Postprint of a Randomized Controlled Trial of Gehu Tiaozhi Formula for Patients with Metabolic Syndrome

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Abstract

Background Approximately one-quarter of the global population suffers from metabolic syndrome (MetS). In recent years, the prevalence of MetS in China has also exhibited a year-by-year upward trend, posing a serious threat to life and health. Traditional Chinese medicine treatment for MetS offers advantages of multiple targets and multiple pathways; however, there is currently a lack of high-quality randomized controlled trials and real-world studies in clinical practice.

Objective To observe the effects of Gehu Tiaozhi Formula (Puerariae Radix 6 g, Dendrobii Officinalis Caulis 6 g) on waist circumference, body weight, body fat percentage, and glucose-lipid metabolism in patients with MetS.

Methods From June 2021 to November 2022, 84 patients with MetS from the outpatient and inpatient departments of Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine were prospectively selected as study subjects. Using SPSS 25.0 statistical software with a specified random seed, subjects were randomly allocated to the Gehu group (42 cases) and the control group (42 cases). The Gehu group received Gehu Tiaozhi Formula granules (Puerariae Radix 6 g, Dendrobii Officinalis Caulis 6 g), taken once in the morning and once in the evening on an empty stomach, one pack per dose, dissolved in water, continuously for 8 weeks. The control group received placebo granule intervention, taken once in the morning and once in the evening on an empty stomach, one pack per dose, continuously for 8 weeks. During the intervention period, both groups received identical health education (including guidance on dietary plans and exercise prescriptions). After 8 weeks of intervention, comparative analysis was conducted on the two groups' patients' waist circumference (WC), body weight, body mass index (BMI), body fat percentage (BFP), triglycerides (TG), total cholesterol (TC), high-density lipoprotein

cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and fasting blood glucose (FBG).

Results Ultimately, 41 cases in the Gehu group and 41 cases in the control group completed the 8-week intervention study. Before treatment, there were no statistically significant differences between the two groups in WC, body weight, BMI, and BFP (P>0.05). The differences in WC, body weight, BMI, and BFP before and after treatment between the two groups were statistically significant (P<0.05). Before treatment, there were no statistically significant differences between the two groups in TG, TC, HDL-C, LDL-C, and FBG (P>0.05). The differences in TG, TC, and FBG before and after treatment between the two groups were statistically significant (P<0.05).

Conclusion Gehu Tiaozhi Formula can effectively improve WC, body weight, BMI, BFP, TG, TC, and FBG in MetS patients, with favorable safety.

Full Text

Abstract

Background Approximately one-quarter of the global population suffers from metabolic syndrome (MetS). In recent years, the prevalence of MetS in China has also shown an upward trend year by year, posing a serious threat to life and health. Traditional Chinese medicine offers multi-target, multi-link advantages in treating MetS, but high-quality randomized controlled trials and real-world studies are currently lacking in clinical practice.

Objective To observe the effects of Gehu Tiaozhi Decoction (Puerariae Lobatae Radix 6 g, Dendrobii Officinalis Caulis 6 g) on waist circumference, body weight, body fat percentage, and glucose and lipid metabolism in patients with MetS.

Methods From June 2021 to November 2022, 84 patients with MetS were prospectively selected from the outpatient and inpatient departments of Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine. Using SPSS 25.0 statistical software with a specified random seed, subjects were randomly divided into the Gehu group (42 cases) and the control group (42 cases). The Gehu group received Gehu Tiaozhi Decoction granules (Puerariae Lobatae Radix 6 g, Dendrobii Officinalis Caulis 6 g), taken orally once in the morning and once in the evening on an empty stomach, one packet each time, for 8 consecutive weeks. The control group received placebo granules with the same administration schedule. During the intervention, both groups received identical health education (including dietary plans and exercise prescription guidance). After 8 weeks of intervention, waist circumference (WC), body weight, body mass index (BMI), body fat percentage (BFP), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and fasting blood glucose (FBG) were compared between the two groups.

Results Ultimately, 41 patients in the Gehu group and 41 patients in the control group completed the 8-week intervention study. No statistically significant differences were found between the two groups in WC, body weight, BMI, or BFP before treatment (P>0.05). The differences in WC, body weight, BMI, and BFP between before and after treatment were statistically significant between the two groups (P<0.05). Similarly, no statistically significant differences were observed in TG, TC, HDL-C, LDL-C, or FBG between the two groups before treatment (P>0.05). The differences in TG, TC, and FBG between before and after treatment were statistically significant between the two groups (P<0.05).

Conclusion Gehu Tiaozhi Decoction can effectively improve WC, body weight, BMI, BFP, TG, TC, and FBG in MetS patients with good safety.

Keywords Metabolic syndrome; Puerariae Lobatae Radix; Dendrobii Officinalis Caulis; Traditional Chinese medicine; Clinical research

Introduction

Since the 21st century, with improvements in socioeconomic conditions and greater refinement and diversification of food varieties, combined with changes in lifestyle and dietary structure, metabolic syndrome (MetS) has become a global epidemic. According to the International Diabetes Federation, approximately 20-25% of the world's population is diagnosed with MetS [1], with epidemiological studies projecting that the global prevalence will increase to 53% by 2035 [2]. Data from the 2011-2016 U.S. National Health and Nutrition Examination Survey showed that 34.7% of American adults over 20 years met the diagnostic criteria for MetS [3]. Analysis of data from the 2010-2012 China National Nutrition and Health Survey revealed that the prevalence of MetS among Chinese adults was 11.0%, increasing with age [4]. MetS can easily induce systemic metabolic disorders and is a major risk factor for cardiovascular and cerebrovascular diseases. Therefore, the prevention and treatment of MetS has become an urgent public health priority in modern society.

Currently, the main measures for preventing and treating MetS recognized by the medical community are therapeutic lifestyle interventions and comprehensive treatment primarily involving regular administration of hypoglycemic, lipid-lowering, and antihypertensive drugs. However, there are no effective multi-target, multi-link therapeutic drugs for MetS. Such treatment regimens require high patient compliance, are difficult to maintain long-term, and impose a heavy economic burden. Effective interventions for MetS require further exploration. Traditional Chinese medicine classifies the clinical symptoms of MetS under categories such as "obesity," "thirst," "fullness," and "spleen heat." Based on TCM theory, numerous clinical practices have used herbal extracts, herbal formulas, and acupuncture to treat MetS. Academician Tong Xiaolin proposed dividing MetS into four stages—stagnation, heat, deficiency, and damage—and suggested using Xiaoxianxiong Decoction to regulate the state of phlegm-heat intermingling, with additions of Weilingxian, Hongqu, and mulberry leaf, mul-

berry branch, and mulberry root bark to respectively reduce blood lipids, glucose, and uric acid [5]. Han Xiao et al. [6], guided by the concept of "dredging meridians and regulating viscera," used acupuncture combined with massage to treat MetS patients with liver-stomach heat stagnation pattern, finding that it not only reduced various physical and chemical indicators but also effectively decreased waist circumference.

Based on the TCM concept of "preventive treatment," our research group believes that yin deficiency with internal heat represents a key pathological stage and important pattern in the development of MetS. Building on preliminary research and combined with clinical experience, we used Gehu Tiaozhi Decoction to treat MetS patients with yin deficiency and internal heat pattern. Through this randomized controlled trial, we compared and analyzed waist circumference, body weight, body fat percentage, and lipid levels in MetS patients to explore the therapeutic effects and safety of Gehu Tiaozhi Decoction, aiming to provide theoretical basis and clinical guidance for TCM treatment of MetS.

Methods

Study Design and Participants

From June 2021 to November 2022, we prospectively selected 84 patients with MetS from the outpatient and inpatient departments of Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine. Using SPSS 25.0 statistical software with a specified random seed, subjects were randomly assigned to treatment in a 1:1 ratio, with 42 cases in the Gehu group and 42 cases in the control group. Medications were distributed according to each patient's order of visit and drug number, which remained unchanged throughout the study.

Ethics Approval

This study was registered with the Chinese Clinical Trial Registry (registration number: CHICTR190002685) and approved by the hospital's internal ethics committee (approval number: SHDC12019X16). All patients signed informed consent forms.

Inclusion Criteria

(1) Aged 18-75 years, regardless of gender; (2) Met the Western diagnostic criteria for MetS and the pattern differentiation criteria for MetS with yin deficiency and internal heat; (3) Voluntarily signed informed consent and committed to participating in corresponding examinations, treatments, and follow-up visits according to the study protocol.

Exclusion Criteria

(1) Pregnant or lactating women; (2) Patients with severe liver or kidney disease or major cardiovascular and cerebrovascular diseases; (3) Patients allergic to the intervention drugs or with allergic constitution; (4) Patients with extremely poor compliance or mental illness; (5) Patients with secondary obesity caused by hypothyroidism or hypothalamic diseases, postmenopausal obesity due to decreased female glandular function, polycystic ovary syndrome, or drug-induced obesity.

Diagnostic Criteria

Western Medicine Diagnostic Criteria Based on the "Guidelines for the Prevention and Treatment of Type 2 Diabetes in China (2020 Edition)" [7] and "Criteria for Determining Adult Body Weight in China" [8], the criteria were established as follows: (1) Central obesity: waist circumference $\geq$ 85 cm (female), waist circumference $\geq$ 90 cm (male); (2) Hyperglycemia: fasting blood glucose $\geq$ 6.1 mmol/L or 2-hour post-load blood glucose $\geq$ 7.8 mmol/L and/or previously diagnosed diabetes receiving treatment; (3) Hypertension: blood pressure $\geq$ 130/85 mmHg (1 mmHg = 0.133 kPa) and/or previously diagnosed hypertension receiving treatment; (4) Fasting triglycerides (TG) $\geq$ 1.70 mmol/L; (5) Fasting high-density lipoprotein cholesterol (HDL-C) $<$ 1.04 mmol/L. Diagnosis of MetS was confirmed if three or more of the above five items were met.

Traditional Chinese Medicine Diagnostic Criteria Based on the "Guiding Principles for Clinical Research of New Chinese Medicines" [9], the diagnostic criteria for MetS with yin deficiency and internal heat pattern were established as follows: Main symptoms: obesity, dry throat and mouth, polyphagia with easy hunger; Secondary symptoms: thirst with desire for drinking, five-center heat, palpitations and insomnia, dry and bound stools, short and yellow urine; Tongue and pulse: red tongue with little fluid, little coating, thin pulse. Diagnosis of MetS-yin deficiency internal heat pattern required at least one main symptom, 1-2 secondary symptoms, and basic correspondence of tongue and pulse.

Intervention Methods

The Gehu group received Gehu Tiaozhi Decoction granules (Dendrobii Officinalis Caulis 6 g, Puerariae Lobatae Radix 6 g), taken orally once in the morning and once in the evening on an empty stomach, one packet each time, for 8 weeks. The control group received placebo granules with identical administration. During the intervention, both groups received the same health education (including dietary regimen and exercise prescription guidance). Both Gehu Tiaozhi Decoction granules and placebo granules were manufactured by Sichuan Neo-Green Pharmaceutical Technology Development Co., Ltd.

Outcome Measures

Efficacy Indicators (1) Waist circumference (WC): measured before and after treatment with the subject standing with feet 25-30 cm apart, at the midpoint between the uppermost iliac crest and the lowermost bony thorax; (2) Body weight, body mass index (BMI), and body fat percentage (BFP), all measured using the Japanese TANITA Innerscan BC-310; (3) Laboratory indicators including fasting blood glucose (FBG), total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL-C), and HDL-C. Differences in each indicator before and after treatment were recorded.

Safety Indicators Liver and kidney function, serum electrolytes, blood routine, urine routine, and 12-lead electrocardiogram were examined before and after treatment in both groups, with adverse events observed and recorded throughout the treatment process.

Statistical Methods

SPSS 25.0 software was used for data analysis. Normally distributed measurement data were described as ($\bar{x}\pm s$), while skewed distribution data were described as M(QR). For normally distributed data, independent samples t-test or t'-test (when variance was unequal) was used for between-group comparisons; for non-normally distributed data, Wilcoxon rank-sum test was used. Chi-square test was used for between-group comparisons of count data. Two-sided test α was set at 0.05, with $P<0.05$ considered statistically significant.

Results

Baseline Characteristics

During the 8-week intervention period, due to the domestic COVID-19 pandemic, one subject in each group was unable to complete follow-up. Ultimately, 41 patients in the Gehu group and 41 patients in the control group completed the 8-week intervention study. The Gehu group comprised 20 males and 21 females with a mean age of $(54.8\$\pm12.3)years; the control group comprised 21 males and 20 females with a mean age of (56.5
P=0.825; t=-0.610, P=0.544).

Comparison of WC, Body Weight, BMI, and BFP

No statistically significant differences were found between the two groups in WC, body weight, BMI, or BFP before treatment ($P>0.05$). The differences in WC, body weight, BMI, and BFP between before and after treatment were statistically significant between the two groups ($P<0.05$) .

Comparison of Lipid Profile and FBG

No statistically significant differences were found between the two groups in TG, TC, HDL-C, LDL-C, or FBG before treatment ($P>0.05$). The differences in TG,

TC, and FBG between before and after treatment were statistically significant between the two groups ($P<0.05$) .

Safety Indicators

No abnormalities were observed in electrocardiogram, routine blood tests, routine urine tests, liver and kidney function, or other indicators before and after treatment in either group. No serious adverse events occurred during treatment or follow-up, indicating that Gehu Tiaozhi granules have good safety.

Discussion

The results of this study demonstrate that after 8 weeks of intervention, Gehu Tiaozhi Decoction showed superior therapeutic effects compared to placebo in MetS patients, effectively improving waist circumference, body weight, BMI, BFP, TG, TC, and FBG, with good clinical safety.

The clinical symptoms of MetS patients are often not obvious, but metabolic disorders have already occurred in the body, making early diagnosis and treatment key measures for prevention and further development. Traditional Chinese medicine has long embraced concepts of "holism," "preventive treatment," and "treating the same disease with different methods." Using TCM approaches, we can provide preventive treatment and comprehensive regulation for the systemic metabolic disorder state in MetS patients to delay the occurrence of complications. Factors such as improper diet, smoking and alcohol preference, sedentary lifestyle, emotional imbalance, constitutional deficiency, and kidney essence depletion are all related to the onset of MetS.

Through long-term clinical observation and experience, our research group found that MetS patients in the early and middle stages commonly present with obesity, polyphagia with easy hunger, dry throat and mouth, thirst with desire for drinking, five-center heat, and dry stools—indicating entry into the pathological stage of "yin deficiency with internal heat." Gehu Tiaozhi Decoction consists of two herbal medicines: Puerariae Lobatae Radix and Dendrobii Officinalis Caulis. Both have long histories of use as natural medicines with high safety profiles and good therapeutic value. Modern pharmacological research demonstrates they can effectively reduce weight, regulate lipids, and modulate glucose. In the formula, Puerariae Lobatae Radix is sweet and cool, entering the spleen, stomach, and lung meridians, with effects of lifting clear yang qi of the spleen and stomach, generating fluids to relieve thirst, relaxing muscles to reduce fever, and dredging meridians and collaterals. It contains puerarin, daidzein, and daidzin. Studies have shown that puerarin has vasoactive properties with clear advantages in regulating blood lipids and pressure, possibly related to increasing vascular endothelin and nitric oxide levels [11]. Puerarin can improve insulin sensitivity in rat models and prevent further evolution toward MetS [12]. Xiang Fang [13] found through puerarin injection in 63 MetS patients that it can reduce blood lipids and pressure and serves as an excellent insulin sensitizer.

Dendrobii Officinalis Caulis in the formula is sweet and cold, entering the stomach and kidney meridians, with effects of benefiting the stomach, generating fluids, nourishing yin, and clearing heat. It is rich in polysaccharides, alkaloids, polyphenols, amino acids, trace elements, and bibenzyl compounds, which can reduce serum lipid content and aortic lipid plaque deposition in ApoE mice fed a high-fat, high-cholesterol diet, inhibit expression of tumor necrosis factor-α and interleukin-6, and thereby reduce atherosclerotic damage [14]. Dendrobium officinale polysaccharides can regulate cellular insulin sensitivity and improve abnormal lipid metabolism through peroxisome proliferator-activated receptor γ (PPAR-γ) [15]. Research feeding Dendrobium officinale dietary fiber to mice on a high-fat diet for 11 weeks found it could effectively alleviate obesity, improve inflammation, and reduce oxidative stress levels [16]. Overall, Dendrobium officinale can reduce blood lipids and glucose by regulating apoptosis signaling pathways and improving inflammatory status [17]. Chinese herbal formulas treat MetS through multi-level, multi-target mechanisms [18]. For this pattern manifestation, combined with clinical experience, Professor Zhou Shigao, a renowned TCM physician at Longhua Hospital, selected Puerariae Lobatae Radix combined with Dendrobii Officinalis Caulis. These two medicinals work synergistically to nourish yin, clear heat, generate fluids, and relieve thirst, precisely addressing the pattern characteristics of MetS patients with yin deficiency and internal heat.

In summary, this study proves that Gehu Tiaozhi Decoction has definite therapeutic effects in treating MetS patients, particularly in improving waist circumference, body weight, body fat percentage, and some lipid indicators. However, this study focused on the effects of Gehu Tiaozhi Decoction on waist circumference, body weight, body fat percentage, and lipid levels in MetS patients, without further exploring other indicators such as insulin function and inflammatory factors. Additionally, this study had a relatively small sample size, a relatively single pattern type, insufficient 论证力度, and did not investigate all TCM patterns of MetS, indicating certain limitations. Moreover, the observation and follow-up period was relatively short, unable to adequately reflect long-term therapeutic effects and prognosis. Future studies should further analyze the mechanisms of action and potential targets of Gehu Tiaozhi Decoction in treating MetS through in vivo and in vitro research, and conduct more rigorous, in-depth, large-sample, high-quality randomized controlled trials or real-world studies to provide more theoretical basis for clinical application of Gehu Tiaozhi Decoction.

Author Contributions

Zheng Rong drafted the manuscript and performed statistical analysis; Zheng Rong, Liu Zhidong, and Chen Junlan collected and organized data; Wang Miao implemented the study and conducted feasibility analysis; Zhang Xiao designed the research protocol; Zhou Shigao revised the manuscript and assumed overall responsibility for the article, providing supervision and management.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] ALBERTI K G, ZIMMET P, SHAW J, et al. The metabolic syndrome—a new worldwide definition[J]. Lancet, 2005, 366(9491): 1059-1062. DOI: 10.1016/S0140-6736(05)67402-8.

[2] ENGIN A. The definition and prevalence of obesity and metabolic syndrome[J]. Adv Exp Med Biol, 2017, 960: 1-17. DOI: 10.1007/978-3-319-48382-5_1.

[3] HIRODE G, WONG R J. Trends in the prevalence of metabolic syndrome in the United States, 2011-2016[J]. JAMA, 2020, 323(24): 2526-2528. DOI: 10.1001/jama.2020.4501.

[4] HE Y N, ZHAO W H, ZHAO L Y, et al. Epidemiological characteristics of adult metabolic syndrome in China from 2010 to 2012[J]. Chinese Journal of Epidemiology, 2017, 38(2): 212-215. DOI: 10.3760/cma.j.issn.0254-6450.2017.02.015.

[5] ZHANG H Y, GOU X W, ZHAO S H, et al. Application of state-target pattern differentiation in metabolic syndrome with phlegm-heat intermingling pattern—Xiaoxianxiong Decoction plus Weilingxian, Hongqu, and three mulberry components[J]. Liaoning Journal of Traditional Chinese Medicine, 2020, 47(6): 1-3. DOI: 10.13192/j.issn.1000-1719.2020.06.001.

[6] HAN X, PIAO C L, SONG H Y. Clinical study on "dredging meridians and regulating viscera" in treating metabolic syndrome with gastrointestinal excess heat pattern[J]. Chinese Journal of Traditional Chinese Medicine Science and Technology, 2017, 24(4): 399-400, 404.

[7] Diabetes Branch of Chinese Medical Association. Guidelines for the prevention and treatment of type 2 diabetes in China (2020 edition) (part 2)[J]. Chinese Journal of Practical Internal Medicine, 2021, 41(9): 757-784. DOI: 10.19538/j.nk2021090106.

[8] DIABETES BRANCH OF CHINESE MEDICAL ASSOCIATION. Guidelines for the prevention and treatment of type 2 diabetes in China (2020 edition) (part 2)[J]. Chinese Journal of Practical Internal Medicine, 2021, 41(9): 757-784. DOI: 10.19538/j.nk2021090106.

[9] National Health and Family Planning Commission of the People's Republic of China. Criteria for adult weight determination: WS/T 428-2013[S]. China Quality Inspection Press, China Standards Press, 2013.

[10] ZHENG X Y. Guiding principles for clinical research of new Chinese medicines: trial implementation[M]. Beijing: China Medical Science and Technology Press, 2002.

[11] LIU Y D, YAN S X, DUAN F. Distribution patterns of TCM syndromes in metabolic syndrome[J]. Journal of Traditional Chinese Medicine, 2022, 37(5): 1059-1066. DOI: 10.16368/j.issn.1674-8999.2022.05.193.

[12] LI D J, CHU X Y, LI J, et al. Regulatory effect of puerarin on vascular active factors in patients with metabolic syndrome[J]. Pharmaceutical Research, 2017, 36(8): 481-482, 493. DOI: 10.13506/j.cnki.jpr.2017.08.013.

[13] ZHAO Y, LI W, ZU Y, et al. Study on the effect of puerarin on blood lipids in experimental metabolic syndrome rats[J]. Chinese Journal of Traditional Chinese Medicine Science and Technology, 2007, 14(1): 29-30. DOI: 10.3969/j.issn.1005-7072.2007.01.013.

[14] XIANG F. Clinical observation of puerarin injection in treating 64 cases of metabolic syndrome[J]. Guiding Journal of Traditional Chinese Medicine and Pharmacy, 2010, 16(11): 48-49. DOI: 10.13862/j.cnki.cn43-1446/r.2010.11.016.

[15] LI Y M. Preliminary study on the effects of Dendrobium officinale on lipid metabolism and inflammatory response in ApoE knockout mice[D]. Changsha: Hunan University of Chinese Medicine, 2013.

[16] QU J, TAN S Y, XIE X Y, et al. Dendrobium officinale polysaccharide attenuates insulin resistance and abnormal lipid metabolism in obese mice[J]. Front Pharmacol, 2021, 12: 659626. DOI: 10.3389/fphar.2021.659626.

[17] ZHENG H, JI H, FAN K, et al. Targeting gut microbiota and host metabolism with Dendrobium officinale dietary fiber to prevent obesity and improve glucose homeostasis in diet-induced obese mice[J]. Mol Nutr Food Res, 2022, 66(10): e2100772. DOI: 10.1002/mnfr.202100772.

[18] LI Y Y, LYU C H, WU G, et al. Research progress on molecular mechanism of Dendrobium officinale and its active components to metabolic syndrome[J]. China Journal of Chinese Materia Medica, 2019, 44(23): 5102-5108. DOI: 10.19540/j.cnki.cjcmm.20190813.402.

[19] LIU L, LI W Z, WANG S H, et al. Review on mechanism of multi-target intervention of traditional Chinese medicine on metabolic syndrome[J]. Chinese Journal of Experimental Traditional Medical Formulae, 2021, 27(3): 214-221. DOI: 10.13422/j.cnki.syfjx.20210341.

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Note: Figure translations are in progress. See original paper for figures.