European Journal of Integrative Medicine 8 (2016) 645–653

Contents lists available at ScienceDirect

European Journal of Integrative Medicine

journal homepage: www.elsevier.com/eujim

Research paper

A formulation of grape seed, Indian gooseberry, turmeric and fenugreek helps controlling type 2 diabetes mellitus in advanced-stage patients

Sangeeta Banerji*, Shanta Banerjee

Phytomed Service UG, Seegefelder Weg 425, 13591 Berlin, Germany

ARTICLE INFO

Article history:
Received 10 March 2016
Received in revised form 31 May 2016
Accepted 22 June 2016

Keywords:
Polyherbal formulation
Type 2 diabetes
Oxidative stress
Dietary supplement
Phytotherapy

ABSTRACT

Introduction: The aim of this clinical study was to determine whether an add-on treatment with a herbal product (Plantabetics®) containing extracts of grape seed, Indian gooseberry, turmeric and fenugreek seeds, improved glycemic control in advanced-stage patients, who were no longer responding to a combination therapy of metformin and sulfonylurea.
Methods: This was an open label, single arm before/after study of 84 days duration. A total of 50 patients with type 2 diabetes, who were on a stable dose of metformin and sulfonylurea but not showing any improvement in diabetic control, were recruited. Patients were not taking any other herbal supplements or medication. They were instructed to take one capsule of the investigational product two times daily along with their diabetes medication. End points were glycated hemoglobin (HbA1c), fasting blood sugar, and postprandial blood sugar. Safety parameters were also evaluated.
Results: Treatment with the investigated herbal product in conjunction with prescribed diabetes medication resulted in a > 1% unit reduction in average glycated hemoglobin value (from 8.8%/73 mmol/mol to 7.5%/58 mmol/mol; $p < 0.001$) as well as significant reduction in average fasting (from 8.8 mmol/l to 6.6 mmol/l; $p < 0.001$) and post prandial blood sugar values (14.6 mmol/l to 10.4 mmol/l; $p < 0.001$) in the majority of the study population. The herbal product was moreover well-tolerated and safe to use.
Conclusions: The investigated product in combination with oral hypoglycemic agents is a promising candidate for regaining glycemic control in advanced-stage type 2 diabetes patients.

1. Introduction

Type 2 diabetes mellitus is a multiple metabolic disorder, including disorder of sugar and fat metabolisms, disorder of endogenous enzyme production and disorder of endocrine function [1,2]. It is manifested by high blood sugar values, resulting in a significantly increased risk of developing microvasculoar (e.g. retinopathy, nephropathy) as well as macrovascular (e.g. stroke, ischemia of heart and lower extremities) complications and increased mortality compared to the population without diabetes. Therefore, the current therapeutic approach for type 2 diabetes targets the sugar metabolism disorder. Indeed, several large studies have shown that reduction of glycated hemoglobin, a marker for the long-term blood glucose level, of just 1% unit (11 mmol) significantly reduces the risk for type 2 diabetes-associated microvascular diseases [3,4]. Glycemic control is initially achieved by oral hypoglycemic agents (OHAs) [5]. Most widely used OHAs are metformin and sulfonylureas. OHAs show good effect in the early stages of type 2 diabetes. However, the disease is of a progressive nature and it becomes increasingly difficult to achieve the targeted glycemic control with OHAs and insulin injection becomes necessary [6]. Progressive reduction in β-cell mass and deregulation of insulin promoter due to chronic exposure to high glucose concentrations are the main reasons for uncontrolled diabetes in later stages [7,8]. The latter effect termed as 'glucose toxicity' is still reversible. The more detrimental effect of prolonged elevated blood glucose concentrations is the formation of reactive oxygen species, e.g. through glucose autoxidation or oxidative phosphorylation. The antioxidative defense system of pancreatic β-cells is particularly weak due to low levels of endogenous antioxidants and can be imbalanced by overproduction of free radicals in hyperglycemic condition [8,9]. The resulting oxidative stress causes irreversible damage to β-cells and eventually leads to apoptosis [1,8,10,11]. Pancreatic islet has the ability to generate new β-cells. However, in later stages of type

* Corresponding author.
E-mail addresses: sangeeta.banerji@phytomedservice.de (S. Banerji), banerjee@phytomedservice.de (S. Banerjee).

http://dx.doi.org/10.1016/j.eujim.2016.06.012
1876-3820/

2 diabetes, a high rate of β-cell apoptosis and interleukin 1β-mediated inflammation in pancreatic islets may prevent generation of new β-cells whereas prevailing oxidative stress prevents their survival [12]. With reduction in β-cell mass, less and less insulin is available to the organism with time. Consequently, OHAs, which act either by increasing insulin release from β-cells or increasing insulin sensitivity of receptors can no more be effective. Apart from hyperglycemia and oxidative stress, hyperlipidemia is also responsible for β-cell apoptosis [12]. It has been reported that β-cell apoptosis and/or necrosis may activate specific immunological phenomena [12,13]. Hence, immune modulatory agents might play a positive role in management of type 2 diabetes. Taken together, high oxidative stress, resulting inflammatory processes, hyperlipidemia and attenuation of immune function have to be specifically targeted in addition to glycemic control for restricting the progression of diabetes and for better diabetes management.

This situation presents an unmet medical need for developing more efficacious and safe treatment options with long-term and better glycemic control for diabetes. In this regard, herbal interventions present a promising option since many of them have anti-diabetic properties [14,15]. Polyherbal formulations have been found to be effective against diabetes in a number of studies [16–18]. All of these studies used phytotherapy as the sole treatment and included one or more herbal blood sugar lowering agents that act like OHAs or insulin, e.g. *Mormordica charantia, Gymnema sylvestre* [16–18]. Conventional OHAs, in spite of their side effects, have a long history of successful usage and doctors as well as patients rely on them heavily. Therefore, we developed a quality-controlled polyherbal formulation, "Plantabetics", as an add-on therapy. For this purpose, our formulation does not contain direct blood sugar lowering ingredients. This has the benefit that people with type 2 diabetes can continue with their prescribed medication and additionally take Plantabetics as an adequate complementary therapy.

The final product (Plantabetics®) was composed of 350 mg standardized extracts of fenugreek (*Trigonella foenum-graecum)*, Indian gooseberry (*Emblica officinalis*), grape seed (*Vitis vinifera*) and turmeric (*Curcuma longa*) filled in a cellulose capsule. These ingredients were specifically chosen to target oxidative stress, inflammation and immune dysfunctions in type 2 diabetes mellitus. Tannins of Indian gooseberry and proanthocyanidins of grape seeds have been reported to induce endogenous antioxidant enzyme production and improve antioxidant status in rat's brain and heart [19,20]. Polyphenols of turmeric have antioxidant as well as anti-inflammatory properties [21,22]. Besides its effects on hyperlipidemia, Fenugreek contains immune regulatory polysaccharides [23,24]. It has been established that immune imbalance can also be a cause of β-cell death in type 2 diabetes, like in case of type 1 [12,25]. In order to determine the effect of the above product on blood sugar control we conducted an open label clinical study with type 2 diabetes patients in advanced stage where OHAs did no longer achieve sufficient glycemic control.

To our knowledge this is the first report of a clinical before/after study with a quality-controlled herbal formulation devoid of hypoglycemic agents specifically designed as an add-on therapy to target metabolic disorders of type 2 diabetes mellitus, which are not adequately addressed in conventional therapy.

2. Research design and methods

2.1. Product composition

The investigational Product (IP) contained 350 mg total extracts of fenugreek (*Trigonella foenum-graecum,* 110 mg), Indian gooseberry (*Emblica officinalis,* 90 mg), turmeric (*Curcuma longa,* 70 mg) and grape seed (*Vitis vinifera,* 80 mg) in the form of capsules. The product is available under the trade name Plantabetics® in Germany and Europe and is registered as a "food for special medical purpose – a partial balanced diet for dietary management of type 2 diabetes mellitus" as per Commission Directive 1999/21/EC .

2.2. Quality control

Herbal products show geographical and seasonal variations in constituents and need proper quality control for maintaining standard and efficacy. Analytical quality control according to GMP is very difficult in polyherbal formulations containing more than 4 or maximum 5 plants. Therefore, the product was limited to 4 plant extracts. Methods for quality control were developed by using a suitable marker substance for each individual ingredient like curcumin for *Curcuma longa* and elagic acid for *Emblica officinalis*.

2.3. Clinical study

2.3.1. Study design

The study was designed as a prospective, single arm, open label investigation of the efficacy and safety of the IP in patients with type 2 diabetes not responding to a therapy of metformin and sulfonylurea, which is usually given in advanced stage. Study duration was 84 days. The study was conducted in India under full GCP compliance at 3 sites. The trial was registered in national trial register according to WHO instruction under the following clinical trial number: CTRI/2011/11/002170; clinical trials registry India (http://www.who.int/ictrp/network/ctri2/en/).

A local clinical research organization, Vedic Lifesciences Pvt. Ltd. (Mumbai), was contracted for clinical research service and implementation of GCP guidelines

2.3.2. Ethical procedure

This study was conducted according to International Conference on Harmonization Good Clinical Practices (ICH-GCP), applicable government regulations and institutional research policies and procedures. The study protocol, informed consent form (ICF) and other required documents were submitted to an independent ethics committee (IEC-Aditya of Ahmadabad, India) and written approval for each study site was granted. The study was conducted throughout under vigilance of IEC. Prospective participants were provided an approved ICF in English and other local languages describing the main feature of the study according to GCP guidelines. Doctors explained the study to them providing sufficient information to make an informed decision about their participation in this study. Patients or patient's legally acceptable representative provided signed and dated informed consent for study participation.

2.3.3. Investigators

The following doctors in Mumbai, India, were responsible for patient recruitment, selection and implementation of the study according to protocol. The patients were recruited in the respective clinics mentioned below.

1. Rajesh Kewalramani, MBSS, Shanti Niketan, Shop No-16, Bldg. No.13-A, Kandarpada, Dahisar (West), Mumbai-400 068, Maharashtra, India.
2. Shrikanta Pensalwar, MBSS, Balaji Clinic, Main Devipada Road, Borivali (East), Mumbai-400 066Maharashtra, India.
3. Sanjay Palimkar, MBSS, Shree Siddhi Clinic, Shop no. 01, H.S Khan Chawl, S. N. Dube road, Rawalpada, Dahisar (E), Mumbai. 400 068, Maharashtra, India.