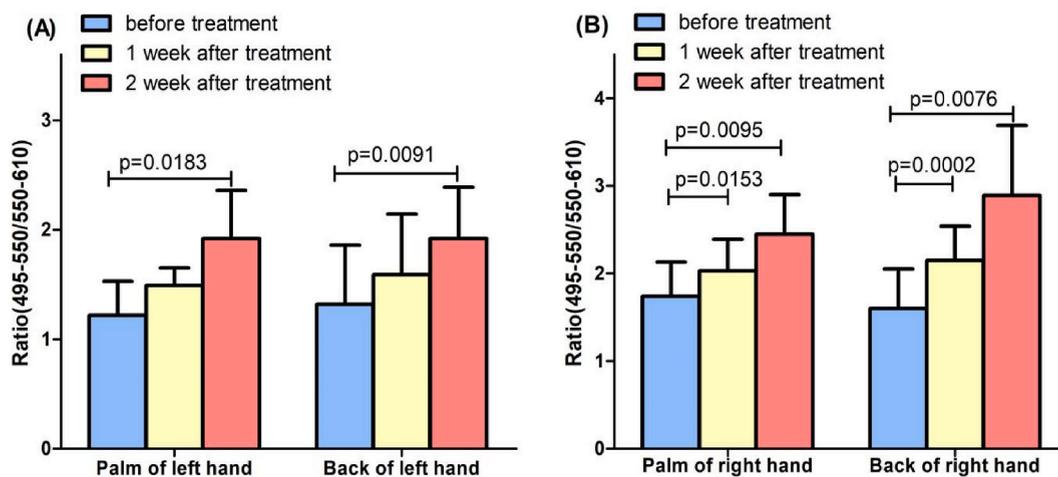
Fig. 6. The ratio of photon counts between 495–550 nm and 550–610 nm of both hands of type 2 diabetes patients with Qi-Yin deficiency before treatment and after 1 and 2 weeks of treatment. (A) The left hand. (B) The right hand.

Table 1
The syndrome scores and blood glucose level of T2DM patients with Qi-Yin deficiency(Mean ± Std.).

Category	Before the treatment	After 1 week of treatment	After 2 weeks of treatment
Syndrome scores	26.09 ± 2.21	19.36 ± 1.96*	9.72 ± 1.74*
Blood glucose level	10.03 ± 3.49	9.77 ± 3.69△	9.43 ± 2.65△

*$p < 0.0001$, △$p > 0.05$ compared to before the treatment.
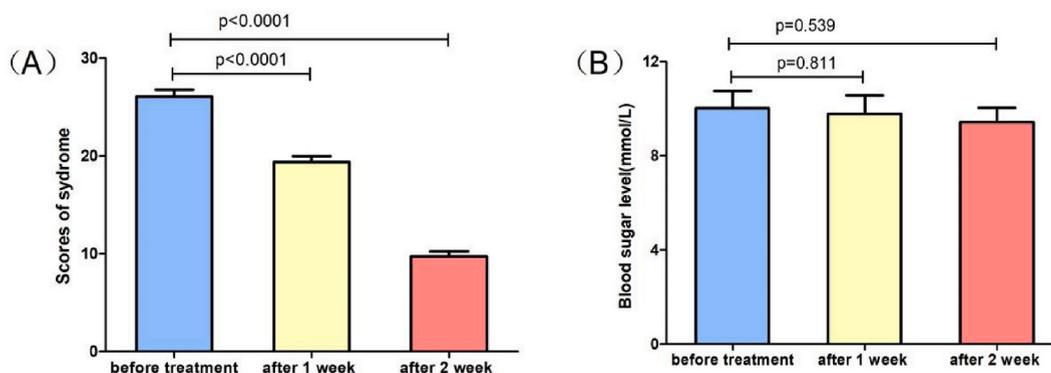
Fig. 7. The syndrome scores(A) and blood sugar level(B) of type 2 diabetes patients with Qi-Yin deficiency before treatment and after treatment for 1 and 2 weeks.

Table 2
Correlation analysis between the ratio (495–550/550–610 nm) and the syndrome scores.

Category	Palm of the left hand	Back of the left hand	Palm of the right hand	Back of the right hand
Correlation coefficient	−0.703	−0.841	−0.819	−0.906
p value	<0.001	<0.001	<0.001	<0.001

and triplet (^{3}P*) excited pigments, and singlet oxygen (^{1}O$_2$) were finally generated [12]. As we mentioned in the above, the high enegy state was not stable, so the ^{3}R═O*,(^{1}P*), (^{3}P*) and ^{1}O$_2$ transition from high energy state to low energy state will produce photons of different wavelength, which was corresponding with 350–550 nm, 550–750 nm and 750–1000 nm, 634 nm and 703 nm, and 1270 nm, respectively.When the physiological or pathological state of the body is abnormal due to the influence of external or internal factors, its metabolic state inevitably changes, and the type and number of corresponding electronically excited species also change, resulting in changes in the intensity and spectral distribution of the UPE [10]. The state of the body can be assessed by detecting and analyzing the
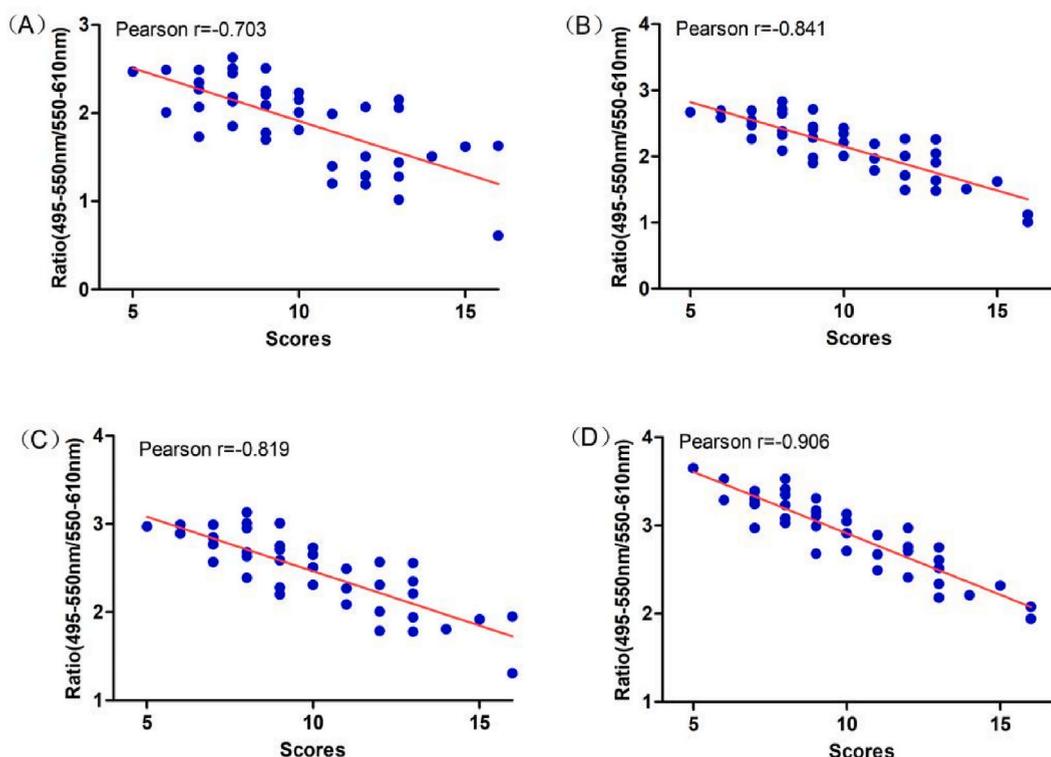
Fig. 8. Correlation analysis between the ratio (495–550 nm/550–610 nm) of the UPE from the palm of the left hand (A), back of the left hand (B), palm of the right hand (C), back of the right hand (D), and the syndrome scores after treatment for 2 weeks. For A–D, p < 0.001.

above changes.

The UPE can characterize the state of the body, and the syndrome of TCM could be characterized by the UPE of the human body [11,21]. Thus, the following questions arise: What is the change law of the human UPE in the process of symptom improvement after TCM treatment? Could the UPE of the human body characterize this improvement? In this study, we measured the UPE intensity and spectral distribution at four sites of hands of T2DM patients with Qi-Yin deficiency before treatment and after 1 and 2 weeks of treatment with TCM. Our results demonstrated that the intensity of UPE in both hands was significantly lower than that before treatment, and decreased gradually with the course of the treatment. Many previous studies have also shown that in the state of disease, the photon intensity is higher than that in the healthy state [12,13,17,22,25–30]. Importantly, our experimental results also showed that the UPE intensity tended to return to normal during the recovery of the body to a healthy state, i.e., the improvement of the body state could be characterized by the UPE detection.

In our previous study, we found that the peak of spectral distribution may serve as an indicator of the body's metabolism [12,13]. In our study, the spectral distribution at the four sites of hands of T2DM patients with Qi-Yin deficiency before treatment and after treatment with TCM for 1 and 2 weeks was measured. The results demonstrated that the photon counts before treatment were higher than those after the treatment for almost the whole wavelength range. Especially, there were obvious differences in the ratio of photon counts between the 495–550 nm and 550–610 nm wavelength of both left and right hands, i.e., the ratio of 495–550 nm and 550–610 nm wavelength tended to increase as the course of treatment increased for both hands, but such a trend was not observed in other ratios.

As mentioned previously, the 495–550 nm and 550–610 nm ranges, respectively, corresponds to the 3R═O*) and 1P* transition from high energy state to the ground state. The ratio (495–550 nm/550–610 nm) tended to increase, suggesting the changes in the type and number of electronically excited species after treatment with TCM, since there were changes in the complex biochemical reactions and energy transition of the human body occurred after treatment. This change was occurred in the patients, who were treated with TCM for 1 week and 2 week, resulted in the change of structural change of the emitter, which is corresponding to different wavelength of photon emission.

Another important finding in our study was that the spectral ratio of 495–550 nm and 550–610 nm wavelength negatively correlated with the corresponding syndrome scores for both hands (for the left palm: $R^2 = -0.703$, p < 0.001; for the left back: $R^2 = -0.841$, p < 0.001; for the right palm: $R^2 = -0.819$, p < 0.001; and for the right back: $R^2 = -0.906$, p < 0.001).This indicates that the degree of symptoms improvement after TCM can be characterized by the ratio (495–550 nm/550–610 nm).It was concluded that the spectral distribution of UPE is sensitive to symptom improvement and could be used as a potential tool for evaluating the therapeutic effect.

5. Conclusions

We reported the UPE intensity and spectral distribution in T2DM patients with Qi-Yin deficiency before treatment and after treatment with Chinese herbs for 1 and 2 weeks using a high-sensitivity two-hand UPE-detection system. Our data showed that the UPE intensity decreased gradually after treatment for 1 and 2 weeks. There were obvious differences in the ratio of photon counts between the wavelength ranges of 495–550 nm and 550–610 nm of both hands in T2DM patients with Qi-Yin deficiency after 1 and 2 weeks of treatment compared with before treatment. The ratio between the wavelength ranges of 495–550 nm and 550–610 nm tended to increase as the course of treatment increased for both hands, and this trend was not observed in other ratios.

There was a significant negative correlation between the spectral ratio (495–550/550–610 nm) and the corresponding syndrome scores of TCM. Our results indicate that the UPE intensity and the spectral ratio (495–550/550–610 nm) from the human body contain abundant metabolic information and are closely related to the state of the body, i.e., the syndrome of TCM. The relationship between the ROS in different treatment stages and the spectral components of the UPE from the body should be studied next. In our opinion, the therapeutic effect of TCM in T2DM patients with Qi-Yin deficiency can be shown at the level of UPE, and the UPE could be a potential and noninvasive tool for evaluating the therapeutic effect of TCM in patients with T2DM.

Ethics statement

The study was approved by the Ethics Committee of Shandong Medical Biotechnology Research Center, and the ethics approval number is 2020-03.

Author contributions

YMN and HJX designed the research study. YMN, ZZW, and FJL performed the research. YZL and ZYB provided help and advice on the diagnostics and treatment of the syndrome of TCM. LJY, PJX, and FH analyzed the data. YMN and ZZW wrote the manuscript. All authors contributed to the changes in the manuscript. All authors read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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