

## Impact of the Synchronization of *portulaca oleracea* and Aerobic Training on Levels of MMP2 and MMP9 and TIMP1 in Diabetic Women Type II

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### Abstract

**Background:** Diabetes has the most important role in development of tissue damage, and by affecting intercellular matrices, may lead to structural and functional changes that ultimately cause failure of related tissue or organ. Exercise and herbal medicine can be effective in reducing organ failure. This study aims to assess the effect of aerobic training combined with consumption of *portulaca oleracea* supplements on Metalloproteinase Matrix 2 (MMP2), Metalloproteinase Matrix 9 (MMP9), and Tissue Inhibitor of Metalloproteinase Matrix (TIMP1) in diabetic women type II.

**Materials and Methods:** 28 women with type II diabetes and average age of 51 years were divided into 4 groups of control (CG), exercise (EG), exercise-supplement (E-SG), and supplement (SG). A course of exercise was designed to cover 60-minute, 3 sessions per week for 8 weeks, with 50-70% maximum heart rate intensity. A 7.5 grams daily supplement of *portulaca oleracea* was administered, consisting of 2.5 grams with luncheon and 5 grams at dinner. Blood samples were taken before and after 8 weeks of intake of supplement and exercise following 48 hours of non-consumption of supplement and 12 hours of fasting. Data were analyzed using variance analysis model.

**Results:** After 8 weeks, MMP2, MMP9 levels significantly reduced in all groups ( $P < 0.05$ ). But the difference between groups was insignificant. TIMP1 level significantly increased in all groups but control, and there was a significant difference in TIMP1 level between control and supplement groups ( $P < 0.05$ ).

**Conclusion:** According to the results, aerobic training together with purslane seed intake, did not positively affect matrix metalloproteinase, but its inhibitors were effective. Thus, further study is required for more accurate results.

**Keywords:** Matrix metalloproteinase; Aerobic training; *Portulaca Oleracea*; Diabetic women type II

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### Introduction

Diabetes mellitus is a common metabolic disorder worldwide, and is associated with high blood glucose, inadequate secretion or dysfunction of insulin (1). Epidemiological studies reveal a growing trend of complications in diabetics, which could be due to the complex nature of this disease and/or lack of full compliance of patients with treatment programs (2). For years, cardiovascular incidences have been the main cause of premature deaths in type II diabetes patients (3-5). Recent studies indicate that matrix

metalloproteinases (MMPs) play an important role in atherosclerosis and remodeling of the vascular wall (6), and existing MMPs in the arteries of patients with type II diabetes are involved in acute myocardial ischemia (7-8), so that, MMP1, MMP2, MMP3, MMP7, MMP9 are activated during the formation and instability of atherosclerosis plaque (9).

Matrix metalloproteinases (MMPs) are a large group of proteinase, responsible for the degeneration of extracellular matrix, and their actions under

physiological conditions such as wound healing and angiogenesis are vital, but transient(10-11). However, in pathological processes like diseases, as well as the pressure of physical and mechanical processes, the expression and action of these proteolysis enzymes increase due to secretion of pre inflammatory cytokines, causing disintegration of collagens and gelatinase, and breakdown of microanatomy and tissue structure of the body, and in time, resulting in sever inflammation and incidence of various diseases such as heart disease and vascular wall damage (12-13). Since the activity of these proteins needs to be accurately adjusted and controlled, specific inhibitors are involved in their control and inhibition. Inhibitors of these enzymes are the family of Tissue Inhibitor of Metalloproteinase Matrix (TIMP), which have a high serum concentration (14).

Studies indicate adequate levels of physical activity can prevent early onset of cardiovascular diseases in obese and overweight people (15). It seems weight loss could have a protective effect against atherosclerosis in diabetic patients. Results of a study showed that 16 weeks of aerobic exercise caused a reduction in MMP2 and MMP9 and an increase in TIMP in obese diabetics (16). New studies consider use of herbal medicine effective in promoting health and prevention and treatment of type II diabetes (17-18). Amongst the herbs, purslane, a strain of fenugreek family, is the most effective anti-diabetes plant, and with analgesic and anti-inflammatory effects, it is considered a source in traditional medicine (17). With a scientific name of *Portulaca Oleracea* L, purslane is a grass like plant with yellow flowers and red or purple stem that grows widely across the world (19-20). Due to its unsaturated fatty acids, phenolic, and polysaccharides contents, purslane has hypoglycemic, hypolipidemic, and insulin resistance reduction properties. Therefore, it may be used as adjuvant therapy for patients with type II diabetes (21-23). Given that, MMPs response to aerobic training and purslane has not been identified, thus, study on the effects of simultaneous aerobic exercise and purslane intake on proteinase, particularly MMP2, MMP9, and TIMP in women with type II diabetes seems necessary, and the present study aims to do that.

## Materials and Methods

### *Study Participants*

This study was a quasiexperimental clinical trial with a control group and pre-test, post-test design. The study population consisted of women with type II diabetes attending Imam Khomani health center in Sari City in 2012. For the purposes of this study, 28 volunteers with ages ranging 44-57 years were selected. These subjects should have been with no

chronic or acute complications of diabetes, and no regular exercises, and with blood sugar levels higher than 130 mg/dl, controlled by metformin only. The selected subjects were randomly divided into four groups (7 each) of control (CG), exercise (EG), exercise-supplement (E-SG), and supplement (SG). All participants individually took part in briefings and learned what was required of each group. Once the study objectives were explained and patients consented to take part, demographic information and medical history including duration of diabetes, level of physical activity, type and dose of drugs taken, and details of other diseases were collected through interviews and questionnaires. History of liver and renal diseases, hyper/hypothyroidism, wild fluctuations of blood glucose, smoking, use of insulin or any vitamin and mineral supplement 3 months prior to commencement of study, meant exclusion of these patients. Also, verbal and written notice was served to all participants regarding prohibition of some activities, and finally, with the proviso that subjects may withdraw from the study at any time they wished, each signed the consent form.

### *Clinical variables*

Prior to start of study, measurements of anthropometric parameters such as height, weight, and BMI were taken. Digital scales with accuracy to 0.1 kg were used to measure patients' weight wearing least clothing and no shoes. A standard measuring tape was used for height measurement of patients in standard position wearing no shoes. After 15 minutes of rest and in a sitting position, blood pressure was measured twice. Then 7 cc blood samples were taken from the brachial vein after 12 to 14 hours fasting between 8 and 10 o'clock in the morning. By the end of the 8 weeks of study, final blood samples were taken in a similar manner. Blood samples were transferred into test tubes containing anti-coagulation solution EDT, and to separate plasma, they were centrifuged at 3000 rpm for 10 minutes at 4 °C. For measurement of MMP2, MMP9, and TIMP, the plasma obtained was kept frozen at -80 °C.

### *Training protocol*

At first, the aerobic training was done at low-intensity with instructions of how to do the moves in order to familiarize the participants with the program. Exercise group subjects performed training at 50-55% of the maximum heart rate for 25 minutes in the first training week. The gradual increase in training intensity and duration were subsequently established such that the subjects performed training at 65-70% of the maximum heart rate for 60 minutes at the end of the eighth week. Main exercises were done at moderate rhythm separately focusing on arms, legs

and torso and increasing the heart rate so that a number of simple combination moves were added to the workout routine at fifth and sixth weeks and combination moves with were done at higher speed, more sets and repetitions as to prepare for the harder stages at eighth week. Warm up in every exercise session was included the light walking, static and dynamic stretching for 15 minute in the first training week, brisk walking at the fifth and sixth weeks, and jogging (at a faster pace) with greater involvement of the arms, and stretching exercises at the eighth week. A cool down program included a set of static

stretching exercises both sitting and lying in the first training week, stretching in standing and sitting positions at the fifth and sixth weeks, and simple stretching and flexibility exercises performed alone or in pairs at the eighth week for 10 minute. The SG and CG maintained routine daily activities and did not participate in the exercise program. Exercise frequency was 3 sessions per week, and the sessions were conducted in groups between 8 am and 10 am (due to limit of diurnal variation) (15). The participant's maximum heart rate stimulated using HRmax equation  $208 - (0.7 \times \text{age})$  (24).

**Table 1.** Clinical characteristics of study subjects at baseline

Variables	EG (n=7)	CG (n=7)	E-SG (n=7)	SG (n=7)	P value
Age, yr	50.83 ± 6.79	50.17 ± 5.34	51.17±4.88	52.33±4.08	0.486
Weight, kg	79.5 ± 8.96	75.67 ± 9.44	70.83±7.88	73.5 ± 4.89	0.738
Height, cm	162.5 ± 6.53	160.67 ± 6.54	154.5 ± 6.53	159.17 ± 6.65	0.662
BMI, Kg/m <sup>2</sup>	30.71 ± 4.34	29.37 ± 4.55	29.88 ± 4.34	29.01 ± 4.34	0.576
SBP, mm Hg	152.12±7.47	152.37±8.97	151.7±5.7	151.53±5.45	0.453
DBP, mm Hg	93.37±8.84	92.5±9.69	91.5±3.6	91.47±7.51	0.645

Values are presented as mean ± standard deviation. EG, exercise group; E-SG, exercise-supplement group; SG, supplement group CG, control group; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

#### Preparation of *Portulaca Oleracea*.L

E-SG,SG were given 7.5 grams purslane seeds powder in 40 ml of skimmed yogurt with food for 8 weeks (2.5 grams with lunch and 5 grams with dinner) (22). *Portulaca Oleracea* dose selected according to the average consumption of purslane as a seed is in some places. Purslane seed prepared from market in Sari and delivered weekly to participants. CG and EG similarly received placebo pills (the flavored maltodextrin). The recommendations for the amount and time consuming noted. Also, a daily diet of 2500-3000 kcal was recommended, which included 50-55 percent carbohydrates, 25-30 percent fat, and 10-15 percent protein (24). Purslane seed was confirmed and recognized by agricultural expert. In addition, all subjects were under medical supervision to record and remove hurt effects.

#### Biochemical Analysis

Fasting blood glucose, TC, TG, HDL-C and LDL-C levels were measured by Biochemical Kit (Pars Azmon Inc., Iran), Device (BS200, Minderly., Germany). MMP2, MMP9 and TIMP1 concentrations were measured by Human enzyme immunoassay Kit (Cusabio biotech Inc., Chinese), Device Elisa Reader (Awareness Stat Fax 2100, USA) in accordance with the guidelines of the kit, respectively, detection range 0.78 -50 ng/ml and sensitivity 0.2 ng/ml, detection range

0.16-10 ng/ml and sensitivity 0.04 ng/ml, detection range 12.5-5000 pg/ml and sensitivity 5 pg/ml. CRP level were measured by Human enzyme immunoassay Kit (Diagnostic Biochem Inc., USA) sensitivity 10 ng/ml and Intraassay CV%:5.4%.

#### Statistical analysis

For the assessment of inter-group variations, paired t-test was used. To determine the differences between groups, statistical analysis of variance (2×4) with the post hoc Tukey test was used. The Kolmogrov-Smirnov test was used to assess normal distribution of variables, and Leven-test used for variance convergence test. Level of significance  $P < 0.05$  was set for all calculations.

#### Results

The general characteristics between participants are presented in table 1. Results showed a reduction in MMP2 concentration in SG ( $p=0.014$ ,  $t=3.42$ ), EG ( $p=0.006$ ,  $t=4.08$ ), and E-SG ( $p=0.000$ ,  $t=9.48$ ). But, this reduction in CG was insignificant ( $p=0.668$ ,  $t=0.422$ ). The MMP9 level showed a reduction in all groups, with SG ( $p=0.003$ ,  $t=4.82$ ), EG ( $p=0.01$ ,  $t=3.67$ ), E-SG ( $p=0.007$ ,  $t=3.95$ ), and in the CG with insignificant reduction ( $p=0.27$ ,  $t=1.21$ ). The TIMP1 level showed a significant increase in the SG ( $p=0.26$ ,  $t=2.95$ ), EG ( $p=0.006$ ,  $t=4.09$ ), and E-SG ( $p=0.001$ ,

t=6.6), but this increase was insignificant in the CG ( $p=0.435$ ,  $t=0.835$ ). Also, there was a significant difference between the CG and SG ( $p=0.023$ ) (table 2). Interestingly, the average concentrations of TG ( $P=0.087$ ), TC ( $P=0.061$ ) and LDL-C ( $P=0.098$ ) were significantly decreased and the average

concentration of HDL-C ( $P=0.006$ ) was elevated after 8 weeks in the all groups. The CRP level showed a reduction in all groups, with SG ( $p=0.008$ ,  $t=3.58$ ), EG ( $p=0.006$ ,  $t=4.11$ ), E-SG ( $p=0.001$ ,  $t=6.39$ ), and in the CG with insignificant reduction ( $p=0.905$ ,  $t=0.125$ ) (Table 2).

**Table 2.** Changes in the measured variables between 4 groups before and after 8 weeks.

Variable	Stage	EG	E-SG	SG	CG	P- value <sup>b</sup>
MMP2, ng/mL	Before	0.63 ± 0.25	0.6 ± 0.33	0.6 ± 0.24	0.44 ± 0.21	0.139
	After	0.37 ± 0.2 <sup>a</sup>	0.16 ± 0.12 <sup>a</sup>	0.33 ± 0.24 <sup>a</sup>	0.42 ± 0.21	
MMP9, ng/mL	Before	1.04 ± 0.32	1.39 ± 0.23	1.1 ± 0.53	0.61 ± 0.21	0.04
	After	0.76 ± 0.47 <sup>a</sup>	0.54 ± 0.23 <sup>a</sup>	0.75 ± 0.61 <sup>a</sup>	0.59 ± 0.4	
TIMP-1, pg/mL	Before	7.03 ± 1.58	4.86 ± 0.85	7.48 ± 1.78	6.39 ± 2.04	0.018
	After	8.55 ± 1.22 <sup>a</sup>	8.88 ± 1.56 <sup>a</sup>	8.84 ± 1.43 <sup>a</sup>	6.48 ± 2.23 <sup>c</sup>	
Glucose, mg/dL	Before	176.29 ± 42.5	190.43 ± 29.47	166.4 ± 41.49	163.3 ± 42.59	0.000
	After	142.43 ± 49.51 <sup>a</sup>	117.29 ± 14.44 <sup>a,c</sup>	145.9 ± 32.27 <sup>a,c</sup>	176.26 ± 19.17	
TG, mg/dL	Before	176.3 ± 42.5	190.43 ± 29.47	181.14 ± 41.49	167.14 ± 40.33	0.087
	After	142.43 ± 49.51 <sup>a</sup>	117.29 ± 14.44 <sup>a</sup>	151.29 ± 39.17 <sup>a</sup>	171 ± 42.5	
TC, mg/dL	Before	183.57 ± 24.6	199.57 ± 22.83	194.43 ± 25.2	190.14 ± 22.15	0.061
	After	158.14 ± 19.26 <sup>a</sup>	152.43 ± 21.1 <sup>a</sup>	169.86 ± 27.2 <sup>a</sup>	201.86 ± 27.84	
HDL-C, mg/dL	Before	38.9 ± 7.8	25.6 ± 5.34	32.41 ± 7.48	37.61 ± 12.02	0.098
	After	44.21 ± 9.99 <sup>a</sup>	43.99 ± 7.57 <sup>a</sup>	43.29 ± 7.57 <sup>a</sup>	39.3 ± 12.61	
LDL-C, mg/dL	Before	96.3 ± 5.8	89.9 ± 6.34	84.1 ± 9.83	84.43 ± 7.42	0.006
	After	82.46 ± 7.4 <sup>a</sup>	64.89 ± 7.56 <sup>a,c</sup>	73.1 ± 8.12 <sup>a,d</sup>	81.63 ± 9.32	
CRP, mg/l	Before	7.7 ± 1.03	7.8 ± 1.6	8.2 ± 1.2	7.9 ± 1.07	0.139
	After	6.5 ± 1.3 <sup>a</sup>	4.7 ± 1.3 <sup>a</sup>	7.2 ± 1.6 <sup>a</sup>	7.5 ± 1.2	

Values are presented as mean ± standard deviation. EG, exercise group; E-SG, exercise-supplement group; SG, supplement group; CG, control group; MMP2, matrix metalloproteinases 2; MMP9, matrix metalloproteinases 9; TIMP-1, tissue inhibitor of metalloproteinase matrix; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; <sup>a</sup> changes of variables within groups; <sup>b</sup> changes of variables between groups; <sup>c</sup> significant difference between EG and E-CG groups; <sup>d</sup> significant difference between EG and SG groups.

## Discussion

After 8 weeks, results of the study showed a significant reduction in at-rest levels of MMP2 and MMP9 in EG, E-SG, SG, but TIMP1 level increased.

Compared to healthy people, MMPs are high in diabetics, due to high levels of glucose, and play an important role in the migration of inflammatory cells, production of inflammatory substances and also, restructuring of inter-cellular matrix. Disruption in their function leads to abnormalities in the function of the matrix, ending in inadequate response against physiological or pathological changes (25). Studies carried out in this area indicate a significant increase in plasma concentration in hs-CRP, TIMP, and MMP2 in type 2 diabetics (25). High circulation of MMP9 indicates diseases and cardiovascular incidences, and so far, only Statins have been used to treat reduction of MMP9 (26). Researches state that

exercise is a major factor in treatment of type II diabetes mellitus, and a moderate level of physical activity can cause improvement in glucose profile and reduction in cardiovascular risk factors in diabetics, which enhances serum MMP2 and MMP9 levels, and also significantly reduces MMP9 to TIMP ratio (27).

Activity level and presence of MMP directly relate to the intensity of endurance exercise and type of muscle fibers, and physical activity that is accompanied by injury to skeletal muscle, leads to stimulation of MMP presence (28). The findings of present study showed that 8 weeks of aerobic training causes a significant reduction in rest levels of MMP2 (42.3%) and MMP9 (32.89%), and a significant increase in TIMP1 level to 17.7%.

In line with this study, Kadoghlo et al. showed 150 minutes exercise per week for 16 weeks significantly

reduced MMP9 to TIMP ratio in diabetics, but MMP2 and TIMP levels did not change (16). Some studies argue that changes in plasma cytokines levels may be the cause of reduction in MMP2 and MMP9 levels following an exercise course. It has been shown that an increase in IL-13 and a reduction in MCP-1(27). Ruleman et al. findings in 2007 showed an increase in MMP9 following 65 minutes exercise. Intensity (28), duration, and type of exercise (29) may explain this difference. Higher-intensity exercise causes more Macrophages, which increases MMP9 secretion (30). In some studies, the role of purslane as a non-medical therapy in reducing blood glucose and insulin resistance due to content of polyunsaturated fatty acids, phelanoides, and polysaccharides has been identified (22). The mechanism of purslane crude polysaccharides function is not yet clear. Maybe purslane causes a reduction in insulin secretion through blocking  $K^+$ -ATP and depolarization membrane channels and stimulation of  $Ca^{2+}$  absorption (31).

Other findings of this study reveal that 8 weeks purslane intake produced similar results to exercising alone, and MMP2 and MMP9 reduced significantly to 45% and 28% respectively, and TIMP1 increased significantly to 21.38%. However, this reduction continued more intensely in exercise-supplement group (74.4% and 62.16% respectively), and TIMP1 increased as well. In a similar study, Lee et al. observed a significant reduction in blood glucose level and MMP2 after 10 weeks intake of liquid purslane extract in diabetic rats, and concluded with improving lipid homestasis, purslane prevents from development of atherosclerosis, and has a preventative effect on vascular pathologic complications (32). In the present study, as the intensity of exercise was lower than in studies that reported an increase in MMP2 and MMP9, consequently, lower inflammatory responses, macrophage deployment, and tearing of the muscle fibers appear normal.

### Conclusion

In summary, according to the findings of this study, aerobic training and intake of purslane did not positively affect matrix metalloproteinase, but did affect its inhibitor. Since diabetes has a destructive effect on various tissues, and with growing number of diabetics, further study is recommended to produce more accurate results.

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