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Slimpid May Boost Plasma IGF-1 Level and Improve the Quality of Life in Patients with Risk of Developing Metabolic Syndrome

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Abstract

Metabolic syndrome (MS) may affect the quality of life (QOL) of patients, and possibly their plasma IGF-1 level. This study is to investigate whether the QOL would be improved and IGF-1 level elevated simultaneously by a Chinese herbal formula, Slimpid (Rhizoma Alismatis, Radix Paeoniae Alba, Semen Cassiae, Pericarpium Arecae, Fructus Crataegi and Astragalus membranaceus). Forty nine subjects with one or more risk factors of MS were divided into Group A (n = 24) and Group B (n = 25) randomly in a double-blinded arrangement. The Chinese Quality of Life Instrument(1) and plasma IGF-1 were engaged as the measure outcomes. Significant improvement in stamina ($P < 0.05$) of test subjects at the 6th week and in complexion ($P < 0.05$) and stamina ($P < 0.001$) at the 12th week after administration of Slimpid were observed. No such changes were observed in the placebo group. Serum IGF-1 level of the test subjects increased significantly ($P < 0.05$) from the 6th week to the 12th week. No such change was observed in the placebo group. In conclusion, Slimpid may be able to improve QOL of subjects associated with MS. The delayed increase in IGF-1 might contribute partially to the improvements of QOL of the test subjects.

KEYWORDS: Slimpid, IGF-1, quality of life, metabolic syndrome

INTRODUCTION

Metabolic syndrome (MS) is a medical condition characterized by central obesity, hypertension, insulin resistance and atherogenic dyslipidaemia [1, 2]. It is responsible for a growing number of premature deaths throughout the world [3]. The epidemic proportion of MS in industrialized countries currently exceeds 20% of individuals who are at least 20 years of age, and 40% of the population older than 40 years of age [4]. In the US, it is estimated that 20% of adults (about 47 million) suffer from MS [5], with 44% of the US population over 50 years of age meeting the criteria recommended by the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) [6]. It has been reported that atherosclerosis is increased and fibrinolytic function is abnormal in people with MS [2, 7, 8]. Fibrinolytic dysfunction increases the risk of arterial thrombosis development that may increase cardiovascular disease in people with MS [9]. On the other hand, Bolger and his co-workers have demonstrated that higher concentrations of insulin-like growth factor 1 (IGF-1) in chronic diseases including MS may be an advantage [10]. It has also been shown that IGF-1 is not only a major survival factor for the heart, but it also plays an important role in improving cardiac function [11]. Therefore, increasing IGF-1 level might protect the cardiovascular system and decrease the morbidity of MS. Moreover, obesity, being one of the risk factors of MS, profoundly affects quality of life (QOL) as assessed by the health-related quality of life (HRQOL) instruments [12]. Impairments have been reported in physical functioning in obese individuals, including general health, bodily pain and psychosocial status [13]. Yet, the QOL of patients suffering from MS has rarely been studied.

Chinese medicinal materials and herbal formulae are known to be able to promote health status in terms of QOL. Furthermore, recent studies conducted in our laboratories demonstrated that Chinese herbal formulae are capable of elevating IGF-1 levels in healthy aging subjects [14] and in chronic hepatitis B carriers [15]. In the present study, the efficacy of a Chinese herbal formula, Slimpid, was assessed for the treatment of patients with MS, or at risk of developing MS, by monitoring IGF-1 levels before and after treatment and using the responsiveness of the Chinese Quality of Life (ChQOL) [16, 17, 18] questionnaire as the instrument for monitoring the patient reported outcomes.

MATERIALS

Patients

Forty-nine subjects (13 males aged 35 to 62 years and 36 females aged 20 to 58 years) were recruited through the community by public announcement. Fasting triglyceride level regarded as borderline or above and or with low HDL cholesterol level were the target of recruitment. Since MS was the preference of the current study, subjects possess risk factors identified with the criteria of NCEP-ATP III, i.e. high systolic blood pressure; high fasting blood glucose and central obesity [6], were preferably recruited. The recruited subjects signed a consent form to take part in the study, and agreed not to receive any other Chinese medicine (CM) treatment during the trial period. Ethical approval was obtained from the Committee on the Use of Human & Animal Subjects in Teaching and Research, Hong Kong Baptist University. All subjects were assessed by a Chinese medicine practitioner (CMP) registered with the Chinese Medicine Council of Hong Kong and a medical doctor registered with the Hong Kong Medical Council for their eligibility prior to the entry of the study. The subjects were recruited based on the following inclusion and exclusion criteria:

Inclusion Criteria

a. Subjects aged 20 or above, both male and female, who met any one of the following criteria:

1. fasting triglyceride level ≥ 150 mg/dl (1.69 mmol/l)
2. HDL-cholesterol level ≤ 40 mg/dl (1.03 mmol/l) for male and ≤ 50 mg/dl (1.29 mmol/l) for female

b. Subjects who met the criteria of (a) with any one or more of the following criteria had preference for recruitment:

1. systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg
2. fasting blood glucose ≥ 110 mg/dl (6.1 mmol/l)
3. central obesity as measured by waist circumference (male > 102 cm; female > 88 cm); these figures have been modified for Asians as men ≥ 90 cm; women ≥ 80 cm

According to the NCEP-ATP III criteria, MS is identified by the presence of three or more of the risk factors from either 'a' or 'b' in one person. Of the 49 recruited subjects, only 24 subjects fulfilled the NCEP-ATP III criteria of MS. The rest possessed 1 to 2 risk factors.

Exclusion Criteria

A subject would be excluded from the study if he / she met any of the following criteria:

1. had major problems associated with cardiac, respiratory, renal and hepatic functions, diabetes mellitus or neoplastic disease
2. HIV infection
3. I.V. or other drug abuse
4. used any traditional Chinese medicine (TCM) therapy one month prior to entering the study
5. used any other investigational drug(s) one month prior to entering the study

Slimpid

Slimpid, an herbal capsule preparation provided by Modern TCM Ltd, an ISO 9000 certified commercial firm registered in Hong Kong, is prepared from the concentrated extract granules of cultivated Chinese herbs including *Radix Astragali membranaceus* (31.2%), *Radix Paeoniae Alba lactiflora* (12.5%), *Semen Cassiae obtusifolia* (12.5%), *Pericarpium Arecae catechu* (12.5%), *Fructus Crataegi pinnatifida* (18.8%) and *Rhizoma Alisma orientalis* (12.5%).

In TCM, *Radix Astragali membranaceus* is used for treatment of deficiency of the *spleen-qi* and *lung-qi* with general debility. *Radix Paeoniae Alba lactiflora* is used to nourish the blood, regulate menstruation, stop sweating and relieve pain. *Semen Cassiae obtusifolia* (12.5%) is used to relax bowels. *Pericarpium Arecae catechu* is used to remove stagnation, descend the adverse flow of *qi* to loosen the bowels and induce diuresis to alleviate oedema. *Fructus Crataegi pinnatifida* is used to improve digestion, promote blood circulation and resolve blood stasis. *Rhizoma Alisma orientalis* is used to induce diuresis, excrete dampness and expel pathogenic heat [19].

The concentrated extract granules were manufactured by a supplier with good manufacturing practice (GMP). The granule-mixture was formulated through standardized procedures to obtain the capsule dosage form according to the quality assurance and quality control requirements of Modern TCM Ltd. Briefly, hot water extraction was used for individual herb. The length of extraction was around 45-60 min which varied for different herbs. The extracts in dry

powder form were mixed in appropriate ratio and finally packed in capsules. Each capsule contains 0.5 g of concentrated extract granules. The amount of extract used, when converted to the crude herbs, is equivalent to the dosage generally applied for tonic preparation with the traditional procedure.

Slimpid has been prescribed by the CMPs of Modern TCM Ltd. in their clinical practice for more than 6 years. It has only been sold to patients directly by the said CMPs. Thus, close communication between patients and CMP is maintained and it is confident that the product shows efficacy with no adverse effects. Slimpid has also been submitted to the Chinese Medicine Council of Hong Kong for registration. It has passed the following quality assurance tests performed by Hong Kong Standards and Testing Centre:

1. Heavy Metals or Toxic Elements Test
2. Microbial Limit Test
3. Residual Pesticides Test
4. Acute Oral Toxicity Test – Maximum Tolerable Dose (> 64g/kg)

The content of the major ingredient, astragaloside IV of one of the herbs, *Radix Astragali membranaceus*, was determined by HPLC and TLC.

Placebo

The concentrated extract granules of the placebo were manufactured by a supplier with good manufacturing practice (GMP). It contains *Oryzai sativa L.* (50%) and *Radix Scrophulariae ningpoensis* (50%) because they simulate the taste and odour to Slimpid capsules. Each capsule contains 0.5 g of concentrated extract granules. *Oryzai sativa L.* serves as a carbohydrate base while *Radix Scrophulariae Ningpoensis* nourishes body fluid and clears away heat [19]. However, the amount used was so low and no significant activity would be expected.

ChQOL Instrument

The ChQOL is a self-reported generic instrument comprising 3 domains, 13 facets and 50 items. The 3 domains are the Physical Form domain, the Spirit domain and the Emotion domain. There are 5 facets under the Physical Form domain including complexion, sleep, stamina, appetite and digestion, and adaptation to climate; 4 facets under the Spirit domain including consciousness, thinking, spirit of the eyes and verbal expression; 4 facets under the Emotion domain including joy, anger, depressed mood, and fear and anxiety. The ChQOL is established in the form of a questionnaire comprising 50 questions. The score for each question ranges from 1 to 5. Each facet score is the sum of the scores for corresponding

questions. The domain score was obtained by taking the mean \pm SD of respective facet scores within that domain. It is one of the very few HRQOL instruments which was developed based on a clear and precise theory of health in the context of traditional Chinese medicine. Field test results indicated that the structure of the ChQOL was valid and the psychometric properties were good [16].

METHODS

Study Design

This is a randomized, double-blinded and placebo-controlled study. Forty-nine participants were divided randomly into 2 groups, i.e., Group A (24 subjects) taking Slimpid and Group B (25 subjects) taking placebo, 6 capsules each time, twice daily for 12 weeks. Three grams of Slimpid, when converted to the crude herbs, is equivalent to the dosage generally used for tonic preparation with the traditional procedure. Randomization was achieved using randomization tables managed by a registered CMP unrelated to the study.

Laboratory Investigations

Ten ml of blood samples were taken on 3 occasions at 0, 6, 12 weeks from each subject for the laboratory investigations. Fasting blood glucose, creatinine, alanine transaminase (ALT), total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride were all analyzed by the Dimension RXL (Dade Behring). Complete blood picture (CBP: red cell count, haemoglobin, platelet count, white cell count including differential count) was performed by the Abbott Cell-Dyne 1300 cell counter. Insulin-like growth factor 1 (IGF-1) was measured by the DPC Immulite.

All the above tests were performed at Diagnostix Medical Centre (DMC), a Hong Kong registered medical laboratory accredited by the National Accreditation Testing Authority of Australia (NATA).

ChQOL Assessment

The assessment of QOL was conducted at 0, end of 6th and 12th weeks during each clinic visit using the Cantonese Chinese version of the ChQOL instrument [16].

Statistics

Paired t-test was used to compare data before and after the administration of Slimpid / placebo. Unpaired t-test was used to compare data between-groups before and after the administration of Slimpid / placebo. A p value below 0.05 was regarded as significant.

RESULTS

There was a significant improvement in the stamina score (p<0.05) of test subjects 6 weeks after administration of Slimpid, and significant improvements in complexion (p<0.05) and stamina (p<0.001) scores were observed after 12 weeks, leading to a significant improvement in the physical form score (p< 0.05) at 12th week. No such changes were observed for the placebo group. The treatment outcomes of QOL over the entire 12-week treatment period for both test and placebo groups are shown in **Table 1**.

Table 1. Improvements of quality of life as assessed by the ChQOL after administration with Slimpid (Group A, n = 24) and placebo (Group B, n = 25) for 6 and 12 weeks. The domain and facets are expressed in terms of numerical scores (mean ± SD) converted from the responses of the ChQOL questionnaire. A p value of < 0.05 is considered significant. All data are compared with the baseline values unless specified otherwise.

Group		Baseline	At 6 th wk	At 12 th wk
		Mean ± SD	Mean ± SD	Mean ± SD
Slimpid	Facet: Complexion	47.66 ± 14.01	49.48 ± 12.62	54.43 ± 16.74*
	Facet: Stamina	54.69 ± 15.51	59.72 ± 16.56*	65.10 ± 13.95**
	Domain: Physical form	62.22 ± 9.80	62.60 ± 9.36	64.70 ± 10.52*
Placebo	Facet: Complexion	43.75 ± 16.14	45.25 ± 15.65	44.25 ± 18.21
	Facet: Stamina	46.17 ± 15.91	50.17 ± 14.08	50.67 ± 13.16
	Domain: Physical form	58.85 ± 10.94	58.60 ± 11.96	59.33 ± 12.19

* p < 0.05 ** p < 0.001

When the between group comparisons were made for complexion, stamina and

physical form at different stages, significant differences were observed for complexion at 12th week (p<0.05) and for stamina at both 6th (p<0.05) and 12th (p<0.001) weeks, but no significant difference for physical form was observed.

For IGF-1, a significant change in Slimpid group subjects at 12th week was observed (p < 0.05) when the results were compared with those of 6th week rather than the baseline. No such difference was observed in the placebo group. However, when the Slimpid group IGF-1 levels were compared with those of the placebo group at all stages, no significant difference was observed. **Table 2** shows the within group changes of serum IGF-1 levels in both groups.

Table 2. Changes of serum IGF-1 levels (mean ± SD) after administration with Slimpid (n = 24) and placebo (n = 25) for 6 and 12 weeks. A p value of < 0.05 is considered significant. Data are compared with the baseline values unless specified otherwise.

Group	IGF-1 (µg/L)		
	Baseline	At 6 th wk	At 12 th wk
Slimpid	169.04 ± 59.94	164.67 ± 41.79	184.38 ± 51.23*
Placebo	164.36 ± 68.17	168.04 ± 57.36	176.96 ± 62.84

* p < 0.05, compared with 6th week

DISCUSSION

Current western treatment of MS primarily focuses mostly on the specific causes of diseases including insulin resistance, glucose intolerance or dyslipidaemia [6, 20]. They mainly emphasize on the observation of changes in biomedical markers after treatment. Nevertheless, a holistically oriented approach, including lifestyle modification and behavioral interventions, has been recommended. Moreover, investigations of the QOL of patients with MS have seldom been conducted.

In the practice of Chinese medicine, disease prevention with a holistic approach is often emphasized. The concept of preventive treatment has dual meanings. It includes a treatment to prevent the occurrence of diseases, and also an early treatment of a disease to prevent the occurrence of complications [21]. As early as 2500 BC, disease prevention and measures to prevent a disease from worsening were mentioned in the Chinese Internal Classic (Huang Di Nie Jing). In this regard, the maintenance of a balance of *Yin* and *Yang* is essential in achieving a healthy status [22]. In order to maintain such a balance, it is

necessary to strengthen body resistance for prevention against the invasion of pathogenic factors. In the present study, the CM approach was adopted for the assessment of the efficacy of a Chinese herbal formula, Slimpid, in patients possibly with MS or at risk of developing MS. Though the actual mechanism of the treatment efficacy is not yet known, most of the ingredients of Slimpid are traditionally believed to exert anti-ageing effects [23], possibly by regulating both *Yin* and *Yang*, via regulating endocrine and metabolic functions. Such effects refer to as “supplementing *Qi* to strengthen *Pi*” and “*eliminating* inner-heat and dampness” in the context of Chinese medicine. Efforts were made to provide scientific evidence including IGF-1 and QOL assessment in support of the efficacy of treatment and patient reported outcomes.

The aim of the study was to study patients ‘preferably’ met NCEP-ATP III criteria with MS. In the present study, only 24 subjects met NCEP-ATP III criteria for MS but all the 49 participants were included, i.e., subjects with only 1-2 risk factors were also included. Patients were not classified into two different groups but made uniform by double-blind randomization.

First of all, results indicate that Slimpid is safe for clinical use as far as the clinical response and laboratory parameters are concerned. There was no report of any adverse event from the participants, both from the test and placebo groups. From the laboratory results (data not shown), the reference haematological (CBP), renal function (creatinine) and liver function (ALT) tests were all within the reference range at baseline, as well as after 6 and 12 weeks treatment, indicating that Slimpid was not associated with any harmful effect on the blood system, kidney and liver, respectively.

It has been demonstrated that growth hormone (GH) decreases in middle-aged (40 – 65 years) and older (> 60 years) populations [24] and that patients with chronic diseases (including MS) may benefit from higher levels of IGF-1 [10] which is known to be a surrogate of GH. In the present study, it was demonstrated that the serum IGF-1 level of the test subjects (Slimpid group) showed a significant increase from 164.67 µg/L at 6th week to 184.38 µg/L at 12th week (increased by 19.71 µg/L or 12.0%). The IGF-1 level at 6th week showed a non-significant decrease (decreased by 4.37 µg/L or 2.6%) when compared with the baseline level. No significant changes were observed when the IGF-1 levels at 6th and 12th weeks were compared with the baseline level, though a slight increase of the 12th week level (increased by 15.3 µg/L or 9.1%) was documented. It is speculated that a longer treatment period with Slimpid may be able to allow a more significant increase in IGF-1.

For the QOL assessment, there were significant changes in the scores of different facets and the domain of physical form in Slimpid Group subjects. A significant improvement in complexion ($p < 0.05$) was observed after administration with Slimpid for 12 weeks. Furthermore, significant improvements in stamina were

documented at 6th week ($p<0.05$) despite the slight decrease in IGF-1 concurrently as mentioned above, and at 12th week ($p<0.001$). Consequently, a significant improvement in the domain of physical form ($p<0.05$) was documented. No such changes were observed for control subjects.

Apparently, the observed beneficial effect of Slimpid in terms of laboratory parameters in this trial could be IGF-1, which showed a delayed response after 6 weeks treatment. However, the lack of significant difference between the test and control groups may indicate that such a significant change could possibly be a placebo effect without clinical significance. On the other hand, should it be a genuine increase, it may not be illogical to speculate that this delayed increase of IGF-1 might contribute partially to the improvements of complexion and stamina of the test subjects as observed in the ChQOL assessment. A larger population study with either higher doses or longer treatment period may strengthen this observation.

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