Tropical Journal of Pharmaceutical Research May 2022; 21 (5): 1055-1060
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i5.20

Original Research Article

Effect and safety of combined Gegen Qinlian decoction/metformin in the treatment of diabetes mellitus in patients, and its influence on serum C peptide and glycosylated hemoglobin

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Sent for review: 7 October 2021 *Revised accepted: 3 May 2022*

Abstract

Purpose: *To investigate the clinical efficacy and safety of combined Gegen Qinlian decoction/metformin in the treatment of diabetes mellitus (DM), and its influence on serum C peptide and glycosylated hemoglobin (HbAlc).*
Methods: *One hundred and eighty-six DM patients who received treatment in Tangshan Gongren Hospital, Tangshan City, China from July 2018 to November 2019 were randomly assigned to group X (n = 93) and group Y (n = 93). Group Y was given metformin, while X received a combination of Gegen Qinlian decoction and metformin. Total effectiveness, incidence of adverse reactions, blood glucose, TCM syndrome scores, as well as serum C peptide and HbAlc were determined and compared between the two groups.*
Results: *Compared with group Y, group X had significantly higher treatment effectiveness ($p < 0.05$), lower incidence of adverse reactions ($p < 0.05$), significantly lower levels of blood glucose and TCM syndrome score after treatment ($p < 0.001$), but significantly higher serum C-peptide levels ($p < 0.001$) and lower levels of HbAlc.*
Conclusion: *the combination of Gegen Qinlian decoction and metformin produces a good anti-diabetic efficacy, with a lower incidence of adverse reactions in patients. Therefore, the combined therapy has potentials for application in clinical practice, but further clinical trials are required.*

Keywords: *Serum C peptide, Glycosylated hemoglobin (HbAlc), Gegen Qinlian Decoction*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Patients with diabetes mellitus (DM) present with abnormal blood glucose and long-term organ damage, leading to cardiovascular diseases and increasing the disease-associated burden [1-3]. Therefore, early diagnosis and treatment should be carried out to strictly control the occurrence of DM. At present, blood biochemical tests are often applied to diagnose and treat DM in clinical practice, with serum C peptide and glycosylated hemoglobin (HbAlc) as common diagnostic markers [4-7]. Serum C peptide shows the frequency of insulinogenesis, while HbAlc is

often applied in the control and monitoring of DM. Indeed, HbAlc is positively correlated with blood glucose concentration and reflects the glucose level of the patient. The combined detection of serum C peptide and HbAlc is beneficial in the diagnosis and treatment of DM [8-10]. Metformin, a popular drug for treatment of DM, inhibits the rate of absorption of glucose in the gastrointestinal tract while accelerating the absorption of blood glucose in peripheral tissues. However, metformin has limited application because it often causes adverse reactions.

In recent years, with more understanding of traditional Chinese medicine (TCM) treatment, some scholars have found that *Gegen Cenlian* decoction effectively controls DM. *Salvia miltiorrhiza*, coptis and other drugs in *Gegen Cenlian* decoction produce positive effects of promoting blood circulation, removing blood stasis, *clearing heat* and *relieving dryness*. This study was carried out to investigate the clinical effect and safety of combined use of *Gegen Qinlian* decoction and metformin in the treatment of DM after the combined measurement of serum C peptide and HbAlc.

METHODS

General profiles of patients

One hundred and eighty-six DM patients treated in Tangshan Gongren Hospital, Tangshan City, China Tangshan Gongren Hospital, Tangshan City, China from July 2018 to November 2019 were randomly assigned to group X (n = 93) and group Y (n = 93). Group X had 49 males and 44 females, with a mean age of 65.19 ± 20.81 years, disease course of 4 - 10 years, and mean course of 7.68 ± 2.32 years. Group Y had 48 males and 45 females, with a mean age of 66.19 ± 20.81 years, disease course of 5 - 11 years, and mean course of 7.68 ± 3.32 years. There were no statistically significant differences in general profile between the two groups *(p* > 0.05). The study was approved by the ethics committee of Tangshan Gongren Hospital (approval no. 20180554), and performed in line with the guidelines of the Declaration of Helsinki [11]. Patients and/or guardians signed informed consent.

Inclusion criteria

Patients in the following categories were included in this study: (1) those with type 2 DM after examination [12], and (2) patients who had no cognitive dysfunction, and could cooperate with treatment and follow-up.

Exclusion criteria

Patients in the following categories were excluded: (1) patients who had mental problems or were unable to communicate with others; (2) patients suffering from hypertension, pancreatitis, infections, malignant tumors or major organ dysfunction, and (3) patients who were allergic to the drugs and examinations used in the study.

Signed informed consent was obtained from all subjects or members of their families after the aim and protocol of the research were explained to them.

Treatments

Both groups received conventional treatment, but Y was given metformin, while X received a combination of *Gegen Qinlian* decoction and metformin. The treatment lasted for 12 weeks. In conventional treatment, the patients were given dietary guidance, exercise intervention, strict control of their body weights and close monitoring of their blood glucose. Metformin (0.5 g; Youcare Pharmaceutical Group Co. Ltd; NMPA approval no.: H20051289) was administered orally three times a day. The *Gegen Qinlian decoction* prescription mainly comprised 30 g of *Pueraria montana* var. lobata, 10 g of coptis, 10 g of *Scutellaria baicalensis,* and 6 g of radix *Glycyrrhizae preparata*. If patients had abnormal sweating*,* calcined dragon bone and light wheat were added. In the presence of dry stool, dry mouth and bad breath, *radix pseudostellariae, radix ophiopogonis*, *Schisandra chinensis* and *Polygonum cuspidatum* were included. If the patients could not sleep at night, spina date seed and *Polygala tenuifolia* were added. The drugs were soaked in 500 mL of water and decocted, and 200 mL of extract was administered. The patients took the decoction before meals in the morning and evening, twice a day.

Evaluation of parameters/indices

Serum C-peptide

Following an overnight fast, 5 mL of blood was taken from the cubital vein of each subject after admission and at 2 h after a meal. After treatment, the blood obtained was subjected assay of serum C-peptide using an automatic chemiluminescence immunoassay analyzer with matching reagents (Cobase 411 Electrochemi-luminescence Analyzer; NMPA certificate no. 20113402843) and operated strictly according to the kit instructions. The test results were used to diagnose the patients' condition. Serum C

peptide levels were compared before and after treatment.

HbAlc and blood glucose

Following overnight fast, blood samples (5-mL) were obtained as before. After treatment, blood levels of HbAlc and glucose were determined with an automatic biochemical analyzer using matching reagents (Tai'an Kangyu Medical Device Co. Ltd; Shandong Food and Drug Administration no. 20142400498). At the same time, the fasting blood sugar (FBS) and 2-h postprandial blood glucose (2 h PBG) of patients were determined. Levels of HbAlc were compared before and after treatment. In addition, FBG and 2-h PBG levels were compared after treatment.

Treatment effectiveness/efficacy

If the patients' symptoms disappeared, and FBG and 2-h PBG returned to normal range or decreased by more than 10 %, the treatment was markedly effective. If the symptoms were relieved, and FBG and 2h PBG decreased by 5 %, the treatment was regarded as effective. Failure to meet the above criteria meant that the treatment was ineffective [13].

$$TE\ (\%) = \frac{ME+E}{T} \times 100 \quad \text{..... (1)}$$

where: *TE* = Total effectiveness; *ME* = number of markedly effective cases; *E* = number of effective treatments, and *T* = total population of subjects.

Incidence of adverse reactions

Adverse reactions included nausea, vomiting, diarrhea, headache and hypoglycemia. The number of patients with adverse reactions was noted.

TCM syndrome score

The TCM syndrome score scale was adopted to evaluate the TCM syndrome score after treatment [14,15].

Statistical analysis

Data processing was done using SPSS 23.0 package, while GraphPad Prism 7 was used for preparation of graphs. Measurement results are expressed as mean ± SD, and were analyzed using ANOVA with repeated measurement data, including total effectiveness, incidence of adverse reactions, FBG, 2 h PBG, serum C peptide and HbAlc. Enumeration data, i.e., total treatment effectiveness and incidence of adverse reactions were analyzed using chi squared test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Clinical effectiveness/efficacy

Treatment effectiveness was significantly higher in group X than in group Y ($p < 0.05$; Table 1).

Incidence of adverse reactions

There were fewer incidence of adverse side effects in group X (2.15 %) than in group Y (15.05 %, $p < 0.05$; Table 2).

Blood glucose levels

The blood glucose level in group X after treatment was notably lower compared with group Y ($p < 0.001$; Table 3).

Table 1: Comparison of treatment effectiveness [n (%), n = 93]

Group	Markedly effective	Effective	Ineffective	Total effectiveness
X	53(56.99)	38(40.86)	2(2.15)	91(97.85)
Y	43(46.24)	38(40.86)	12(12.90)	81(87.1)
χ^2	2.153	0.000	7.724	7.724
P-value	0.142	1.000	0.005	0.005

Table 2: Comparison of incidence of adverse reactions [n(%)]

Group	Nausea and vomiting	Diarrhea	Headache	Hypoglycemia	No adverse reactions
X	1(1.08)	0(0.00)	0(0.00)	1(1.08)	91(97.85)
Y	4(4.30)	2(2.15)	3(3.23)	5(5.38)	79(84.95)
χ^2	1.850	2.022	3.049	2.756	12.109
P-value	0.174	0.155	0.081	0.097	0.001

Table 3: Comparison of blood glucose levels (mean ± SD, mmol/L)

Group	FBG	2 h PBG
X	5.67 ± 1.02	7.01 ± 1.03
Y	6.98 ± 1.37	8.68 ± 1.55
T	7.396	8.654
P-value	< 0.001	< 0.001

Note: FBG = fasting blood glucose level; PBG = 2-hour postprandial blood glucose level

TCM syndrome scores

The TCM syndrome score in group X (2.61 ± 0.27) after treatment was significantly lower than in group Y (5.22 ± 1.08, $p < 0.001$).

Serum C-peptide levels

The post-treatment serum C-peptide level was significantly up-regulated in group X, relative to group Y ($p < 0.001$; Figure 1).

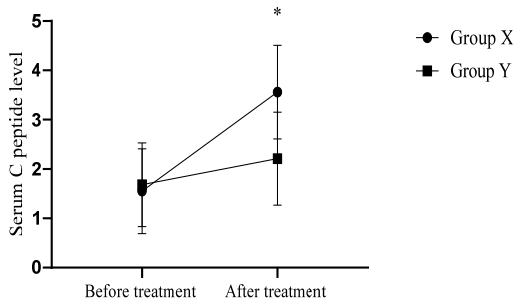

Figure 1: Comparison of serum C-peptide levels before and after treatment. *$P < 0.001$, group X serum C-peptide concentration vs serum C-peptide level in group Y after treatment

HbAlc levels before and after treatment

Group X had markedly lower HbAlc level than group Y ($p < 0.001$; Figure 2).

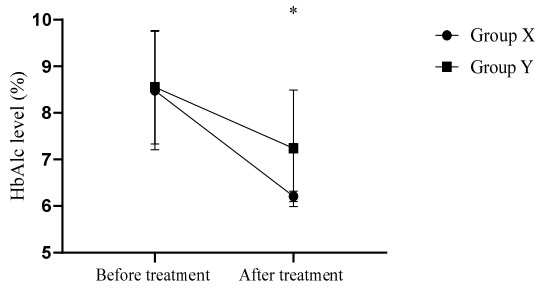

Figure 2: Comparison of HbAlc levels pre- and post-treatment (%). *$P < 0.001$, HbAlc level in group X after treatment vs the HbAlc level in group Y after treatment

DISCUSSION

The number of DM cases worldwide has exceeded 400 million, of which Chinese DM patients account for 25 %, and spend more than one trillion annually on the treatment, indicating that the disease has become a serious social and medical problem [16]. Patients with DM are prone to cardiovascular diseases, kidney diseases and other organ diseases due to changes in blood glucose which seriously affect the physical and mental status of patients. In addition, continuous medication after diagnosis leads to gradually decreasing compliance and uncontrolled complications in patients. Therefore, early intervention in diagnosis and treatment can effectively alleviate the condition and reduce the possibility of complications.

Serum C peptide and HbAlc are clinical indicators used for the diagnosis and treatment of DM. Indeed, HbAlc is known as the gold standard for evaluating the efficacy of DM due to an irreversible reaction between HbAlc and blood glucose, and lower HbAlc indicates better DM control [17]. This study showed improved HbAlc levels in both groups, because metformin directly acts on glucose metabolism, accelerates the decomposition of glucose, and enhances the absorption capacity of peripheral tissues while reducing glucose absorption and inhibiting hepatic glucose production. There was lower post-treatment HbAlc level in group X than in group Y, due to the efficacy of *Gegen Cenlian* decoction. *Gegen Cenlian* decoction contains many Chinese herbs such as *Salvia miltiorrhiza* and *Scutellaria baicalensis*. *Salvia miltiorrhiza* relieves pain, while *Scutellaria baicalensis* removes toxins and expels pus, and there is a good synergistic effect between the two drugs. In addition, radix *Rehmanniae recen* nourishes *yin* and blood, and *Pueraria montana* var. lobata relieves symptoms and removes heat. The combination of multiple drugs has substantial benefits in the treatment of DM. Thus, group X showed better blood biochemical indices and blood glucose control than group Y.

Although metformin controls blood glucose level, it has limited application due to its short-term effect in patients during medication, and adverse reaction such as diarrhea. *Gegen Cenlian* decoction improved the patients' physical conditions, promoted blood circulation and removed blood stasis. Moreover, Chinese medicinal materials do not cause toxic and side effects, and do not cause serious drug reactions. Therefore, group X had a lower TCM syndrome

score and a lower possibility of adverse reactions in patients.

There was higher treatment effectiveness in group X than in group Y. In a study by Horii *et al*., DM patients in experimental group received metformin in combination with Chinese medicinal herbs such as *Scutellaria baicalensis* and *Salvia miltiorrhiza*, while those in the control group received metformin only. There was markedly higher treatment effectiveness in the experimental group (98.00%) than in control group [18]. This is in agreement with the results obtained in the present research, and it reveals that the medicinal materials in *Gegen Cenlian* decoction effectively enhanced therapeutic effect of metformin on DM patients and achieved the therapeutic goal.

CONCLUSION

Gegen Qinlian decoction in combination with metformin demonstrates higher efficacy in DM patients than metformin alone. The combined therapy also produces a low incidence of adverse reactions in patients. Therefore, the combined therapy has potentials for use in clinical practice, but further clinical trials are required application.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Jie Chen and Weijuan Li conceived and designed the study, and drafted the manuscript. Jie Chen, Yi Xu, Yan Zhao, Geling Liu, Jia Cui and Yan Li collected, analyzed and interpreted the experimental data. Yi Xu and Weijuan Li revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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REFERENCES

1. *Arbe MF, Agnetti L, Breininger E, Glikin GC, Finocchiaro LME, Villaverde MS. Glucose 6-phosphate dehydrogenase inhibition sensitizes melanoma cells to metformin treatment. Transl Oncol 2020; 13: 100842.*
2. *Romagnoli A, Santoleri F, Costantini A. Drug utilisation pattern over 3 years in the real-world treatment of type II diabetes. Int J Clin Pract 2021; 75: e14120.*
3. *Luo H, Lin Y, Li J, Xu W. Relationship between adherence to anti-diabetic medication and depression among patients with diabetes mellitus in three selected Chinese hospitals. Trop J Pharm Res 2021; 20(1): 183-190.*
4. *Kwon CS, Seoane-Vazquez E, Rodriguez-Monguio R. Cost-effectiveness analysis of metformin+dipeptidyl peptidase-4 inhibitors compared to metformin+ sulfonylureas for treatment of type 2 diabetes. BMC Health Serv Res 2018; 18: 78.*
5. *Samuel SM, Varghese E, Varghese S, Büsselberg D. Challenges and perspectives in the treatment of diabetes associated breast cancer. Cancer Treat Rev 2018; 70: 98-111.*
6. *El Massry M, Alaeddine LM, Ali L, Saad C, Eid AA. Metformin: A Growing Journey from Glycemic Control to the Treatment of Alzheimer's Disease and Depression. Curr Med Chem 2021; 28: 2328-2345.*
7. *Bishnu A, Sakpal A, Ghosh N, Choudhury P, Chaudhury K, Ray P. Long term treatment of metformin impedes development of chemoresistance by regulating cancer stem cell differentiation through taurine generation in ovarian cancer cells. Int J Biochem Cell Biol 2019; 107: 116-127.*
8. *Evans V, Roderick P, Pollock AM. Adequacy of clinical trial evidence of metformin fixed-dose combinations for the treatment of type 2 diabetes mellitus in India. BMJ Glob Health 2018; 3: e000263.*
9. *Yandrapalli S, Jolly G, Horblitt A, Pemmasani G, Sanaani A, Aronow WS, Frishman WH. Cardiovascular Safety and Benefits of Noninsulin Antihyperglycemic Drugs for the Treatment of Type 2 Diabetes Mellitus-Part 1. Cardiol Rev 2020; 28: 177-189.*
10. *Losada E, Soldevila B, Ali MS, Martínez-Laguna D, Nogués X, Puig-Domingo M, Díez-Pérez A, Mauricio D, Prieto-Alhambra D. Real-world antidiabetic drug use and fracture risk in 12,277 patients with type 2 diabetes mellitus: a nested case-control*
11. *World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310(20): 2191-2194.*
12. *Al Hassan M, Fakhoury I, El Masri Z, Ghazale N, Dennaoui R, El Atat O, Kanaan A, El-Sibai M. Metformin Treatment Inhibits Motility and Invasion of Glioblastoma*

Cancer Cells. Anal Cell Pathol (Amst) 2018; 2018: 5917470.

13. *Jacob S, Dötsch A, Knoll S, Köhler HR, Rogall E, Stoll D, Tisler S, Huhn C, Schwartz T, Zwiener C, et al. Does the antidiabetic drug metformin affect embryo development and the health of brown trout (Salmo trutta f. fario)? Environ Sci Eur 2018; 30: 48.*
14. *Bolívar S, Noriega L, Ortega S, Osorio E, Rosales W, Mendoza X, Mendoza-Torres E. Novel Targets of Metformin in Cardioprotection: Beyond the Effects Mediated by AMPK. Curr Pharm Des 2021; 27: 80-90.*
15. *Salas J, Morley JE, Scherrer JF, Floyd JS, Farr SA, Zubatsky M, Barthold D, Dublin S. Risk of incident dementia following metformin initiation compared with non-initiation or delay of antidiabetic medication therapy. Pharmacoepidemiol Drug Saf 2020; 29: 623-634.*
16. *Dawra VK, Liang Y, Wei H, Pelletier K, Shi H, Hickman A, Bass A, Terra SG, Zhou S, Krishna R, et al. Bioequivalence of Ertugliflozin/Metformin Fixed-Dose Combination Tablets and Coadministration of Respective Strengths of Individual Components. Clin Pharmacol Drug Dev 2020; 9: 50-61.*
17. *Bagepally BS, Gurav YK, Anothaisintawee T, Youngkong S, Chaikledkaew U, Thakkinstian A. Cost Utility of Sodium-Glucose Cotransporter 2 Inhibitors in the Treatment of Metformin Monotherapy Failed Type 2 Diabetes Patients: A Systematic Review and Meta-Analysis. Value Health 2019; 22: 1458-1469.*
18. *Horii T, Iwasawa M, Shimizu J, Atsuda K. Comparing treatment intensification and clinical outcomes of metformin and dipeptidyl peptidase-4 inhibitors in treatment-naïve patients with type 2 diabetes in Japan. J Diabetes Investig 2020; 11: 96-100.*