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ORIGINAL RESEARCH

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Hongjing Qiwei formula combined with tadalafil in the treatment of erectile dysfunction associated with type 2 diabetes mellitus: study protocol for a double-blind, single-dummy, randomized controlled trial

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Abstract

Background: Traditional Chinese Medicine (TCM) has been utilized for the treatment of sexual dysfunction in China for thousands of years, and in recent years, despite advancements in this field, the efficacy of phosphodiesterase-5 inhibitors (PDE5i) for managing diabetes mellitus erectile dysfunction (DMED) remains limited. Therefore, many patients with type 1 DMED or type 2 diabetes mellitus erectile dysfunction (T2DMED) are turning to combination therapy involving PDE5i and TCM. The Hongjing Qiwei (HJQW) formula, a traditional TCM formulation, has been used to address DMED based on TCM principles. **Methods**: This study presents a randomized, controlled, double-blind, single-dummy clinical trial protocol designed to evaluate the efficacy and safety of combining TCM with PDE5i in the treatment of T2DMED. The participants will be randomly assigned to one of two groups: the treatment group, receiving tadalafil 5 mg combined with the HJQW formula, and the control group, receiving tadalafil 5 mg combined with a placebo mimicking the HJQW formula. The intervention will be administered over 6 consecutive weeks, with an additional 4 weeks allocated for follow-up. Primary and secondary outcomes will be assessed at baseline and at weeks 2, 4, 6 and 10. **Results**: Although emerging evidence suggests that TCM therapies may enhance erectile function in patients with sexual dysfunction, their specific efficacy in T2DMED remains underexplored. **Conclusions**: This study aims to address this gap and provide empirical evidence supporting the use of combination therapy in treating male sexual dysfunction. **Clinical Trial Registration**: This study was registered with http://www.chictr.org.cn as: ChiCTR2400085314.

Keywords

Diabetes mellitus; Erectile dysfunction; Hongjing Qiwei formula; Protocol

Fórmula Hongjing Qiwei combinada con tadalafilo en el tratamiento de la disfunción eréctil asociada a la diabetes mellitus de tipo 2: protocolo de estudio para un ensayo controlado aleatorizado, doble ciego y con un único inóculo

Resumen

Antecedentes: La medicina tradicional China (MTC) se ha utilizado para el tratamiento de la disfunción sexual en China durante miles de años, y en los últimos años, a pesar de los avances en este campo, la eficacia de los inhibidores de la fosfodiesterasa-5 (IPDE-5) para el manejo de la diabetes mellitus disfunción eréctil (DMDE) sigue siendo limitada. Por lo tanto, muchos pacientes con diabetes mellitus tipo 1 DMDE o diabetes mellitus tipo 2 con disfunción eréctil (T2DMDE) están recurriendo a la terapia de combinación que involucra IPDE-5 y MTC. La fórmula Hongjing Qiwei (HJQW), una formulación tradicional de MTC, se ha utilizado para tratar la DMDE sobre la base de principios de MTC. **Métodos**: Este estudio presenta un protocolo de ensayo clínico aleatorizado, controlado, doble ciego, diseñado para evaluar la eficacia y la seguridad de la combinación de MTC con IPDE-5 en el tratamiento de T2DMDE. Los participantes serán asignados al azar a uno de dos grupos: el grupo de tratamiento, que recibe 5 mg de tadalafilo combinado con la fórmula HJQW, y el grupo de control, que recibe 5 mg de tadalafilo combinado con un placebo que imita la fórmula HJQW. La intervención se administrará durante 6 semanas consecutivas, con 4 semanas adicionales asignadas para el seguimiento. Los resultados primarios y secundarios se evaluarán al inicio y a las semanas 2, 4, 6 y 10. **Resultados**: Aunque la evidencia emergente sugiere que los tratamientos con MTC pueden mejorar la función eréctil en pacientes con disfunción sexual, su eficacia específica en T2DMDE sigue siendo poco explorada. **Conclusiones**: Este estudio tiene como objetivo abordar esta brecha y proporcionar evidencia empírica que apoye el uso de la terapia combinada en el tratamiento de la disfunción sexual masculina. **Registro del Ensayo Clínico**: Este estudio fue registrado en http://www.chictr.org.cn con el número: ChiCTR2400085314.

Palabras Clave

Diabetes mellitus; Disfunción eréctil; Fórmula Hongjing Qiwei; Protocolo

1. Introduction

Diabetes mellitus (DM) is a major chronic disease recognized globally by the World Health Organization, with projections estimating that the number of DM patients will reach approximately 783.2 million by 2045 [1]. Men with DM are at a significantly higher risk of developing erectile dysfunction (ED), being three times more likely to experience this condition compared to healthy men [2]. Notably, up to 75% of male patients with DM report a diminished quality of life due to comorbid ED [2]. In China, type 2 diabetes mellitus (T2DM) constitutes about 90% of the DM population [3]. T2DM-related erectile dysfunction (T2DMED) involves complex neurovascular pathophysiological mechanisms [4] and is considered more challenging to treat than psychogenic ED, often classified as refractory ED [5].

In recent decades, significant advancements have been made in the treatment of ED, particularly for men with T2DMED. Phosphodiesterase-5 inhibitors (PDE5i) are recommended as the first-line therapy for T2DMED [6]. Despite their widespread use, the efficacy and long-term satisfaction with PDE5i are frequently suboptimal. Research indicates that approximately 11% to 44% of ED patients do not respond positively to PDE5i therapy alone [7], and the effectiveness of PDE5i in men with T2DMED is lower compared to non-T2DM patients with ED [8]. The efficacy of PDE5i is contingent upon the formation of endogenous nitric oxide (NO), and severe endothelial dysfunction and neurological damage resulting from T2DM may lead to a deficiency of endogenous bioavailable NO, thus limiting the effectiveness of PDE5i alone [9]. Consequently, most current clinical studies for T2DMED involve combining PDE5i with other therapeutic modalities [10], with evidence suggesting that combination therapy offers advantages [11].

In several Asian countries, Traditional Chinese Medicine (TCM) formulas have increasingly been used to treat ED [12], and various clinical trials have confirmed their efficacy in managing ED [13]. However, there is a paucity of clinical trials specifically evaluating the efficacy of TCM formulas in T2DMED. The Hongjing Qiwei (HJQW) formula, developed in accordance with TCM principles, has been used in China to treat ED. This formula includes Rhodiola Rosea, Rhizoma Polygonati, and other herbs known for their properties in strengthening the kidney and enhancing blood circulation, thereby improving erectile function. Preliminary studies on the HJQW formula and other classical TCM formulations for T2DMED have indicated that side effects are generally limited to occasional gastrointestinal reactions, such as diarrhea, which typically resolve upon discontinuation of the medication. Notably, previous research has not investigated the combined use of TCM formulas and PDE5i in T2DMED. Thus, we designed this present study to address this gap by evaluating the efficacy and safety of combining PDE5i with HJQW granules in patients with T2DMED.

2. Materials and method

2.1 Study design

This research will be conducted as a randomized controlled trial in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 guidelines [14]. A total of 76 participants will be enrolled, with 38

participants allocated to each of the two groups. Upon signing the informed consent form, participants will undergo a 6-week treatment period, receiving either tadalafil combined with the HJQW formula or tadalafil combined with a placebo resembling the HJQW formula (Table 1 and Fig. 1).

2.2 Study participants

2.2.1 Recruitment strategy

The participants will be screened and recruited from June 2024 to March 2025 at the Department of Andrology, Xiyuan Hospital, Chinese Academy of Traditional Chinese Medicine. The trial procedures will be thoroughly explained to researchers, who will undergo systematic training. Before enrollment, the participants will be required to sign an informed consent form. Participation in the trial is entirely voluntary, and participants have the right to withdraw at any time without penalty.

2.2.2 Diagnostic criteria

The diagnostic criteria for diabetes mellitus (DM) will follow the American Diabetes Association Guidelines [15], which include:

(a) Typical diabetic symptoms with a plasma glucose level $\geq$11.1 mmol/L at any time;

(b) Typical diabetic symptoms with a fasting plasma glucose level $\geq$7.0 mmol/L;

(c) Typical diabetic symptoms with an abnormal oral glucose tolerance test;

(d) Typical diabetic symptoms with a 2-hour oral glucose tolerance test blood glucose level $\geq$11.1 mmol/L;

(e) Typical diabetic symptoms with a Hemoglobin A1C (HbA1c) level $\geq$6.5%.

For individuals with unclear hyperglycemia, a repeated diagnosis will be required. Typical diabetic symptoms include excessive thirst, polyuria, polyphagia, and unexplained weight loss.

The diagnostic criteria for ED will follow the European Association of Urology guidelines [16], which include:

(a) Inability to achieve or maintain an erection sufficient for satisfactory sexual intercourse for more than 3 months;

(b) The severity of ED will be assessed using the International Index of Erectile Function-5 (IIEF-5); an IIEF-5 score $\leq$21 indicates the presence of ED.

2.2.3 Inclusion criteria

Participants must meet the following criteria:

(a) Diagnosis of T2DM and ED, with T2DM occurring prior to the onset of ED;

(b) Meet TCM diagnostic criteria for kidney deficiency and

TABLE 1. Trial process chart.

Time point	Baseline		Treatment phase			Follow-up phase
	Week 0	Week 1	Week 2	Week 4	Week 6	Week 10
Enrollment						
Inclusion/exclusion criteria	X					
Informed consent[a]	X					
Physical examination	X					
Randomization and allocation	X					
Demographic characteristics[b]	X					
Intervention						
Treatment group		X	X	X	X	
Control group		X	X	X	X	
Assessment						
IIEF-5	X		X	X	X	X
EHS	X		X	X	X	X
SEP2	X		X	X	X	X
SEP3	X		X	X	X	X
CMSS	X		X	X	X	X
Safety evaluation						
General condition	X		X	X	X	X
Adverse events			X	X	X	X
Laboratory assessments[c]	X		X	X	X	X

"X" indicates yes; IIEF-5: International Index of Erectile Function-5; EHS: Erection Hardness Score; SEP: Sexual Encounter Profile; CMSS: Chinese Medicine Symptoms Score; [a]: Informed consent will be signed by the participants themselves and the questionnaires will be filled out in person; [b]: Demographic characteristics consist of body mass index, marital status, and comorbidities; [c]: Laboratory evaluations consist of routine blood and urine tests, liver function (alanine transaminase and aspartate aminotransferase levels), kidney function (blood urea nitrogen and creatinine levels), and electrocardiography.

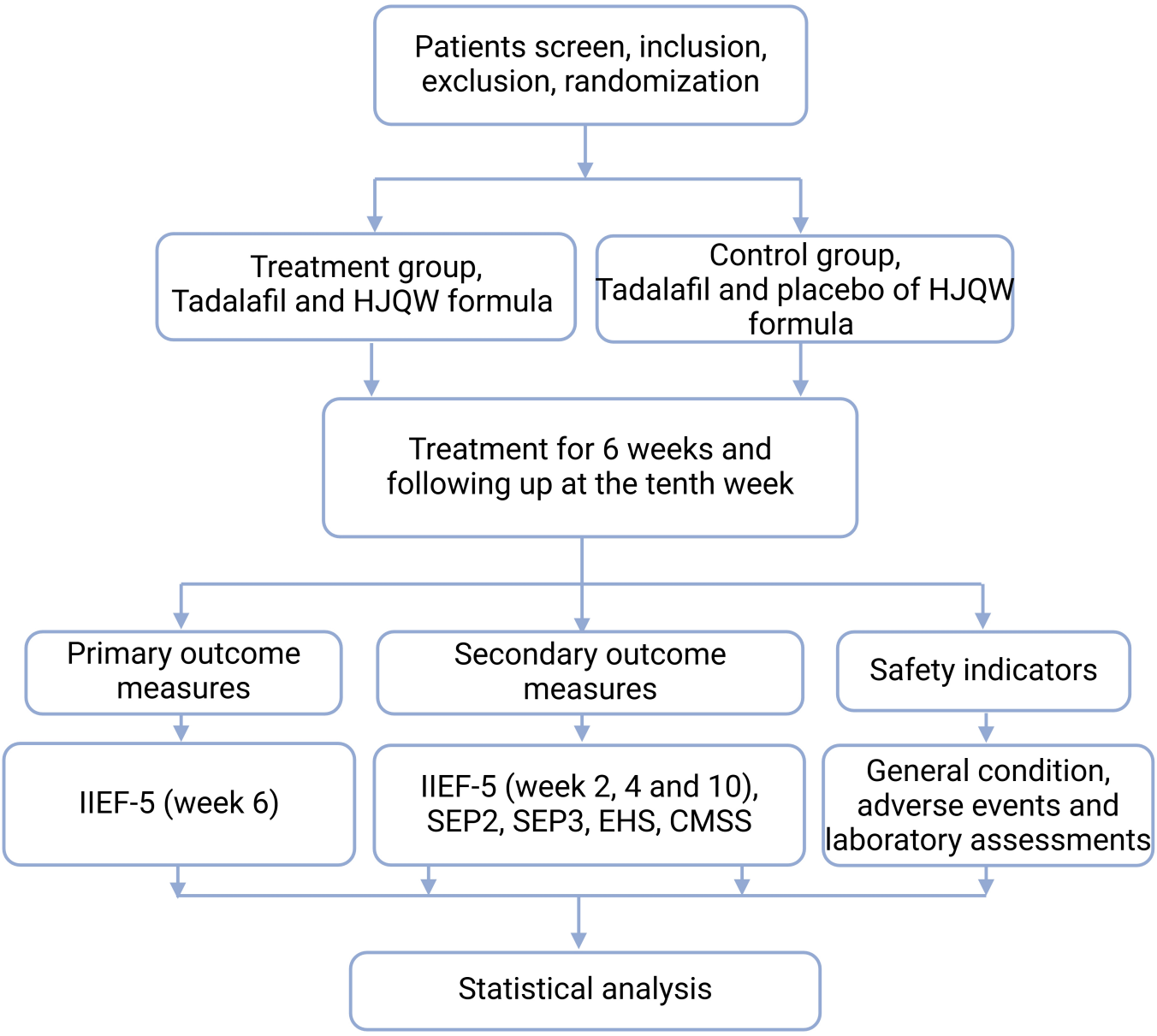

FIGURE 1. Study flowchart. IIEF-5: International Index of Erectile Function-5; EHS: Erection Hardness Score; SEP2: Sexual Encounter Profile 2; SEP3: Sexual Encounter Profile 3; HJQW: Hongjing Qiwei; CMSS: Chinese Medicine Symptoms Score.

blood stasis;

(c) IIEF-5 score $\leq$21;

(d) Age between 22 and 65 years;

(e) HbA1c $<$7%;

(f) Have a regular sexual partner and a stable sex life, with a frequency of $\geq$1 time per week during treatment;

(g) Have accepted and signed the informed consent form.

2.2.4 Exclusion criteria

Participants will be excluded if they meet any of the following criteria:

(a) Psychiatric or neurological disorders, a self-rating anxiety scale $>$69, a self-rating depression scale $>$72, or inability to guarantee discontinuation of anti-anxiety or depression medication during the trial;

(b) Clinically significant penile anatomical or structural abnormalities, such as micropenis, congenital curvature of the penis, or penile cavernous fibrosis;

(c) Other sexual dysfunction disorders (*e.g.*, ejaculatory disorders, premature ejaculation) or incurable endocrine disorders (*e.g.*, hypogonadotropic hypogonadism, hyperprolactinemia, hyper/hypothyroidism, Cushing's disease, or hypopituitarism);

(d) ED resulting from spinal cord/nerve injury, radical prostate cancer, or other trauma, surgery or radiation therapy;

(e) History of heart disease with any of the following:

① Myocardial infarction, shock, or life-threatening arrhythmia within the last 6 months;

② Unstable angina pectoris within the last 3 months or angina pectoris during previous sexual intercourse;

③ Coronary artery bypass graft or percutaneous coronary intervention within the last 3 months;

④ New York Heart Association class $\geq$II heart failure

within the past 6 months;

(f) Significant hepatic or renal dysfunction (alanine transaminase and/or aspartate aminotransferase >1.5 times the upper limit of normal, or creatinine >20% of the upper limit of normal);

(g) History of severe central nervous system injury (*e.g.*, cerebrovascular disease, inflammatory brain disease, craniocerebral trauma or spinal cord injury) or peripheral musculoskeletal neurologic disease within the past 6 months;

(h) History of abnormal color vision, pigmentary retinitis, macular degeneration, or non-arteritic anterior ischemic optic neuropathy;

(i) History of malignant tumors;

(j) History of sudden hearing loss or hearing loss;

(k) Use of penile prostheses;

(l) Allergy to PDE5i drugs or ineffective treatment with PDE5i resulting in adverse reactions leading to discontinuation;

(m) Regular use (for more than 1 month) and inability to discontinue nitrates or NO donors, antiandrogens, guanylate cyclase agonists, or other ED medications during the study;

(n) Sexual partner is breastfeeding, pregnant, preparing for pregnancy, or restricts sexual activity due to gynecologic conditions;

(o) Participation in other experimental studies within the last 3 months.

2.2.5 Termination criteria

The following criteria will determine the termination of participation from the trial:

(a) Worsening of the participant's condition as judged by the physician, leading to discontinuation of the clinical trial and alternative treatment to protect the participant. Such cases will be considered invalid.

(b) Occurrence of comorbidities or complications that render the participant unsuitable for continued participation.

(c) Poor compliance with the trial protocol, including the use of prohibited drugs.

(d) Emergence of adverse events or serious adverse events.

(e) Unblinding of the participant.

Case record forms will be retained following case discontinuation, and data on efficacy and adverse reactions will be analyzed using the last available test result. Researchers are required to document reasons for any participant withdrawal and provide a follow-up treatment plan tailored to the participant's needs and preferences. Additionally, therapeutic outcomes at the time of discontinuation will be carefully evaluated to ensure accurate reporting of results.

2.2.6 Sample size

Based on preclinical trials, the mean alteration in IIEF-5 scores for HJQW formula + tadalafil 5 mg was 4.3 $\pm$ 1.9, while previous studies [17] reported a mean alteration of 2.9 $\pm$ 1.5 for ED patients with T2DM receiving tadalafil 5 mg daily. Sample size calculations were performed using PASS 2021 software (NCSS LLC., Kaysville, UT, USA) with parameters $\alpha = 0.05$, $\beta = 0.1$, and power = 0.9. Assuming a 1:1 ratio between the treatment and control groups, 33 participants per group were calculated, with an anticipated dropout rate of 15%. Thus, the trial will include a total of 76 participants.

2.2.7 Randomization and allocation

Simple randomization will be used with a 1:1 allocation ratio between the treatment and control groups, and statistical professionals will generate the random allocation codes using SAS software (version 9.4, SAS Institute, Cary, NC, USA). The participants will be assigned to intervention and observation groups based on the serial numbers corresponding to the randomized coding table. Group information will be sequentially numbered and concealed in sealed, opaque envelopes.

2.2.8 Blinding

To prevent bias, all data entry staff, investigators, statistical analysts, and participants will be blinded to group assignments. The HJQW formula placebo will be indistinguishable from the real medication in terms of shape, size, color, weight, labeling and packaging [18]. Unblinding will be permitted if adverse effects occur to ensure participant safety and appropriate management.

2.3 Intervention

The participants will be randomly assigned to either the treatment group or the control group, with each group consisting of 38 participants. General health guidance will be provided based on previous studies [19, 20]. All T2DMED participants will receive health education, active physical exercise recommendations, and specialized dietary and glucose-lowering advice tailored to their conditions. Participants will be instructed to report any significant fluctuations in blood glucose to the researchers, who will evaluate these changes and adjust the glucose-lowering program if necessary. In addition, the participants will also be advised to refrain from smoking, alcohol consumption, the use of other erection-assisting devices during sexual activity, and other ED medications.

The treatment group will receive tadalafil 5 mg combined with the HJQW formula, while the control group will receive tadalafil 5 mg combined with a placebo of the HJQW formula. Tadalafil will be sourced from Eli Lilly and Company. The HJQW formula and its placebo will be provided by the Pharmacy Department of Xiyuan Hospital, China Academy of Chinese Medical Sciences, and have undergone aqueous extraction and proprietary processing. Participants will take HJQW or its placebo twice daily, with a daily dosage equivalent to 54 g of raw medicine. All participants will take 5 mg of tadalafil before bedtime every night, with the intervention period being 6 weeks.

2.4 Outcome measures

The primary outcome measure for this study is the IIEF-5 score at week 6. The IIEF-5 scale is a simplified questionnaire with five questions related to erections, commonly used to evaluate erectile function and the extent of ED [21].

Secondary outcome measures include IIEF-5 scores at weeks 2, 4 and 10. Penile erectile hardness and its correlation with the success of sexual intercourse will be assessed using the Erection Hardness Score (EHS) [22]. The EHS

questionnaire, which involves four scales without a time limit, is designed to be straightforward and minimize subjectivity. Additionally, the Chinese Medicine Symptoms Score (CMSS) will be evaluated based on changes at four-time points in comparison to baseline. The Sexual Encounter Profile (SEP) questions, specifically SEP2 and SEP3, will be used to assess penile penetration and completed intercourse [23]. The percentage change in "yes" responses to SEP2 and SEP3 questions at weeks 2, 4, 6 and 10 will be compared to baseline.

Safety assessments will include a general well-being evaluation, laboratory tests, and monitoring of adverse events (AEs). General condition analysis will involve physical examinations and vital sign checks during each visit. Laboratory tests will include standard blood and urine tests, liver function assessments (alanine transaminase and aspartate aminotransferase levels), kidney function evaluations (blood urea nitrogen and creatinine levels), and electrocardiograms, performed at the start of the study, and at weeks 2, 4 and 6. The study evaluators will record all AEs.

2.5 Data management and quality control

The data will be collected by two experienced research assistants. To prevent bias, the researchers and data analysts will remain blinded to treatment allocations until statistical analysis is complete. The principal investigator will oversee the trial's coordination, including recruitment, intervention, and follow-up procedures. A quality control team will conduct biweekly reviews to ensure the study's quality, establishing and maintaining a treatment control and quality assurance system. Effective management measures will be implemented throughout both the clinical trial and data processing phases.

2.6 Data analysis

Statistical analyses will be performed using SPSS software (version 25.0, IBM, Chicago, IL, USA) and Origin software (version 2022, OriginLab, Northampton, MA, USA) for graphical representations. The significance level is set at $\alpha = 0.05$, with $p < 0.05$ indicating statistical significance. Measurement data that follow a normal distribution will be presented as mean $\pm$ standard deviation (SD). Paired-sample *t*-tests will be used for within-group comparisons, and independent-sample *t*-tests will be used for between-group comparisons. Data not meeting normal distribution will be expressed as median (interquartile range), with the Wilcoxon rank-sum test used for between-group comparisons, and the Mann-Whitney U test for comparisons between two groups. Repeated measures data will be analyzed using analysis of covariance (ANCOVA). Count data will be reported as frequencies (%), with the chi-square test applied for unordered categorical data.

3. Discussion

The pathogenesis of T2DMED is multifaceted, involving mechanisms such as endothelial cell dysfunction and smooth muscle contractile dysfunction [24, 25]. Despite the availability of various treatment options for T2DMED, many therapies exhibit limited efficacy, often necessitating surgical interventions to restore erectile function [26]. Oral medications remain the preferred treatment modality due to their convenience and non-invasive nature, which enhances patient compliance. In recent years, herbal formulas have garnered increasing attention for the treatment of ED [27]. Meta-analyses indicate that combining Chinese herbs with PDE5i can improve efficacy without significantly increasing adverse events (AEs) [28]. However, numerous clinical studies investigating herbal formulas in conjunction with PDE5i have not specified the type of ED or categorized participants according to their ED classification [29, 30]. Consequently, the effectiveness of herbal formulas in treating T2DMED and their potential advantages over PDE5i alone remains unclear. Additionally, there is a lack of research on the specific mechanisms of the HJQW formula in T2DMED. Thus, this clinical trial aims to confirm its efficacy and safety, followed by further investigation into the mechanism of action through subsequent animal studies.

Combination therapies have demonstrated efficacy in managing complex ED cases. For instance, combining PDE5i with vacuum erectile devices has proven effective in post-prostatectomy ED [31]. Similarly, low-intensity extracorporeal shockwave therapy combined with vacuum erectile devices has shown promise in treating DMED [32]. However, no published studies have evaluated the efficacy of combining PDE5i with TCM for T2DMED. Thus, our trial incorporates this combination therapy approach to explore potentially more effective management strategies. The rationale for using combination therapy is twofold: T2DMED is often resistant to treatment, and TCM alone may not provide immediate effects comparable to PDE5i. Therefore, we excluded the use of a placebo alone to avoid ethical concerns and potential non-compliance. Additionally, the immediate efficacy of PDE5i necessitates that we avoid comparing TCM alone with PDE5i alone.

Lastly, outcome indicators for this study will be based on our previous research, utilizing the internationally recognized IIEF-5 as the primary efficacy measure [33, 34]. The trends in SEP2, SEP3 and EHS will be analyzed using repeated measures ANOVA to further evaluate erectile function. Our bibliometric analysis of ED has shown that TCM is frequently applied in China [35, 36], with TCM practitioners often classifying ED into various syndrome types [37]. Notably, the syndrome of kidney deficiency and blood stasis is prevalent among ED patients, particularly in T2DMED cases [35]. Therefore, this study will include T2DMED participants with these TCM syndrome types and assess the related TCM scale, which will not only evaluate improvements in erectile function but also provide insight into the relief of other associated symptoms.

4. Conclusions

To our knowledge, this study represents the first protocol designed to evaluate the efficacy and safety of combining PDE5i with a TCM formula for the treatment of T2DMED. This treatment strategy holds the potential to offer significant benefits to patients who are not candidates for surgical interventions, thereby mitigating adverse events associated with local physical therapies.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

HW—drafted the trial protocol. FW and JWZ—critically supervised and corrected the manuscript. JWZ, HYC, AMW, DCL, DYM and ZWZ—were referred to and recruited patients. All the authors designed the trial and critically reviewed the manuscript. All authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study involving human participants was reviewed and approved by the Research Ethical Committee of Xiyuan Hospital, China Academy of Chinese Medical Sciences (2024XLA056-2). And the study has also been registered with the http://www.chictr.org.cn (ChiCTR number is ChiCTR2400085314). The patients/participants provided their written informed consent to participate in this study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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