RESEARCH ARTICLE

Effect of pre-meal water intake on the serum levels of Copeptin, glycemic control, lipid profile and anthropometric indices in patients with type 2 diabetes mellitus: a randomized, controlled trial

Gohar Sedaghat[1] · Farzaneh Montazerifar[2] · Mahmood Ali Keykhaie[3] · Mansour Karajibani[4] · Shadi Shourestani[1] · Alireza Dashipour[5]

Abstract

Background Water pre-load affects insulin secretion by altering the level of copeptin (C-terminal component of the arginine vasopressin hormone (AVP)) and preventing obesity by reducing food intake.

Aims The present randomized controlled trial (RCT) aimed to investigate the effects of pre-meal water intake on type 2 diabetes Mellitus (T2DM).

Materials and methods In this study, 40 patients with T2DM were randomly assigned to two intervention groups for 8 weeks; a) drinking 1 liter of water per day before each main meal (PW group)., and b) no water consumption before any meal (NPW group). At the beginning and at the end of the study, blood samples were taken to assess glycemic indices, lipid profile, copeptin and anthropometric indices.

Results Pre-meal water intake was associated with lower energy intake, BMI, waist circumference (WC) and greater weight loss, in compared with the controls ($P < 0.0001$) after 8 weeks. At the end of the trial, the concentrations of fasting blood sugar (FBS) ($P < 0.0001$), triglyceride (TG) ($P < 0.05$), low-density lipoprotein cholesterol (LDL-C) ($P < 0.05$) and copeptin ($P < 0.05$) were significantly reduced following water drinking before meals.

Conclusion To sum up, the present study revealed that pre-meal water intake is associated with lower BMI, body weight, WC, FBS, TG, LDL-C and copeptin levels in patients with T2DM.

✉ Farzaneh Montazerifar
  fmontazerifar@gmail.com

1 Department of Nutrition, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

2 Pregnancy Health Research Center, Department of Nutrition, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

3 Genetics of Non-Communicable Disease Research Center, Department of Internal, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

4 Health Promotion Research Center, Department of Nutrition, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

5 Cellular and Molecular Research Center, Department of Food and Technology, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disease with a wide range of pathologic conditions, including insulin resistance, hyperglycemia, systemic inflammation, and lipid profile disorders [1, 2]. The role of arginine vasopressin (AVP), a water retention hormone), has been reported in the pathogenesis of diabetes in previous studies [3, 4]. Copeptin (C-terminal component of AVP), has been distinguished as a reliable marker of serum AVP concentration. Hence, elevated plasma copeptin levels are associated with insulin resistance and metabolic disorders such as high waist circumference, hypertension, hypertriglyceridemia, obesity and greater risk of diabetes [3]. Obesity is the most common risk factor for T2DM that may affect insulin resistance and its progression. Additionally, previous studies have reported that weight loss could improve glycemic indices and reduce the risk of cardiovascular diseases in diabetic patients [4–6].

There is a growing trend towards finding ways to treat diabetes. In line with this, some studies have shown that increasing both water intake and weight loss might improve hyperglycemia and insulin resistance [4], and lower body weight [7]. Epidemiological data have shown that the energy intake is estimated to be 9% lower in additional water consumers rather than normal daily consumers [8]. According to the previous reports from The National Health and Nutrition Examination Survey (NHANES), 30% of subjects who managed to lose weight in the United States were given greater amount of water [9]. Some studies have suggested that drinking 500 cc of water before meals led to increased energy expenditure along with decreased food intake in each meal, which could positively affect the weight loss process [10, 11]. In addition, it has been documented that water intake before meals reduces hunger and increases satiety, that resulting in decreased energy intake in overweight and obese adults [12]. In addition, limited studies with inconsistent results examined the effect of higher water intake on serum copeptin levels in patients with T2DM [13, 14]. Therefore, the present RCT aimed to investigate the effects of pre-meal water intake on the levels of serum copeptin, glycemic control, and lipid profile and anthropometric indices in type 2 diabetics.

Materials and methods

Study participants

Enrolled participants

Subjects with diagnosed T2DM in the last 5 years (with serum glucose levels and medication doses that had been stable for at least 6 months), age range of 30–65 years and body mass index (BMI) < 30 Kg/m^2 were recruited from outpatients attending diabetes clinic of *Boali hospital* in Zahedan, Iran. Sample size was calculated according to the previous study regarding to the type I error of 5% ($\alpha = 0.05$) and type II error of 20% [15].

Excluded participants

The patients treated with insulin; women who are pregnant or lactating; consumption of NSAIDs drugs; smokers; patients who taking medication affecting energy intake or appetite, being on a special diet in the last 3 months, anti-hyperlipidemic, and anti-hypertensive medications, having history of underlying illnesses including renal, liver, cardiovascular diseases and other endocrine disorders were excluded from the study.

Informed consent

All participants were informed about the study objectives, procedures using a leaflet and a signed written informed consent was obtained. The procedure of this study was conducted according to the Declaration of *Helsinki*. The study protocol was approved by the Ethics Committee on Human Experimentation of Zahedan University of Medical Sciences (approval date: 15.07.2018; No. IR.Zamus.Rec.1397.202).This trial was also registered at the Iranian Registry of Clinical Trials (ID number: IRCT 20180910040986 N1, trial ID: 33757).

Study design

This randomized controlled trial was conducted from April to September 2018. A total of 40 patients (17 males and 23 females, mean age: 51.9 ± 8.8 years; age range: 31–65 years) with T2DM were randomly divided 1:1 into two groups (20 participants in each group). Randomization was performed by a qualified statistician based on a computer-generated code in blocks of four. The intervention group was recommended to intake 1 liter of drinking water daily (250 cc; 30 min before breakfast, 500 cc; 30 min before lunch, and 250 cc; 30 min before dinner [10] for 8 weeks (pre-meal water group: PW). The control group did not receive any recommendation regarding water intake (non-pre-meal water group: NPW). Participants in the intervention group were contacted weekly to assess compliance with the recommendations through telephone interviews. We also asked them not to change their level of physical activity during the study.

Assessment of study variables

Anthropometric indices were measured at the beginning of arrival and after 8 weeks of intervention. Body weight was measured using a digital scale (Seca, Hamburg, Germany) with an accuracy of 0.1 kg with minimal coverage and without shoes. Height was measured without shoes using a non-stretched tape to the nearest 0.5 cm. The trained researchers obtained further information about age, medical history, medication and smoking through face-to-face interviews. At the beginning and end of the study, after 12 h of fasting, venous blood samples (10 cc) were taken from each participant. Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), fasting blood sugar (FBS), and glycated hemoglobin (HbA1C) were assessed using standard kits (Pars Azmoon Inc., Tehran, Iran) via auto-analyzer machine (BT-1500, Italy).

Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as (fasting insulin [(μU/ml] - fasting glucose [mmol/l] (/ 22.5 [16].

Serum copeptin (Bioassay Technology lab, No E1129HU / 96 Test, China (and insulin (Monobind Inc., No 5825–300/ 96 test. USA) levels were also measured using enzyme-linked immunoassay kits.

Dietary intake was assessed by three 24-h Diet Recall at the entry and at end of study. Modified Nutritionist IV software (First Data bank) for Iranian foods was used to compute the findings from this questionnaire to calorie and nutrient content [17].

Statistical analysis

The Statistical Package for Social Sciences (SPSS) software version 21 (SPSS, Inc. Chicago, IL, USA) was used for randomization and all statistical analyses. Data were presented as mean ± SD, mean ± SEM with range and percent,as appropriate. Normal distribution of the data was assessed using Kolmogorov–Smirnov test. A repeated measures ANOVA was used to estimate the statistical difference between two groups, including pre- and post-intervention and within each group between pre- and post-intervention. The baseline and end values of the trial were used to measure and percentage of changes in each of the study variables. In order to identify differences between two groups, t-test or Mann–Whitney U test were planned. P values <0.05 were assumed to be statistically significant.

Results

Table 1 outlines the main demographic characteristics of the enrolled patients. All of the selected patients were enrolled to the trial (17 males and 23 females), and they were aged 52 ± 9.2 and 51 ± 8.2 in the intervention and control groups, respectively.

Pre-meal water drinking was associated with the lower levels of copeptin ($P < 0.05$ and $P < 0.001$), serum FBS ($P < 0.0001$ and $P < 0.001$), TG ($P < 0.05$ and $P < 0.001$) and LDL-C (both $P < 0.05$) compared to baseline and NPW group, respectively (Table 2). Additionally, body weight ($P < 0.001$), BMI ($P < 0.0001$) and WC ($P < 0.001$) were significantly decreased in group receiving pre-meal water in compare with the NPW (Table 2). In contrast, total cholesterol, HbA1c, serum insulin, HOMA-IR and HDL-C were not statistically significant affected by pre-meal water intake ($P > 0.05$) (Table 2).

As shown in Fig. 1, compared to controls, the percentage of changes was higher for anthropometric indices, FBS, and

Table 1 Demographic and clinical characteristics in the water and non-water groups before and after the 8 weeks intervention

Groups Variables	NPW group (n=20) Baseline	After 8 weeks	Pv	PW group (n=20) Baseline	After 8 weeks	Pv
Age (years)	51±8.2			52±9.2		
Weight (Kg)	77.30±12.7	78.4±13.3	0.15	77.9±13.2	76.6±12.3$^\epsilon$	0.0001
BMI (Kg/m^2)	27±4.4	27.4±4.7	0.14	27.2±3.9	26±3.8 $^\epsilon$	0.0001
WC (Cm)	104±8.9	104.2±10	0.15	105±8.7	102.0±8.3 $^\epsilon$	0.001
WHR	0.95±0.8	0.95±0.8	0.48	0.98±0.7	0.96±0.63	0.069
FBS (mg/dL)	221.7±77.4	227±57	0.51	225.7±56.4	193.2±32 $^\epsilon$	0.0001
HbA1C (%)	8.2±1.9	8.3±1.9	0.35	8±1.4	7.8±1.0	0.52
Insulin (ml/µIU)	8.7±1.3	9.1±1.8	0.14	8.5±0.93	8.7±1.9	0.35
HOMA-IR	4.0±0.68	4.7±0.91	0.11	3.8±0.49	4.2±0.52	0.15
TC (mg/dL)	172.4±62.5	167.8±31.9	0.13	176.6±77	160.8±38.1	0.19
TG (mg/dL)	155.6±65.5	174.6±72.0	0.12	150±63.2	127.7±50 $^\epsilon$	0.049
HDL-C (mg/dL)	47.9±12.7	45.9±11.5	0.37	44.4±7.6	44.7±7.9	0.48
LDL-C (mg/dl)	92.7±39.1	88.5±31.5	0.15	87.7±35.5	74.3±34.1 $^\phi$	0.03
^{a}Copeptin (pmol/L)	10.6±3.4 (0.96–58.1)	11.4±4.5 (1.64–61.6)	0.27	10.3±3.2 (2.86–61.6)	7.6±2.2 $^\epsilon$ (1.38–52.6)	0.046

Data are presented as mean ± SD

^{a} Data are presented as mean ± SEM and range, because the data were not normally distributed
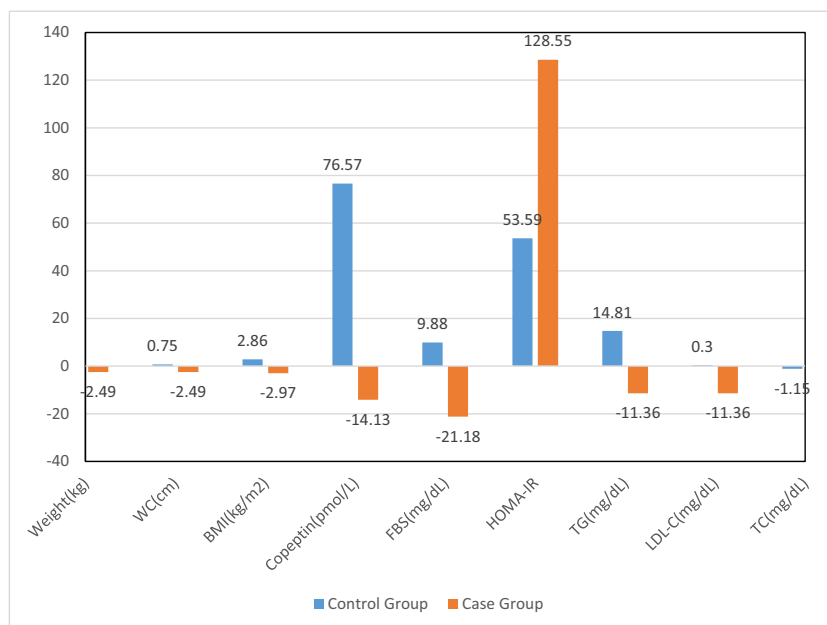
Abbreviations: *NPW* Non-Pre-meal Water, *PW* Pre-meal Water, *BMI* Body Mass Index, *WC* Waist Circumference, *WHR* Waist to Hip Ratio, *FBS* Fasting Blood Sugar, *HbA1C* Hemoglobin A1c, *HOMA-IR* Homeostatic Model Assessment of Insulin Resistance, *TC* Total Cholesterol, *TG* Triglycerides, *HDL-C* High-Density Lipoprotein-Cholesterol, *LDL-C* Low-Density Lipoprotein- Cholesterol

ϵ Difference between two groups after 8 weeks, $P < 0.001$; $^\phi$ Difference between two groups after 8 weeks, $P < 0.05$

Table 2 Variation of the studied variables after 8 week intervention versus baseline between two groups

Variables	Groups	Mean	Pv
Weight (Kg)	NPW	0.9	0.0001
	PW	−1.35	
BMI (Kg/m^2)	NPW	0.40	0.0001
	PW	−1.28	
WC (Cm)	NPW	0.20	0.0001
	PW	−3.0	
WHR	NPW	0.00	0.46
	PW	−0.01	
FBS (mg/dL)	NPW	5.3	0.003
	PW	−32.6	
HbA1C (%)	NPW	0.1	0.96
	PW	−0.2	
Insulin (ml/μIU)	NPW	0.45	0.13
	PW	0.22	
HOMA-IR	NPW	0.74	0.17
	PW	0.42	
TC (mg/dL)	NPW	−13.57	0.61
	PW	−15.75	
TG (mg/dL)	NPW	−19.00	0.01
	PW	22.05	
LDL (mg/dL)	NPW	−4.2	0.04
	PW	−13.37	
HDL (mg/dL)	NPW	−2	0.79
	PW	−0.30	
*Copeptin (pmol/L)	NPW	0.8	0.01
	PW	−2.7	

Abbreviations: *NPW* Non-Pre-meal Water, *PW* Pre-meal Water, *BMI* Body Mass Index, *WC* Waist Circumference, *WHR* Waist to Hip Ratio, *FBS* Fasting Blood Sugar, *HbA1C* Hemoglobin A1c, *HOMA-IR* Homeostatic Model Assessment of Insulin Resistance, *TC* Total Cholesterol, *TG* Triglycerides, *HDL-C* High-Density Lipoprotein-Cholesterol, *LDL-C* Low-Density Lipoprotein- Cholesterol

LDL-C, and lower for total cholesterol, triglyceride and copeptin levels in treatment group.

Table 3 presents the distribution of energy and dietary intakes in two studied groups at the baseline and end of intervention. Pre-meals water intake significantly decreased energy ($P < 0.0001$) and fat ($P < 0.001$) intakes rather than baseline in the PW group. Moreover, the consumption of protein and energy in PW group was significantly higher than NPW group after 8 weeks of intervention ($P < 0.01$). In multiple linear regression analysis adjusted for age and BMI, none of the parameters was significantly corrected with copeptin.

Discussion

In the present study, we found a significant improvement of serum levels of copeptin, FBS, TG, LDL-C, body weight, BMI and WC, after increasing pre-meals water intake for 8 weeks compared to the habitual water intake in patients with T2DM. In addition, no parameters were significantly corrected with copeptin in multiple linear regression analysis adjusted for age and BMI, which could follow the small sample size and short duration of intervention.

Regarding copeptin, our result complements the finding of previous studies indicating relationship between water intake and the levels of copeptin. Several studies have reported that extra water intake was associated with the lower level of copeptin in adults [16, 18]. Lemetais et al. demonstrated that plasma copeptin concentrations could be modulated through increasing water intake in healthy adults [19]. They stated that the high intake of water might be a potential approach to reduce the risk of metabolic disorders. In addition, in several cohort studies, increased circulating copeptin has been related

Fig. 1 Variation percent of studied variables

Table 3 Dietary intake and physical activity in water and non-water groups before and after the 8 week intervention

Groups Variables	NPW (n=20)		Pv	PW (n=20)		Pv
	Baseline	After 8 weeks		Baseline	After 8 weeks	
Energy (Kcal)	2190 ± 331	2169 ± 413	0.1	2265 ± 254	2091±307 €	0.0001
Carbohydrate (gr)	225 ± 38	231 ± 51	0. 053	234 ± 38	231±37	0.25
Protein(gr)	80 ± 14	77 ± 17	0.07	82 ± 18	87±17 €	0.20
Fat(gr)	108 ± 34	104 ± 39	0.45	112 ± 27	91±27	0.001

Data are presented as mean ± SD

Abbreviations: *NPW* Non- Pre-meal water, *PW* Pre-meal Water

€ Difference between two groups after 8 weeks, $P < 0.01$

to the occurrence of metabolic diseases [14, 19]. Several mechanisms have been reported for this relationship [20–22]. The presence of vasopressin receptors V1a and V1b in the pancreas and liver is a reasonable explanation for the association among water intake, copeptin concentrations, and metabolic diseases [19, 23]. In addition, previous studies have obtained a favorable effect of increased water intake on decreasing the risk of some chronic diseases such as cardiovascular disease, chronic kidney disease, and type 2 diabetes [24, 25]. In a clinical study, water intake for 6 weeks in patients with chronic kidney disease showed an inverse effect between a high water intake of up to 1.5 l / day and the serum copeptin levels [26].

In line with our findings, Dennis et al. [27] have reported that water drinking decreases serum LDL-C and TG levels. In the study of Enhörning et al. [14], 1 week of high water intake did not change serum FBS and insulin levels.

Diabetes is one of the complications of obesity [5, 7]. Hence, it has been hypothesized that improvement of body weight in diabetic patients would be associated with appropriate management of diabetes [4]. Drinking a lot of water is often recommended for weight loss [9]. The exact mechanism responsible for the greater weight loss with increased water consumption is presently unknown and further investigations are needed to explain the underlying mechanisms. However, an animal study reported a helpful role of high intake of water and subsequently reduced circulating vasopressin for health conditions [23]. Another studies reported that drinking water might cause weight loss through reducing energy intake [13, 24]. Several studies also reported that consuming water before or with a meal declines the sensations of hunger, and intensifies satiety [11, 12]. Additionally, substituting energy-containing sweet drinks and juices in the diet with water may lead to a decrease in energy intake [28]. Consequently, reducing energy intake in meals is thought to be a beneficial weight loss strategy. In our study, pre-meals water intake was associated with a significant reduction of body weight, BMI and WC in intervention group when compared to the baseline and NPW group. Stookey et al. [29] found that overweight women who reported drinking ≥ 1

liter/day of water over a 12 months period experienced more weight loss compared to those who did not drink such amount water (≈ 2 kg). In the study of Dennis et al. [26] water intake reduced body weight and WC in adults.

The present study also demonstrated that water intake before eating each main meal significantly reduced energy and fat intakes in type 2 diabetic patients. In agreement with our study, Dennis et al. [26] found an inverse association between drinking water and energy intake in adults. They also reported that combining a hypocaloric diet with consuming 500 ml water before each main meal could lead to lower energy intake and greater weight loss. Moreover, Davy et al. [12] reported that pre-meal water intake decreased meal energy intake in overweight and obese adults.

The relationship between serum copeptin and anthropometric indices has been reported in few studies. In a studies, copeptin levels were markedly higher in obese children than in thin children, but there was no significant correlation between metabolic syndrome and copeptin [30]. However, another study found that obese people had lower levels of copeptin than people with normal weight [31]. In another study, the copeptin levels were indirectly related to BMI and WC as indicators of metabolic syndrome [32].

Our findings should be interpreted while considering the study limitations; i) we could not collect other valuable anthropometric and biochemical parameters which linked to the obesity status in these patients such as evaluation of body composition and adipose tissue hormones ii) This study was performed in a short term with low sample size. Therefore, future studies with greater sample size and longer period are needed to evaluate other specific markers that may be related to possible mechanisms of high water intake in energy expenditure and body weight loss.

Conclusion

In conclusion, the present study showed that increasing daily water intake before each main meal leads to an improvement

of body composition, lipid profile, serum glucose and copeptin levels. Pre-meals water intake could also resulted in the lower energy and fats intake, which are play an important role in obesity, diabetes and cardio-metabolic disorders.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

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