Clinical Observations

Effects of the Modified Linggui Zhugan Decoction (加味苓桂术甘汤) Combined with Short-term Very Low Calorie Diets on Glycemic Control in Newly Diagnosed Type 2 Diabetics

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Objective: To evaluate the effects of the modified Linggui Zhugan Decoction (加味苓桂术甘汤) combined with short-term very low calorie diets (VLCDs) on glycemic control in newly diagnosed type 2 diabetes mellitus (T2DM) patients.

Methods: A total of 20 subjects with newly diagnosed T2DM were treated with the modified Linggui Zhugan Decoction (one-month administration) combined with short-term VLCDs (5 days), and 3-months follow-up. A standard 75-g oral-glucose-tolerance test (OGTT) indexes fasting plasma glucose (FPG), post-prandial 0.5 h and 2 h plasma glucose (P0.5hPG, P2hPG), glycated hemoglobin A1C (GHbA1C), body weight, body mass index (BMI), insulin function, insulin resistance index, incidence of hypoglycemia, and the liver and renal functions were evaluated before and after treatment. Correlations of BMI with insulin function and insulin resistance were also assessed.

Results: After the treatment, the patients’ plasma glucose decreased steadily, FPG decreased from 5.8±0.9 mmol/L at pre-treatment to 5.0±0.6 mmol/L at 3-months follow-up (P<0.05), and P2hPG decreased from 11.7±3.8 mmol/L at pre-treatment to 6.9±0.9 mmol/L at 3-months follow-up (P<0.01). The level of GHbA1C declined from (6.47±1.24)% at pre-treatment to (6.14±0.99)% at 3-months follow-up (P<0.01). Body weight and BMI also declined significantly. Insulin resistance index was improved obviously and no event of hypoglycemia occurred. Part of the patients companied with fatty liver had a transient increase in hepatic transaminase during the treatment, but it turned to normal after the treatment.

Conclusions: The modified Linggui Zhugan Decoction combined with short-term VLCDs can be safely implemented for steady glycemic control in newly diagnosed T2DM patients.

Keywords: Modified Linggui Zhugan Decoction; Very Low Calorie Diets; Type 2 diabetes; Plasma glucose

Type 2 diabetes mellitus (T2DM) is a metabolic disorder with chronic course. The key pathogenic process involved in the onset of T2DM is insulin resistance with a β-cell defect in insulin production. Insulin resistance in the main cause which and exists throughout the process, but only those with an inability to increase β-cell production of insulin develop T2DM, followed by a vicious circle.1 A persistent hyperglycemia may aggravate β-cell failure as well as insulin resistance.1, 2 Therefore, it is very important for the newly diagnosed T2DM patients to have an ideal glycemic control in a short time.

The available researches have demonstrated that short-term intensive insulin therapy like continuous subcutaneous insulin infusion (CSII) or multiple daily insulin injection (MDI) may rapidly correct hyperglycemia and lay a foundation for long-term good glycemic control in new-onset T2DM patients.3-7 CSII imitates the physiologic characteristic of insulin secretion in humans and delivers 24 h basal infusion rates continuously and a bolus dose to cover food eaten, provides intensive glycemia management and correct of the glucose toxicity in a short period.8-9 Quantities of the data suggest that intensive insulin therapy may achieve the goals of correction of toxicities of glucose and lipid to β-cell and prolong the benefit at the early stage in diabetes patients.10

However, the previous studies show that the risk of hypoglycemia in T2DM treated by insulin therapy was greater; and in intensive insulin therapy, the risk was even 3-fold higher than that of conventional diabetes management.11 More recently, reports have suggested that severe hypoglycemia may be reduced by CSII as much as 8-fold as compared with MDI treatment. But the cost of CSII treatment is about ¥ 170 a day,12 which most of the patients can’t afford. Moreover, the adverse effects of CSII, including allergic reactions, insulin
edema, hyperinsulinemia, weight gain, and reactions at injection area (inflammation, fever, itching and subcutaneous callosity, subcutaneous fat atrophy or fibrosis hyperplasia) make a discouraged clinical practice even in the developed countries. Considering the above situation, it is worthy to develop new economical alternative to control glycemia safely and effectively within a short time.

Very low calorie diets (VLCDs) have drawn attention since 1990s due to its effect on weight loss to reduce the risk factors of cardiovascular disease in obese patients with T2DM. However, few of the randomized studies have specifically addressed the evidences of long-term effects of VLCDs on weight loss, glycemic control and reduction in risk factors of cardiovascular disease. A consensus statement from the International Diabetes Federation does not recommend the use of VLCDs in diabetes prevention due to lack of evidence for reduction of diabetic complications and mortality. VLCDs are mainly used as a regimen for severe obese T2DM patients (body mass index (BMI), ≥35 kg/m²) in Western countries, and BMI <25 kg/m² as well as BMI 25–30 kg/m² are absolute and relative contraindications, respectively.

The modified Linggui Zhugan Decoction (加味苓桂术甘汤) combined with short-term VLCDs is a new kind of natural therapy incorporating of Chinese medicine with fasting therapy systematically. The treatment requires the participants not to have any solid food, but only drink millet soup. The modified Linggui Zhugan Decoction with the effects of warming and resolving the mucus, strengthening the spleen and removing the turbidity is simultaneously administered to restore normal function of the spleen in transportation and transformation. In present study, we evaluated the effects of modified Linggui Zhugan Decoction combined with short-term VLCDs on glycemic control in newly diagnosed T2DM patients. A report follows.

METHODS

Subjects
Total 20 eligible patients (14 men and 6 women, 18 inpatients and 2 outpatients,) participated in the treatment with the modified Linggui Zhugan Decoction combined with short-term VLCDs in the authors’ Chinese Medicine Department in the period starting from October 1st, 2009. The diagnosis of T2DM was in accord with the criteria issued by the WHO in 2006. Before the program began, all the subjects were fully informed about the course, effects and potential risks in the program, and then they gave the written informed consents. The protocols were approved by the Review Board and Ethical Committee for Clinic Research in the First Affiliate Hospital, Sun Yat-Sen University (Guangzhou, China).

The mean age of all subjects was 49.4±10 (range 38-65) and the mean BMI was 29.3±5.1 kg/m² (range 22.5-38.2).

Treatment Protocol
As previously described, the treatment fell into three phases: pre-treatment phase, VLCDs phase and restoring phase. The treatment was preceded by 3 relief days to decrease food intake gradually from the normal level to 2/3 of the normal, and then to 1/3 of the normal; when the patients felt hungry, they may take some fruits or vegetables. Only fruits were allowed to be taken at the day they admitted in the hospital. The VLCDs phase (5 days): at the first day, 10–20 g thienardite powder was used to clean the bowel. The modified Linggui Zhugan Decoction was administered twice a day, consisting of Fu Ling (Poria), Gui Zhi (Ramulus Cinnamomi), Bai Zhu (Atractylodes Macrocephala), Gan Cao (Radix Glycyrrhiza), Dang Shen (Radix Codonopsis) and Da Huang (Radix et Rhizome Rhei Palmati). And the patients were recommended to sip millet soup, which was boiled by 150 g millet added with 1 L water, and advised to drink 3 L of mineral water or moderate quantity of sports beverages to maintain electrolyte balance. But the solid food was forbidden during the VLCDs phase. In the restoring phase, the patients restore food intake by increasing the amount gradually, changing the fluid diet into solid food slowly, and from light diet to normal food, which lasted at least 3 days. After the above treatment, Chinese medicine decoctions were prescribed according to the patients for a period of one month, and the patients were suggested to keep a healthy life-style.

Evaluations
1. Efficacy
The OGTT indexes (FPG, P0.5hPG, P2hPG), GHbA1C, body weight, BMI, insulin function, and insulin resistance index were evaluated before and after treatment and during the follow-up period of three months. The correlations of BMI with insulin function and insulin resistance were also assessed.

Plasma glucose was determined by the glucose oxidase technique, Insulin level was measured by radio-immunooassay, and GHbA1C level was tested by Bio-Rad HPLC. The function of β cell and index of insulin resistance (IR) were calculated by Homeostasis Model Assessment (HOMA): HOMA-β = 20 × fasting insulin level / (FPG – 3.5), and HOMA-IR = FPG × fasting insulin level/22.5.

2. Safety
Hypoglycemic events, either the symptoms of strong hunger, palpitations, cold sweats, tremor, pale face or the monitored FPG ≤3.9 mmol/L, were recorded. The liver and renal functions were also observed.

Statistical Analysis
All the normal variables are expressed as mean ± standard deviation (mean ± SD). Data of pre- and post-treatment were compared using the paired-sample t test. Correlations of BMI to insulin function index and insulin resistance index were analyzed by Pearson correlation test. Differences were considered statistically significant at P<0.05 level. All the data were analyzed with the Statistical Package for Social Sciences (SPSS 17.0).
RESULTS

Effects of Modified Linggui Zhugan Decoction Combined with Short-term VLCDs on Glycemic Control (Table 1)

All the patients included in the study showed an increase in post-prandial plasma glucose, but none of their FPG levels was ≥7 mmol/L before treatment. Significantly decreases of FPG, P0.5hPG and P2hPG were observed in post-treatment and 3-month follow-up compared with pre-treatment (P<0.05 or P<0.01), and these values in 3-months follow-up didn’t change significantly compared with post-treatment. GHbAIC level decreased significantly in 3-months follow-up compared with pre-treatment (P<0.01).

<table>
<thead>
<tr>
<th>Measurement Time</th>
<th>FPG (mmol/L)</th>
<th>P0.5hPG (mmol/L)</th>
<th>P2hPG (mmol/L)</th>
<th>GHbAIC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td>5.8±0.9</td>
<td>10.5±2.3</td>
<td>11.7±3.8</td>
<td>6.47±1.24</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>4.8±0.8*</td>
<td>8.6±1.6**</td>
<td>8.1±2.3</td>
<td>-</td>
</tr>
<tr>
<td>3-months follow-up</td>
<td>5.0±0.6*</td>
<td>8.6±1.2**</td>
<td>6.9±0.9**</td>
<td>6.14±0.99**</td>
</tr>
</tbody>
</table>

Notes: OGTT, oral glucose tolerance test. FPG, fasting plasma glucose. P0.5hPG, post-prandial 0.5 h plasma glucose. P2hPG, post-prandial 2 h plasma glucose. GHbAIC, glycated hemoglobin A1C. Data is expressed as mean ± SD. *P<0.05, compared with pre-treatment; **P<0.01, compared with pre-treatment.

Effects of the Modified Linggui Zhugan Decoction Combined with Short-term VLCDs on BMI and Insulin Function (Table 2)

The parameters of body weight, BMI, and HOMA-IR decreased significantly in post-treatment and 3-month follow-up compared with pre-treatment (P<0.05 or P<0.01), and these values in 3-month follow-up didn’t change significantly compared with post-treatment. There was no obvious difference in HOMA-β throughout the study. The changes of body weight and BMI were not associated with HOMA-IR.

<table>
<thead>
<tr>
<th>Measurement Time</th>
<th>Body weight (kg)</th>
<th>BMI (kg/m²)</th>
<th>HOMA-β</th>
<th>HOMA-IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td>84.8±23.3</td>
<td>29.3±5.1</td>
<td>159.3±88.3</td>
<td>4.1±1.7</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>80.7±21.4*</td>
<td>27.9±4.6**</td>
<td>275.2±25.9</td>
<td>2.3±1.1**</td>
</tr>
<tr>
<td>3-months follow-up</td>
<td>80.4±20.9**</td>
<td>27.8±4.5**</td>
<td>149.5±84.6</td>
<td>2.2±0.9**</td>
</tr>
</tbody>
</table>

Notes: BMI, body mass index. HOMA, Homeostasis Model Assessment. IR, insulin resistance. Data is expressed as mean ± SD. *P<0.05, compared with pre-treatment; **P<0.01, compared with pre-treatment.

Adverse Reactions

No hypoglycemic events were found in all the 20 subjects during the program, including 4 patients susceptible to hypoglycemia.

Six patients showed higher hepatic transaminase (alanine aminotransferase (ALT) ≥40 IU/L and/or aspartate aminotransferase (AST) ≥37 IU/L) before treatment, and the indexes increased further during the treatment. And in one of the other 14 patients with normal level of ALT and AST, BMI was extremely high (38.2 kg/m²) after treatment. However, the elevated ALT and AST in all the 7 patients returned to normal when rechecked one month later. All 20 subjects did not show any renal impairment.

DISCUSSION

The modified Linggui Zhugan Decoction in combination with short-term VLCDs in a new therapy of Chinese medicine integrated with German fasting therapy, which develops natural characteristics in VLCDs. Millet with rich nutrition value, containing 9.2%–14.7% protein, 3.0%–4.6% fat, vitamin B1, and inorganic salt, can strengthen the Spleen and harmonize the Stomach. The modified Linggui Zhugan Decoction and millet soup can effectively promote the Spleen function in transportation and transformation.

The present therapy showed a rapid control of glycemia without rebound in 3-month follow-up in the newly diagnosed T2DM patients, and GHbAIC decreased to normal level, suggesting that it may have the effects similar to intensive insulin therapy. That no events of hypoglycemia were found in all the 20 subjects indicates that the safety of the treatment is superior to intensive insulin therapy. And the treatment lasted only 5 days, with a period much shorter than that of VLCDs usually for over one month, which may greatly promote the patients’ acceptance.

According to the results of HOMA, there was no change in β-cell function throughout the study, but the index of IR in 3-month follow-up decreased obviously as compared with that of pre-treatment, suggesting that the potential mechanism for rapid glycemic control of our intervention may be associated with improvement of insulin resistance.

Generally, VLCDs achieves the benefits in prevention of T2DM by weight loss. Whereas, it was found from the pretest study that the decreases of body weight and BMI were not correlated to the improvement of insulin resistance. The reason may refer to the insufficient
subjects, and the mechanism of our intervention is not the mere function of weight loss.

In the 3-month follow-up, the plasma glucose, BMI and IR kept stable as compared with those of post-treatment, indicating that the effects of the Modified Linggui Zhugan Decoction combined with short-term VLCDs could be maintained at least for 3 months.

Seven patients had higher hepatic transaminase and BMI >25 kg/m² with a history of fatty liver before the program, and they underwent a further increase of transaminase during the treatment. But, the indexes returned to normal when rechecked one month later. Transient rise in transaminase may be possibly due to the rapid mobilization of intracellular triglycerides and the fatty acid release causing the portal inflammation, or due to hepatic overload of ketogenesis. However, the long-term effect of the treatment is beneficial to improvement of the liver function.

REFERENCES


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