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Ficus carica Leaves Decoction on Glycemic Factors of Patients With Type 2 Diabetes Mellitus: A Double-Blind Clinical Trial

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Abstract

Background: It is advisable to pay sufficient heed to the high prevalence of diabetes mellitus (DM) management, which has heavy burden and remarkable impact on the patients' life quality.
Objectives: The current study aimed to evaluate hypoglycemic effects of *Ficus carica* (FC) decoction (common fig leaf) in patients with type 2 DM.
Patients and Methods: It was a double-blind cross-over clinical trial. There were two groups of 14 subjects. During the first phase of the study, one group received fig leaf decoction for 21 days and the other one received green tea as placebo. After a one-week wash-out period, the patients changed their medications and continued for another 21 days. Variables including fasting blood sugar (FBS), 2 hours postprandial blood sugar (2hpp), fructosamine, HbA1c, C-peptide, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were analyzed at baseline, and at the end of two phases of the study and were compared.
Results: Thirteen patients in each group completed the trial. FBS, fructosamine, HbA1c, and C-peptide baseline and post-trial amounts in the case group were 152.76 $\pm$ 53.75, 146.92 $\pm$ 51.28 mg/dL (P = 0.073), 2.92 $\pm$ 0.515, 2.83 $\pm$ 0.482 mM/L (P = 0.276), 7.48% $\pm$ 0.535, 7.33% $\pm$ 0.532 (P = 0.114), 2.90 $\pm$ 1.01, 3.06 $\pm$ 1.15 ng/mL (P = 0.419), respectively; 2 pp at baseline was 230.80 $\pm$ 64.67 mg/dL, which significantly decreased to 193.15 $\pm$ 61.70 mg/dL after treatment with FC decoction; while it was 229.65 $\pm$ 70.13 mg/dL after treatment with placebo (P $<$ 0.001).
Conclusions: Addition of FC decoction to oral hypoglycemic drugs might significantly decrease 2hpp in patients with DM type 2. It is a safe and inexpensive method. The mechanism for this decrease is something other than increased insulin secretion.

Keywords: Hyperglycemia, Diabetes Mellitus, Type 2, HbA1c

1. Background

Diabetes mellitus (DM) is a chronic disorder characterized with hyperglycemia. Prevalence of DM is increasing throughout the world (1). More than 18% of persons over 65 have diabetes (2). DM can cause several debilitating complications and leads to significant loss of patients' quality of life (3, 4). Considering its high prevalence, heavy burden, and remarkable impact on life quality of the patients, it is advisable to pay sufficient heed to DM management. There are different therapeutic strategies to control patients' blood glucose including exercise, diet and pharmacological options. Pharmaceutical drugs are either too expensive or have undesirable side effects (5). Regarding high cost and poor availability of the current medicaments in many rural populations, particularly in the developing countries, administration of complementary medicine to treat DM is popular in recent years. Meanwhile, the World Health Organization (WHO) recommended the evaluation of the plants' effectiveness and conditions where there is a lack of safe modern drugs (6).

Several herbal remedies are used for DM adjunctive therapy. Some reports indicate that more than 400 plant species have anti-diabetic activities (7) and some of them, such as *Phyllanthus simplex* (8), *Ficus religiosa linn* (9), *Gymnema montanum* (10), *Casearia esculenta* (11), *Gongronema latifolium* (12), *Ichnocarpus frutescens* (13), *Terminalia chebula Retz* (14), and *Annona squamosa* (15), were studied and their property were approved.

Some studies reported therapeutic effects of decoction of *Ficus carica* leaves (common fig) on lipid (16, 17) and antioxidant profiles (18) of patients with diabetes . Meanwhile, Rashidi and Noureddini in their study fed the rats with diabetes with *F. carica* leaves extract for four days and

then results showed that glucose tolerance improved compared to the control group. *Ficus carica* is extensively studied regarding the control of blood glucose (19); however, studies on hypoglycemic effect of *F. carica* (FC) are limited to one study on rats with diabetes (20) and another study on 10 insulin-dependent humans (21).

2. Objectives

The current study aimed to evaluate hypoglycemic effects of FC in a large human sample size under the treatment of oral hypoglycemic agents.

3. Patients and Methods

It was a double-blind cross-over clinical trial to evaluate the hypoglycemic effect of FC decoction in the patients with DM type 2. FC leaves were collected from fig trees of Shoush city in Khuzestan province, South-West Iran, under supervision of Khuzestan Agricultural and natural resources research cfenter. The samples were identification by standard botanical monographs. Collected leaves were washed and shade dried to obtain a completely dried product. The dried leaves were then milled to fine powder and stored in packs. Each pack contained 13 grams of the FC leave powder. The aqueous decoction was prepared by boiling the contents of one pack in 500 mL of distilled water for 15 minutes followed by cooling and filtering.

Twenty-eight patients with type 2 DM aged 40 - 60 years with HbA1c level of 7% - 8.5% and under treatment with oral hypoglycemic agents were randomly selected among the patients referred to DM clinic of Golestan hospital in Ahvaz, south-west of Iran. Golestan hospital is affiliated to Ahvaz Jundishapur University of Medical Sciences. All participants signed written informed consent. The subjects were randomly divided into two groups. The study was a double blind clinical trial which was conducted in two 21-day phases and there was a one-week wash-out period between the phases. Patients were advised to continue their common oral hypoglycemic agents and diet. In the first phase, the intervention group received FC decoction once a day; while the control group received green tea as placebo, once a day during breakfast. After 21 days, the patients discontinued the intervention for seven days. Thereafter, the groups changed their medications, as the intervention and control groups received green tea and FC decoction, respectively. If any patient forgot to take the medication twice or did not desire to continue the study, he/she was excluded from the study. When the patients were receiving FC decoction, they were considered as the intervention group; and when they were receiving green tea, they were considered as the control group. Therefore, there were 28 cases and 28 controls. Since it was a cross-over study, there was no need to match the patients' age and gender in the two groups.

Preparation of the decoction was educated to all patients. Blood sampling was done at baseline and at the end of the first and second phases of the study, and the levels of fasting blood sugar (FBS), 2 hours postprandial blood sugar (2hpp), fructosamine, HbA1c, C-peptide, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were assessed. On blood sampling days and after measuring FBS, all patients had a standard breakfast and two hours later another blood sampling was done to evaluate their 2hpp.

All data were transferred into a predesigned questionnaire and analyzed by SPSS software version 16. Descriptive variables are presented as mean $\pm$ standard deviation. Repeated measures test was used to compare variables before and after the trial. A P value of < 0.05 was considered as statistically significant.

Protocol of the study conformed to the declaration of Helsinki and approved by ethics committee of Ahvaz Jundishapur University of Medical Sciences.

4. Results

Of the 28 initially recruited patients, 26 completed the trial. Therefore, authors considered 26 cases and 26 controls. Mean age of the patients in the first and second groups and overall was 52.15 $\pm$ 6.71, 53.46 $\pm$ 5.57 and 52.80 $\pm$ 6.08 years, respectively. In the intervention group, there were five male (38.5%) and eight female (61.5%) patients; while there were four male (30.8%) and nine female (69.2%) patients in the control group.

Data on the amounts of the variables at baseline, and post-trial in the intervention and control groups are summarized in Table 1. Statistical results showed that there were no significant differences between baseline and post-trial amounts of FBS, fructosamine, HbA1c, C-peptide, AST and ALT ($P > 0.05$). The only variable, which significantly changed after treatment with FC decoction, was 2hpp, which decreased from 230 $\pm$ 64.67 mg/dL at baseline to 193 $\pm$ 61.70 mg/dL in the intervention group after treatment; while it was 229 $\pm$ 70.13 mg/dL in the control group ($P < 0.001$).

5. Discussion

It was a double-blind cross-over clinical trial to evaluate the hypoglycemic effect of FC decoction in the patients with DM type 2. Twenty-eight patients were studied and the results showed that FC decoction could significantly decrease 2hpp in patients with type 2 DM ($P < 0.001$); but

Table 1. Comparison of the Variables at Baseline and Post-Trial in the Intervention and Control Groups Variable-Base[a,b]

Variable	Minimum	Maximum	Mean ± SD	P Value [c]
FBS				0.073
FBS-Base, mg/dL	79	350	152.76 ± 53.75	
FBS-Intervention, mg/dL	80	337	146.92 ± 51.28	
FBS-Control, mg/dL	90	347	148.96 ± 53.85	
2hpp				< 0.001
2hpp-Base, mg/dL	108	400	230.80 ± 64.67	
2hpp-Intervention, mg/dL	95	364	193.15 ± 61.70	
2hpp-Control, mg/Dl intervention	128	452	229.65 ± 70.13	
Fructosamine				0.276
Fructosamine-Base, mM/L	2.15	4.00	2.92 ± 0.51	
Fructosamine-Intervention, mM/L	2.17	3.60	2.83 ± 0.48	
Fructosamine-Control, mM/L	1.90	5.92	3.99 ± 0.51	
HbA1c				0.114
HbA1c-Base, %	7.0	8.5	7.48 ± 0.53	
HbA1c-Intervention, %	6.8	8.5	7.33 ± 0.53	
HbA1c-Control, %	5.9	9.0	7.29 ± 0.62	
C-peptide				0.419
C-peptide-Base, ng/mL	1.80	6.60	2.90 ± 1.01	
C-peptide-Intervention, ng/mL	1.85	6.98	3.06 ± 1.15	
C-peptide-Control, ng/mL	1.86	4.80	2.84 ± 0.80	
AST				0.376
AST-Base, mg/dL	15	54	22.84 ± 8.18	
AST-Intervention, mg/dL	16	38	21.30 ± 5.12	
AST-Control, mg/dL	15	38	21.46 ± 4.90	
ALT				0.131
ALT-Base, mg/dL	13	45	23.7 ± 9.95	
ALT-Case, mg/dL	14	40	21.19 ± 7.55	
ALT-Control, mg/dL	13	39	22.80 ± 6.69	

[a] Variable-base: Amount of the variable at baseline; variable-intervention: amount of the variable after treatment with FC decoction (the intervention group); variable-control: amount of the value after treatment with placebo (the control group).
[b] Repeated measures test was used to compare variables before and after the trial.
[c] A P value of < 0.05 was considered as statistically significant.

it could not change patients' FBS, fructosamine, HbA1c and C-peptide (P > 0.05).

Serum fructosamine, known as glycated serum protein, is formed by a nonenzymatic reaction between carbonyl group of glucose and amino group of plasma proteins, mostly albumin. Since the half-life for albumin is approximately 17 days, serum fructosamine is a means to monitor the effectiveness of DM management over an intermediate interval (22). Besides, glycosilated hemoglobin (HbA1c) is formed by binding hemoglobin and glucose. While the half-life of a red blood cell is 120 days, the HbA1c is a reliable marker of chronic hyperglycemia and is the test of choice to evaluate the average glycemic control over the preceding three months (23, 24). According to the American diabetes association guidelines published in 2007, HbA1c levels should be maintained below 7% in the patients with DM (25). Participation of the patients in the current study was about two months; but duration of treatment with FC decoction was 21 days. Mean HbA1c level of the patients was higher than that of the goal at

baseline (7.48 ± 0.535), and remained higher than that of the goal after the trial (7.33 ± 0.532 in the intervention group). Although the levels of HbA1c and fructosamine decreased after treatment with FC decoction, the differences were not statistically significant (P = 0.114 and 0.276, respectively). Conducting studies with longer duration of therapy would be beneficial to further evaluate the effect of FC decoction on HbA1c and fructosamine levels. Similarly, patients' FBS decreased after administration of FC decoction but the difference was not significant (P = 0.073). The difference could be statistically significant if the sample size was larger hemoglobin and glucose. According to the American diabetes association guidelines published in 2007, HbA1c levels should be maintained below 7% in the patients with DM (25). Participation of the patients in the study was about two months; but duration of treatment with FC decoction was 21 days. Mean HbA1c level of the subjects was higher than that of the goal at baseline (7.48 ± 0.535), and remained higher than that of the goal after the trial (7.33 ± 0.532 in the intervention group). Although the levels of HbA1c and fructosamine decreased after treatment with FC decoction, the differences were not statistically.

Mean baseline 2hpp level was 230.80 ± 64.67 mg/dL. After administration of FC decoction, patients' 2hpp decreased to 193.15 ± 61.70 mg/dL in the intervention group; while 229.65 ± 70.13 mg/dL in the controls (P < 0.001). It seems that adjunctive therapy with FC decoction could significantly decrease 2hpp in the patients with DM type 2.

The connecting peptide, or C-peptide, connects insulin's A and B chains in the proinsulin molecule, and is secreted together with insulin in equimolar quantities following the cleavage of insulin from proinsulin. Thus, it could be used to assess the level of insulin in the patients with DM. The current study showed that administration of FC decoction does not change the levels of C-peptide and therefore, the levels of insulin in the patients with DM type 2 (P = 0.419). It seems that hypoglycemic effect of FC decoction on 2hpp is not associated with increased insulin secretion.

Also no significant differences were observed in the levels of AST and ALT after administration of FC decoction between the groups (P = 0.376 and 0.131, respectively). It did not have any adverse effects on liver function, and can be considered safe in this regard.

FC decoction may improve lipid (16, 17) and antioxidant profiles (18) of the patients with DM. Meanwhile, studies on hypoglycemic effect of *F. carica* (FC) are limited to one study on rats with diabetes (20) and one study on 10 insulin-dependent humans (21). In consistence with the current study, Pérez et al. suggested that FC extract decreased plasma glucose in rats with diabetes, and had a clear hypoglycemic effect in them. They also suggested that such an effect cannot be mediated by an enhanced insulin secretion; therefore, an undefined insulin-like peripheral effect may be involved (20). Serraclara et al. studied ten insulin-dependent patients with DM and reported that addition of FC decoction to the diet in those patients could help to control postprandial blood sugar. Average insulin dose was 12% lower during FC decoction administration (21). To the best of the authors' knowledge, is the current study was the first study on hypoglycemic effect of FC decoction in the patients with DM type 2 under treatment with oral hypoglycemic drugs. Conducting further studies on more patients and longer therapy duration is necessary to confirm the current study findings.

It was concluded that addition of FC decoction to oral hypoglycemic drugs might significantly decrease 2hpp in patients with DM type 2, which is a safe and inexpensive method. The mechanism of this decrease is something other than increased insulin secretion. Considering that effect along with previously-reported antioxidant and antihyperlipidemic effects, it is suggested to add FC decoction to the diet of the patients with DM.

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Footnotes

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