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Effect of Hydroalcholic Nettle (*Urtica dioica*) Extract on Some Cardiovascular Risk Factors in Patients With Type 2 Diabetes

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Type 2 diabetes is a metabolic disorder which is strongly associated with cardiovascular risk and requires intervention to improve glycemic control and other cardiovascular risk factors. In this study, hydro alcoholic extract of Nettle (*Urtica dioica*) on some cardiovascular risk factors in type 2 diabetic patients were studied. A randomized single-blind clinical trial of 50 men and women with type 2 diabetes aged 52.39±13.75 years was conducted. Patients were adjusted by age, sex and duration of diabetes, then randomly divided into an intervention and control groups, they received, 100 mg kg^{-1} day^{-1} nettle extract or placebo in 3 portions for 8 weeks. Fasting Blood Sugar (FBS), glycated Hemoglobin (HbA1C), Fasting Insulin concentration, Total Cholesterol (TC), Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Triglycerides (TG), systolic blood pressure(SBP), Diastolic blood pressure (DBP) were measured, TC/HDL-cholesterol, LDL/ HDL cholesterol ratio , Log (TG/HDL-c) and Insulin Resistance were calculated, at the beginning and end of the study. The data were analyzed by SPSS version 18, $p<0.05$ was considered significant in all measurement. After 8 weeks, FBS ,HbA1C , TG , Log (TG /HDL-c) and SBP showed a significant decrease and HDL-cholesterol showed a significant increase in the intervention group compared to the control group ($p<0.05$). The findings of this study suggest that the hydro alcoholic extract of nettle has a beneficial effect on FBS, HbA1C, TG, HDL-c concentration, Log (TG /HDL-c) and SBP in patients with type 2 diabetes after eight weeks intervention.

Key words: Nettle, glycemic indexes, lipid profile, insulin resistance, diabetes mellitus

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INTRODUCTION

Diabetes mellitus is a metabolic disorder altering metabolism of carbohydrate, lipid and protein (Taylor, 2008). The world prevalence of diabetes among adults (aged 20-79 years) was 6.4%, in 2010 and will increase to 7.7%, by 2030. Between 2010 and 2030, there will be a 69% increase in diabetes patients in developing countries and a 20% increase in developed countries (Shaw *et al*., 2010). Diabetes mellitus leads to acute and chronic complications if not controlled and remains an important risk factor for cardiovascular disease. Since, risk of death from heart disease in patients with diabetes mellitus is 2-4 times greater than non-diabetic patients (Young *et al*., 2008). Often poor control of blood sugar is associated with lipid disorder. Improvement lipid profile can play an important role in prevention cardiovascular disease in diabetic patients (Shekhar *et al*., 2006). On the other hands, insulin resistance in type 2 diabetic patients represents a major underlying abnormality driving cardiovascular disease. The links between insulin resistance and the associated dyslipidemia, hypertension, hypercoagulability and atherosclerosis are numerous (Ginsberg, 2000). Consequently, control of blood sugar and lipid profile is an efficient way to prevent insulin resistance and cardiovascular disease in type 2 diabetes patients. In response to the increasing use of alternative medicine among the general public (Khan and Safdar, 2003), the American Diabetes Association encourage researchers to study about herbs and dietary supplement (Egede *et al*., 2002). One medicinal plant that is used to control glucose in folk medicine and traditional healing system around the world is *Urtica dioica* (Mehri *et al*., 2011). *Urtica dioica* from the Urticaceae family, also known as Stinging Nettle (Thorn, 2007). Nettle is used in most European countries to reduce inflammation and treat rheumatoid arthritis. There have been also other reports, indicating the benefits of using Nettle in different conditions, for example: bladder infection, inflammation of urinary tract and hypertrophy of prostate, seasonal allergies especially in children, dandruff, acne and rheumatic pain treatment (Chrubasik *et al*., 2007).

Some experimental and *in vitro* studies reported decreasing effect of *Urtica dioica* on blood sugar with or without changes in insulin secretion (Mehri *et al*., 2011) Other studies suggested beneficial effects for Nettle on glucose, lipid profile and blood pressure (Chrubasik *et al*., 2007).

It seems that the effects of Nettle on patients with type 2 diabetes are not studied. Therefore, the aim of this study was to investigate the effects of hydro alcoholic extract of Nettle on some cardiovascular risk factors in patients with type 2 diabetes.

MATERIALS AND METHODS

A Randomized single blind clinical trial was conducted on 50 patients with type 2 diabetes (T2DM) in Sina Hospital of Tabriz (one of city in Iran) diabetes clinic and diabetes society of East Azarbaijan. The inclusion criteria for the trial were as follows: both genders over the age of 30 years old, HbA1C levels less than 10%, common diabetes drugs usage (Metformin and Glibenclamide), patients with triglyceride levels less than 400 mg dL^{-1}. The exclusion criteria included patients with cardiovascular, renal, liver, or thyroid diseases, infections, allergies, angina, the regular use of NSAIDs (Non-Steroid Anti Inflammatory Drugs), warfarin, smoking, alcohol, herbal tea, dietary supplements and insulin injection.

Patients fulfilling above criteria were invited to participate in this study, they were fully informed with respect to the purpose of the study and patients were free to ask questions throughout the investigation and signed an informed consent form witnessed by one of the investigators prior to participation. They were advised to maintain their normal dietary and exercise habits, they were asked to inform our group if their regular medicine were changed by their physician.

After adjusting the patients by age, sex and duration of diabetes, they were randomly divided into intervention and control groups, they received 100 mg kg^{-1} day^{-1} of nettle extract or placebo, that divided into 3 portion, dissolved each portion in 1 glass of water and drank after each 3 main meals for 8 weeks. Patients were contacted every week by telephone and were asked about any compliance to medications. Each two weeks, patients were asked to return any unused bottle of extract to measure their daily compliance. Biochemical, anthropometric, blood pressure measurement, dietary record and physical activity questionnaire (Hagstromer *et al*., 2006) were performed at the beginning and end of the study. Forty-five patients completed the study (Fig. 1).

This research was approved by the Ethics committee and Human Studies review board of Iran-Tabriz University of Medical Sciences.

Extract specifications: Stinging Nettle certified by the Pharmacogenosy department in Gorgan Medical University aerial parts of nettle dried and powdered, extract were prepared with percolation method and ethanol (60°), final hydro alcoholic extract of Nettle contained, 45% ethanol, 55% water and 2.7 g of dry matter in 1 L of extract. Water and alcohol percent in placebo

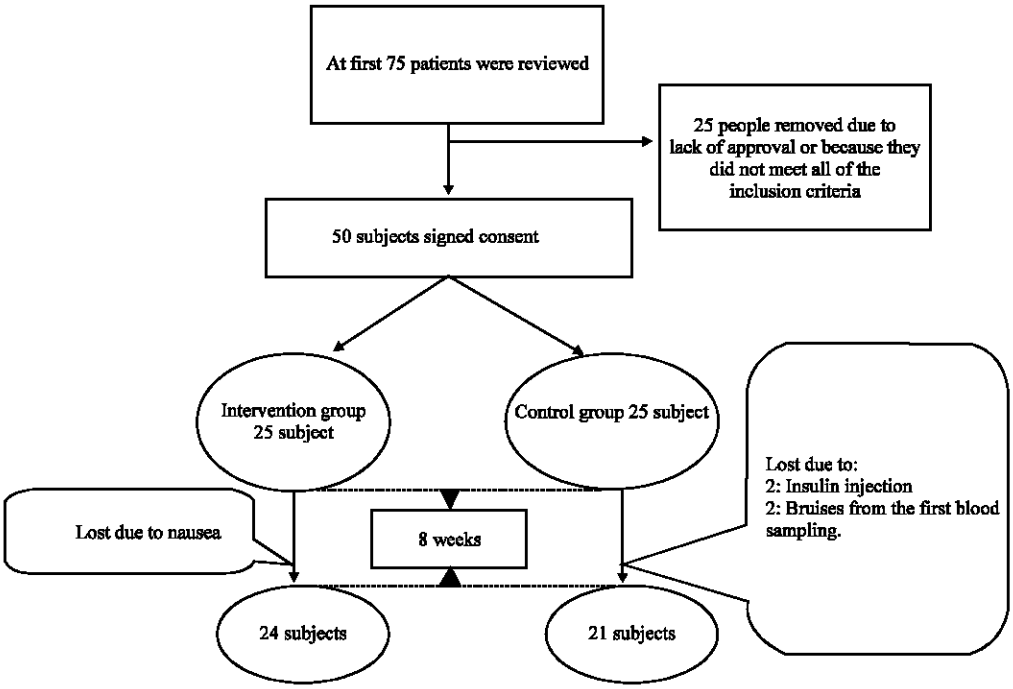

Fig. 1: Algorithms and status of patients during the study

was the same as Nettle extract, in additional some chlorophyll. There was not any difference in color between extract and placebo.

Participants were instructed to complete 24 h dietary recall for three days (2 weekdays and 1 weekend day) at baseline and end of study. These records were used to calculate the habitual dietary energy and nutrient intake. International Physical Activity (IPA) questionnaires (Hagstromer *et al*., 2006) were filled out with face to face interview by researcher at baseline and end of the study. Patients classified in 4 groups as IPA questionnaire.

Anthropometry and blood pressure measurement: The subjects were dressed with light clothes and wore no shoes throughout the measurements. Body weight (in kilograms) was measured to the nearest 0.1 kg with an electronic scale (SECA; Germany). Body height was measured to the nearest 0.5 cm as stood erect against a vertical wall-mounted scale with heels, buttocks and occipital in the Frankfort plane with anthropometric square BMI (kg m^{-2}) was calculated as the ratio of the body weight to the square of body height.

Blood pressure measured while patients seated comfortably, allowed them, 5 min to adjust to the temperature in the examining room, they recommended not taking any morning doses of high blood pressure medicine. SBP and DBP measured by Mercury manometers (Micro life, Swiss) from right arm at baseline and end of the study.

Biochemical measurements: Five millilitere of blood was taken from forearm vein after an overnight fast (12-14 h) at the beginning and end of the study. One aliquot of blood sample was separated into EDTA-containing tubes for the measurement of HbA1C, using a commercially available enzyme-linked immunoassay. The rest of the blood was clotted and immediately centrifuged to separate serum at 2000 RPM for 15 min which was rapidly cooled and frozen at -70°C before analysis of other factors. Serum samples were used for the determination of lipids, glucose and insulin.

FBS, TC, TG and HDL-C concentration were measured by an enzymatic method (Moghadasian *et al*., 2002) and Autoanalyser engine (Alcycon 300, America-France). Insulin concentration was measured by chemiluminescent immunoassay (Liaison, Italy).

Insulin resistance was calculated with HOMA-IR formula (Bonora *et al*., 2002). The LDL-C concentration was calculated using the Fried Wald formula (Mendes de Cordova *et al*., 2004). The Inter-assay precision and Intra-assay precision (CV%) for TC, TG, HDL-Cs and FBS were 1.41, 1.62 1.6, 1.53 as well as 1.4, 1.58, 1.41 and 1.74, respectively .The glucose kit sensitivity was 5 mg dL^{-1}.

Statistical analysis: Values are presented as Mean±SD. For determination of normal distributions of the data, Kolmogorov-Smirnov test was used. Result is compared to their own baseline values by paired Student's t-test.

Comparison between groups was performed by Student's t-test. SPSS version 18 (IBM Inc, USA) was used for data statistical analyses. The $p<0.05$ was considered significance for all variables.

RESULTS

Baseline characteristics of patients in each group are outlined in Table 1. The mean values of age, sex and duration of diabetes at the baseline, did not indicate any significant differences because of adjusting before dividing patients into two groups. BMI, percent of menopause women and medicine information showed no significant differences in two groups at the baseline ($p<0.05$). So, these variables did not play as a confounder on results.

None of biochemical parameters showed significant differences at the baseline in two study groups. Paired sample t-test showed that there was statistical significant differences in LDL-C/HDL-C ratio (1.28±0.41 at the baseline, 0.98±0.31 at the end; $p = 0.003$) in intervention group but this difference was not significant compare to control group. Independent t-test showed that there were no statistically significant differences between two groups in insulin, insulin resistance, TC, LDL-C and DBP.

But Independent t-test showed statistically significant reduction in FBS (112.56±39.57 in intervention group compare to 141.47±38.60 mg dL^{-1} in control group; $p = 0.013$) and HbA1C (6.11±1.19 in intervention group vs. 7.62±1.50 in control group; $p = 0.001$) (Table 2).

Also, at the end of 8th week of intervention, compare to control group, intervention group showed a significant reduction in concentration of TG (129.42±61.98 in intervention group vs. 167.71±67.05 in control group; $p = 0.004$), Log (TG/HDL-C) (0.34±0.15 in intervention group vs. 0.50±0.17 in control group; $p = 0.003$) and a significant increase in HDL-C concentration (53.92±12.37 mg dL^{-1} in intervention group vs. 47.95±8.61 mg dL^{-1} in control group; $p = 0.04$) (Table 3).

SBP and DBP of patients in each group are outlined in Table 4. Independent t-test showed statistically significant reduction in SBP (129.42±61.98 in intervention group vs. 167.71±67.05 in control group; $p = 0.004$).

Table 1: Baseline characteristics of patients in intervention and control groups

Variable	Control	Intervention
Subjects No.	n = 21	n = 24
Age (years)	53.16±7.76	53.92±6.82
Sex (M/F)	12 M/10 F	13 M/10 F
Menopause (%)	70	80
Duration of diabetes (years)	8.79±4.52	8.25±5.04
Metformin per day	2.28±0.89	2.33±0.85
Glibenclamide per day	1.40±0.90	1.73±0.93
Body mass index (kg m^{-2})	30.18±10.73	28.62±2.98

Table 2: Glycemic index and insulin resistance at the baseline and end of study two groups

	Intervention		Control		
Variable	Beginning	End	Beginning	End	p-value
FBS (mg dL^{-1})	129.65±31.16	112.56±39.57	142.52±37.77	141.47±38.60	0.013*
HbA1C (%)	7.30±1.40	6.11±1.19	7.44±1.35	7.62±1.50	0.001*
Fasting Insulin (μU mL^{-1})	6.20±0.52	4.90±0.40	5.00±0.51	4.70±0.40	0.570
Insulin resistance	3.00±0.30	1.90±0.21	2.50±0.30	2.40±0.22	0.110

Values are Mean±SD. *Significant at $p<0.05$ using student test

Table 3: Lipid profile at the baseline and end of study in two group

	Intervention		Control		
Variable	Beginning	End	Beginning	End	p-value
TG (mg dL^{-1})	143.68±74.11	129.42±61.98	146.35±62.48	167.71±67.05	0.004
TC (mg dL^{-1})	136.17±29.81	134.04±30.30	138.38±26.82	136.76±28.60	0.210
LDL-C (mg dL^{-1})	58.24±42.18	52.00±16.56	59.71±14.78	56.24±20.55	0.130
HDL-C (mg dL^{-1})	45.29±9.96	53.92±12.37	45.86±9.18	47.95±8.61	0.040
TC/HDL-C	3.00±0.51	2.55±0.70	3.06±0.62	2.91±0.76	0.101
LDL-C/HDL-C	1.28±0.41	0.98±0.31	1.32±0.34	1.21±0.50	0.069
Log (TG/HDL-C)	0.42±0.35	0.34±0.15	0.44±0.34	0.50±0.17	0.003

Values are as Mean±SD

Table 4: Blood pressure at the baseline and end of study in two group

	Intervention		Control		
Variable	Beginning	End	Beginning	End	p-value
SBP (mmHg)	116.9±13.30	100.0±61.98	124.2±14.9	123.6±13.1	0.006
DBP (mmHg)	79.1±10.1	78.7±10.3	86.3±7.80	84.7±7.9	0.370

Values are as Mean±SD

DISCUSSION

This study demonstrates that hydro alcoholic extract of Nettle reduced FBS, HbA1C, TG, SBP and Log TG/HDL-C in type 2 diabetes patients after 8 weeks.

Glycemic index and insulin resistance: Present results confirm numerous of previous studies results. Studies that showed reductive effects of *Urtica dioica* on glucose level, suggested different mechanisms that can be categorized into pancreatic and extra pancreatic ways. Present study showed no changes in insulin concentration and insulin resistance which is similar to some previous studies (Bnouham *et al*., 2003; Onal *et al*., 2005; Petlevski *et al*., 2001). Bnouham *et al*. (2003) showed anti-hyperglycemic activity of aqueous extract of nettle on rat, reducing glucose transport from small intestine was a probable mechanism. Onal *et al*. (2005) showed potent α-glucosidase inhibitory activity of aqueous *Urtica dioica* extract *in vitro*. Petlevski *et al*. (2001) showed anti-diabetic effects of ethanol extract of *Urtica dioica* on alloxan-induced non-obese diabetic mice.

Other studies showed hypoglycemia effects of nettle with pancreatic mechanism. An *in vivo* study showed that active component of *Urtica dioica* increased insulin concentration of blood in normal and streptozotocin-induced diabetic rats, so glucose level reduced (Farzami *et al*., 2003). Aqueous extracts of nettle leaves show anti-diabetic activity by improving the glycemic status in type 2 diabetic model which may be mediated by the central effect on the histological and/or functional status of pancreatic β-cells (Das *et al*., 2009). Morshed *et al*. (2011) showed that dried frozen nettle extract increase insulin secretion and caused hypoglycemia in rats, they suggested that anti-inflammatory effect of nettle was effective in regeneration of β-cells.

In contrast to present study, Leaves extract of nettle had no hypoglycemic activity after 4 weeks of treatment in streptozotocin-diabetic rats (Golalipour *et al*., 2006). But hydro alcoholic nettle extract showed protective effect on hyperglycemia and β-cells in hyperglycemic rat (Golalipour *et al*., 2007). Another study showed hyperglycemic effect of *Urtica dioica* (Swanston-Flatt *et al*., 1989), dose of extract, solvent (water or alcohol) and duration of intervention may cause different results.

Lipid profile and blood pressure: Some studies showed anti-lipidemic effects of *Urtica dioica* (Nassiri-Asl *et al*., 2009; Alisi *et al*., 2008; Daher *et al*., 2006) and others showed no effects of *Urtica dioica* on lipid profile. Nassiri-Asl *et al*. (2009) showed that ethanolic extract of *Urtica dioica* reduced TC and LDL-C in hypercholesterolemic rats but in present study TC and LDL-C did not decrease. Patients in present study had usual diet but in Nassiri-Asl *et al*. (2009) study, rats had high fat diet, it may be caused different results. Alisi *et al*. (2008) showed decreasing in all lipid factors, except HDL-C, but in present study, nettle showed increasing effect on HDL-C. Differences in dose, method of studies and type of nettle extract may lead to different results. Daher *et al*. (2006) showed decreasing effects of nettle on TC, LDL-C and LDL/HDL-C.

Log (TG)/HDL-C is an Index to estimate atherogenic dyslipidemia (AD) and the residual cardiovascular risk it confers in type 2 diabetes. AD closely associates with major cardiometabolic and glucose homeostasis determinants and poorer metabolic control. The ratio also relates to macroangiopathy prevalence and ranks of future CAD risk and is well-suited to capture non-LDL-related macrovascular residual risk and major glycemic determinants. The present study showed reducing in this atherogenic index.

In vitro and animals studies showed that nettle reduced hypertension (Tahri *et al*., 2000). Legssyer *et al*. (2002) in a study that was conducted on rats, showed that Nettle reduces blood pressure and heart rate. These studies are partly consistent on present study results. Nettle contains relatively large amounts of flavonoids and reduced blood pressure through the effects on vessels epithelial cells and coronary dilatation (Perez-Vizcaino *et al*., 2009; McGrowder and Brown, 2007; Mudgal *et al*., 2010).

In present study, our results indicated that Urtica Dioica does not affect on insulin secretion, so other mechanism for example antioxidant (Bitiren *et al*., 2010) and anti inflammatory effects of nettle (Turkdogan *et al*., 2003), enhanced glucose transports into cells and reduced glucose intestinal absorption. These mechanisms may cause reducing some risk factors of cardiovascular disease in type 2 diabetic patients. limitation of our study was Inability to control stress in life of patients that could be affect on blood sugar and blood pressure, more studies with longer intervention period is suggested.

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