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The Effect of Hydro Alcoholic Nettle (*Urtica dioica*) Extracts on Insulin Sensitivity and Some Inflammatory Indicators in Patients with Type 2 Diabetes: A Randomized Double-blind Control Trial

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Abstract: Type 2 diabetes is a metabolic disorder that is strongly associated with cardiovascular risk. Inflammation is a potential risk factor for cardiovascular disease. In this study, hydro alcoholic extract of Nettle (*Urtica dioica*) on insulin sensitivity and some inflammatory indicators in type 2 diabetic patients were studied. A randomized double-blind clinical trial on 50 men and women with type 2 diabetes was done for 8 weeks. Patients were adjusted by age, sex and duration of diabetes, then randomly divided into two groups, an intervention and control group. They received, 100 mg kg^{-1} nettle extract or placebo in three portions a day for 8 weeks. Interleukin 6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), High Sensitive C-Reactive protein (hs-CRP) and Fasting Insulin concentration were measured. Insulin Sensitivity was calculated, at the beginning and the end of the study. The data were analyzed by SPSS version 18, $p<0.05$ was considered significant for all variables. After 8 weeks, IL-6 and hs-CRP showed a significant decrease in the intervention group compared to the control group ($p<0.05$). The findings showed that the hydro alcoholic extract of nettle has decreasing effects on IL-6 and hs-CRP in patients with type 2 diabetes after eight weeks intervention.

Key words: Nettle, insulin, inflammation, complications, prevention, diabetes mellitus

INTRODUCTION

Diabetes mellitus is a metabolic disease with disorders in metabolism of carbohydrate, lipid and protein (Taylor, 2008). The world prevalence of diabetes in adults was 6.4%, in 2010 and will increase to 7.7%, by 2030 (Shaw *et al*., 2010). Hyperglycemia increases complications of diabetes such as cardiovascular disease (CVD). Diabetes and related metabolic diseases, for example hyperinsulinemia, insulin resistance and central obesity, are recognized as major contributors to cardiovascular morbidity and mortality (Biondi-Zoccai *et al*., 2003). Consequently, improving of insulin sensitivity and inflammation status can be an efficient way to prevent CVD in type 2 diabetes patients (Wellen and Hotamisligil, 2005).

In response to increasing use of alternative medicine among general people in the world (Khan and Safdar, 2003), the American Diabetes Association (ADA) encourage researchers to study about medical herbs and dietary supplement (Egede *et al*., 2002).

Consumption of Medicinal herbs is one of the alternative therapy in diabetes, *Urtica dioica* have been widely used in the world as traditional treatment in diabetes (Mehri *et al*., 2011). *Urtica dioica* is from the Urticaceae family and known as Stinging Nettle (Thorn, 2007). Studies showed good effects for improving inflammatory markers and treatment of rheumatoid arthritis. Nettle has showed many pharmacological properties such as improving of bladder infection, inflammation of urinary tract, hypertrophy of prostate, Seasonal allergies and rheumatic disease (Chrubasik *et al*., 2007).

Some experimental and *in vitro* studies reported decreasing effect of *Urtica dioica* on inflammatory markers (Obertreis *et al*., 1996). But studies showed different results for effects of Nettle on insulin sensitivity (Mehri *et al*., 2011).

It seems that the effects of Nettle on insulin sensitivity and inflammatory markers in patients with type 2 diabetes are not studied, yet. Therefore, the aim of this study was to investigate the effects of hydro alcoholic extract of Nettle on insulin sensitivity and some inflammatory markers in patients with type 2 diabetes.

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MATERIALS AND METHODS

A Randomized single-blind clinical trial was done on 50 patients with type 2 diabetes (T2DM) in Clinic of Diabetes in Sina Hospital of Tabriz .The inclusion criteria for the trial were as follows: both genders over the age of 30 years old, HbA1C levels equal or 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 and the regular use of NSAIDs (Non-Steroid Anti Inflammatory Drugs), warfarin, alcohol, herbal tea, dietary supplements and insulin injection.

Patients were informed about purpose of the study, every patient that is satisfied about participate in the study, signed an informed consent form, they were advised to continue their diet and physical activity habits without any changes during intervention.

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} of nettle extract or placebo in 3 portions a day, They dissolved each portion in 1 glass of water and drank after each 3 main meals for 8 weeks. Patients were contacted every week with telephone, They were asked for any compliance about nettle extract usage. Each two weeks, patients were asked to return any used bottles of extract and received new bottles. 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.

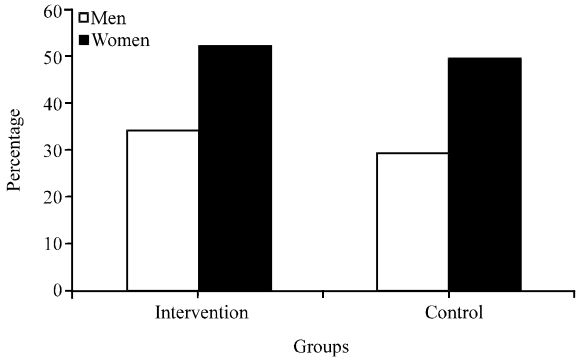

Fig. 1: Comparison of patients with abdominal obesity in two groups at the baseline

Extract specifications: Stinging Nettle certified by the Pharmacogenosy department in Gorgan University of Medical Science. Aerial parts of Nettle dried and powdered, extract were prepared with percolation method, ethanol (60°) was used. 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 was equal to Water and alcohol percent in Nettle extract, chlorophyll color added to placebo. 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 the 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 by researcher with face to face interview at the baseline and the end of study.

Anthropometry measurement: The patients were dressed with light clothes, without shoes throughout the measurements of weight and height. Body weight (kg) was measured to the nearest 0.1 kg with an electronic scale (SECA; Germany) and height was measured to the nearest 0.5 cm as stood erect against a vertical wall-mounted scale with heels, buttocks and occipital in Frankfort plane. Body Mass Index (BMI), body weight in kilogram to the square of body height in centimeter ratio was calculated.

Waist Circumference (WC) measurements is an indicator for abdominal fat content. It is obtained by measuring the distance around the smallest area below the rib cage and above the umbilicus with the use of a nonstretchable tape measure, then Waist to Straight Height Ratio (WtSR) was calculated.

Biochemical measurements: Five milliliter of blood was taken from forearm vein after an overnight fast (12-14 h) at the beginning and end of the study. Samples were centrifuged immediately 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 Inflammation markers (IL-6, TNF-α and hs-CRP) and insulin concentration by ELISA Method (Meier-Ewert *et al*., 2004). Insulin Sensitivity was calculated with Katz formula that is showed bellow (Katz *et al*., 2000):

$$QUIKI = \frac{1}{[\text{Log (Fasting blood sugar)} + \text{Log (Fasting insulin concentration)}]}$$

Where:
QUIKI = Quantitative Institute Sensitivity Check Index

Statistical analysis: Values are presented as Mean±SD. Kolmogorov-smirnov test was used to determine of normal status of the data. Data with Abnormal distribution were converted to normal distribution by calculating logarithmic ratio. Then data at the end of study were compared to their own baseline values by Paired t-test. Comparison between two groups was performed by Student's t-test. SPSS version 18 (IBM Inc, USA) was used for data statistical analyses. $p<0.05$ was considered significance for all variables.

RESULTS

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, WC, 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 confounder factors on results (Table 1).

At the baseline 34 and 29.2% of men and 51.7 and 49.3% of women showed abdominal obesity in intervention and control groups, respectively (Fig. 1).

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 TNF-α (11.5±0.62 at the baseline, 10±0.83 at the end; pv = 0.006) in intervention group but this difference was not significant compare to control group. Independent t-test showed significant decreasing of hs-CRP and IL-6 in intervention group compare to control group, respectively ($p = 0.03$ and $p = 0.003$) (Table 2). But no statistically significant differences between two groups in Insulin Concentration, Insulin Sensitivity , TNF-α and anthropometric indicators (Table 3) were seen ($p>0.05$).

Table 1: Characteristic of patients in intervention and control groups at baseline

Variable	Intervention	Control
Subjects number	n = 24	n = 21
Age (years)	53.92±6.82	53.16±7.76*
Sex (M/F)	13M/11 F	11 M/10 F
Duration of diabetes (years)	8.25±5.04	8.79±4.52
Menopause (%)	66	57

*Mean±SD. Independent Samples t-test for comparison of two groups at the baseline

DISCUSSION

This study showed that hydro alcoholic extract of Nettle reduced IL-6 and hs-CRP levels, with no changes in insulin sensitivity, insulin secretion and TNF-α in type 2 diabetes patients after 8 weeks. Comparison and disunion about results classified in two parts as follows:

Insulin concentration and insulin sensitivity: Present results confirm numerous of previous studies results. Present study showed no changes in insulin concentration and insulin sensitivity which is similar to some previous studies (Bnouham *et al*., 2006; Onal *et al*., 2005; Petlevski *et al*., 2001).

Other studies showed hypoglycemia effects of nettle with Changes in insulin secretion or insulin sensitivity that are in contradiction of present study. An *in vivo* study showed that active component of *Urtica dioica* increased insulin concentration of blood in normal and streptozotosin-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 functional status of pancreatic β-cells (Das *et al*., 2009). Qujeq *et al*. (2011) showed that dried frozen nettle extract

Table 2: Comparison of inflammatory markers and Insulin status between two groups at the baseline and the end

	Intervention		Control		
Variable	Beginning	End	Beginning	End	p-value
IL-6 (pg mL^{-1})	3.52±2.11	1.19±0.27†	4.11±1.07	3.49±0.54	00.00
TNF-α (pg mL^{-1})	11.50±0.62*	10.00±0.83	10.50±0.50	10.00±0.90	00.09
hs-CRP (mg dL^{-1})	2.52±1.06	1.37±0.11†	3.01±1.07	2.95±0.87	00.03
Insulin sensitivity	0.32±0.03	0.31±0.02	0.33±0.02	0.32±0.01	00.75

*Mean±SD, †$p<0.05$ considered as Significant difference between two groups. Independent Samples t-test for comparison of two groups and Pair t-test for comparison before and after intervention

Table 3: Comparison of anthropometric indicators between two groups at the baseline and the end of study

	Intervention		Control		
Variable	Beginning	End	Beginning	End	p-value
Body mass index (kg m^{-2})	29.97±06.02*	29.99±06.16	28.63±3.05	28.73±3.18	0.34
WC (cm) in men	96.12±10.45	96.75±10.41	93.38±5.74	93.11±5.77	0.36
WC (cm) in women	111.14±10.74	110.82±10.54	109.18±8.63	109.09±9.03	0.31

*Mean±SD. Independent Samples t-test for comparison of two groups and Pair t-test for comparison before and after intervention

increased insulin secretion and caused hypoglycemia in rats, they suggested that anti-inflammatory effect of nettle was effective in regeneration of β-cells. Differences in Dose, Nettle type, solvent and methodology may cause different results in studies.

Inflammation markers: Inflammatory cytokines such as IL-6, TNF-α and hs-CRP are related to insulin resistance and type 2 diabetes. Cytokines inhibit the transcriptional activity and protein expression of several molecules related to insulin signaling and action, such as GLUT-4. So impairing its ability to bind to the insulin receptor and initiate downstream signaling and caused insulin resistance (Rotter *et al*., 2003).

This study showed that hydro alcoholic extract of nettle decreased IL-6, hs-CRP without significant reduction in TNF-α level in diabetes patients. But Obertreis *et al*. (1996) showed decreasing effect of Nettle extract on TNF- α, that their result about TNF- α changes are in contradiction with the present study. Obertreis *et al*. (1996) studied nettle extract on healthy volunteers but present studied was done on patients, maybe this difference caused different results.

Obertreis *et al*. (1996) tested caffeic malic, an acid phenolic ingredient in Nettle on biosynthesis of arachidonic acid metabolites *in vitro*. They suggested that caffeic malic is one of the benefit ingredients in nettle that inhibits cytokines, so it makes nettle as a good supplement in rheumatoid diseases.

Riehemann *et al*. (1999) suggested that a part of the anti-inflammatory effect of Urtica extract may be related to its inhibitory effect on NF-κB (Nuclear factor kappa-B) activation. Flavonoids, caffeic malic or unknown substances in Urtica extracts can mediate NF-κB inhibitory effects. Other naturally occurring compounds that inhibit NF-κB activation potentionaly, are sesquiterpene lactones or gliotoxin that are finded in plants.

Present study is the first study that assessed effects of Nettle extract on inflammatory indicators in type 2 diabetes patients, so exact mechanism of Urtica Dioica on inflammatory cytokine is unknown. More studies are essential to discover mechanism of nettle extract.

CONCLUSION

Hydro alcoholic extract of Nettle decreased IL-6 and hs-CRP in type 2 diabetes patients after 8 weeks intervention. So it seems that hydro alcoholic extract of Nettle can play a protective role from CVD in patients with type 2 diabetes by decreasing some inflammatory factors.

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