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**Beneficial effects of replacing diet beverages with water on  
Type 2 diabetic obese women following a hypo-energetic  
diet - a randomized, 24 week clinical trial**

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2  
3 **Title page**  
4

5 **Title of the article:**  
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7  
8 **Beneficial effects of replacing diet beverages with water on Type 2 diabetic obese**  
9  
10 **women following a hypo-energetic diet - a randomized, 24 week clinical trial**  
11

12 Ameneh Madjd<sup>1, 2</sup> (D. Pharm), Moira A. Taylor<sup>1</sup> (PhD), Alireza Delavari<sup>3</sup> (MD), Reza  
13 Malekzadeh<sup>3</sup> (MD), Ian A. Macdonald<sup>1</sup> (PhD) and Hamid R Farshchi<sup>1, 2</sup> (MD, PhD)  
14

15  
16  
17 - Author Affiliations  
18

19  
20 1. *School of Life Sciences, Queen's Medical Centre, University of Nottingham,*  
21 *Nottingham NG7 2UH, UK. (AM, MAT, IAM, HRF)*  
22

23  
24 2. NovinDiet Clinic, Tehran, Iran. (AM, HRF)  
25

26  
27 3. Digestive Disease Research Institute, Tehran University of Medical Sciences,  
28 Tehran, Iran. (AD, RM)  
29

30  
31 - To whom correspondence should be addressed. Dr. Hamid R Farshchi, Tel:  
32 +9821-22263002, Fax: +9821-22274192, E-mail: [hfarshchi@gmail.com](mailto:hfarshchi@gmail.com),  
33

34  
35 [hamid.farshchi@nottingham.ac.uk](mailto:hamid.farshchi@nottingham.ac.uk)  
36

37  
38 - To whom requests for reprints should be addressed: Name Dr. Ameneh Madjd,  
39 Email: [mbxsama@nottingham.ac.uk](mailto:mbxsama@nottingham.ac.uk)  
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42 - Running title: **Effect of Replacing Diet Beverage by Water in T2DM**  
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44  
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**Abbreviations:**

- Analysis of variance: ANOVA
- Cognitive behavioral therapy: CBT
- Diet beverages: DBs
- Fasting plasma glucose: FPG
- Glycated hemoglobin: Hb A<sub>1c</sub>
- Homeostasis model assessment of insulin resistance: HOMA-IR
- Hour: h
- Liter: l
- Mole: mol
- Standard deviation: SD
- Sugar sweetened beverages: SSBs
- Total cholesterol: TC
- Triglyceride: TG
- 2 hour post prandial glucose: 2hpp
- Waist circumference: WC

### Abstract

**Aims:** To compare the effect of replacing diet beverages (DBs) with water or continuing to drink DBs, in Type 2 diabetes during a 24 week weight loss program. **The primary endpoint was the effect of intervention on weight over 24 weeks. The main secondary endpoints included anthropometric measurement, glucose and fat metabolism during the 24 weeks.**

**Methods:** 81 Overweight and obese women with type 2 diabetes, who usually consumed DBs in their diet, were asked to either substitute water for DBs or continue drinking DBs five times per week after their lunch for 24 weeks (DBs group), while they were on a weight loss program.

**Results:** Compared with the DBs group, the Water group had a greater decrease in weight (Water:  $-6.40 \pm 2.42$  kg; DBs:  $-5.25 \pm 1.60$  kg;  $P=0.006$ ), BMI (Water:  $-2.49 \pm 0.9$  2kg/m<sup>2</sup>; DBs:  $-2.06 \pm 0.62$  kg/m<sup>2</sup>;  $P=0.006$ ), FPG(Water:  $-1.63 \pm 0.54$  mmol/l; DBs:  $-1.29 \pm 0.48$  mmol/l,  $P=0.005$ ), fasting Insulin (Water:  $-5.71 \pm 2.30$  m IU/ml; DBs:  $-4.16 \pm 1.74$  m IU/ml,  $P=0.011$ ), HOMA IR (Water:  $-3.20 \pm 1.17$ ; DBs:  $-2.48 \pm 0.99$ ,  $P=0.003$ ) and 2h post prandial glucose (Water:  $-1.67 \pm 0.62$  mmol/l; DBs:  $-1.35 \pm 0.39$  mmol/l;  $P=0.027$ ) over the 24 weeks. However, there was no significant group \* time interaction for waist circumference, lipid profiles and HbA<sub>1c</sub> within both groups over 24 weeks.

**Conclusion:** Replacement of DBs with water after the main meal in patients with type 2 diabetes obese **adult women** may lead to more weight reduction during a weight loss program.

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3 24 **Introduction:**  
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5 25 There is evidence that the risk of developing type 2 diabetes is associated positively  
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8 26 with BMI (1, 2). Obesity also complicates the management of type 2 diabetes by  
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10  
11 27 increasing insulin resistance and blood glucose concentrations (3). In contrast, weight  
12  
13 28 reduction is an effective goal for overweight/ obese type 2 diabetes in order to improve  
14  
15 29 glycemic control (4).  
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17  
18 30 In the last decades, the amount of energy consumed in beverages has increased,  
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20 31 providing a significant source of daily energy intake (5). Also, to promoting weight gain,  
21  
22 32 a higher intake of sugar sweetened beverages (SSBs) is associated with the  
23  
24 33 development of metabolic syndrome and an increased risk of type 2 diabetes (6). On  
25  
26  
27 34 the other hand, diet beverages (DBs) are of interest as dietary tools which offer sweet  
28  
29 35 taste without energy (7-9).  
30

31  
32 36 Nutritionists usually advise individuals who wish to lose weight to raise their water  
33  
34 37 consumption (10, 11). Conversely, many obese and diabetic patients believe that they  
35  
36 38 can drink DBs during a diet plan without any deleterious effects on their weight and  
37  
38 39 diabetes management (12). A previous review indicated that DBs might be the ideal use  
39  
40 40 of intense sweeteners in the setting of a weight control plan, while they have been  
41  
42 41 shown to be associated with some modest weight loss (13). Thus, it would be expected  
43  
44 42 that Type 2 diabetic patients could consider DBs in order to help them to lose weight  
45  
46 43 and control their blood glucose.  
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51 44 Nevertheless, SSBs and DBs intake were associated with a significantly higher risk of  
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53 45 type 2 diabetes (14) and a subsequent observational study revealed that consumption  
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55 46 of DBs was significantly associated with an increased risk for type 2 diabetes (15). More  
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3 47 experimental study is needed to determine the effect of DBs consumption on the  
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5 48 management of diabetes and metabolic syndrome.  
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8 49 Recently, we investigated the effect of replacing DBs with water, on promoting weight  
9  
10 50 reduction in obese adults without diabetes who were on a hypo-energetic diet (16). The  
11  
12 51 Water group had a greater decrease in weight and insulin resistance over the 24 weeks  
13  
14 52 of study compared with DBs group. Due to beneficial effects of substitution of DBs with  
15  
16 53 water in overweight/ obese women, it would be interesting to repeat this protocol in  
17  
18 54 those with Type 2 diabetes.  
19  
20

21  
22 55 Thus, the purpose of this study was to investigate the effects of replacing DB  
23  
24 56 consumption with water during a comprehensive 24-wk weight-loss program on body  
25  
26 57 weight as a primary outcome, along with abdominal adiposity, carbohydrate and lipid  
27  
28 58 metabolism as secondary outcomes, in overweight and obese women with Type 2  
29  
30 59 diabetes.  
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32

## 33 34 **Materials and Methods**

### 35 36 **Study participants**

37  
38 62 Obese female adults with diabetes were selected between April 2015 and June 2015  
39  
40 63 from the participants attending NovinDiet Clinic, Tehran, Iran to lose weight and control  
41  
42 64 diabetes. Inclusion criteria were female, 18-50y of age, BMI = 27 -35 kg/m<sup>2</sup>,  
43  
44 65 6.5<Hb<sub>A1C</sub><7.2 and only taking Metformin to control their diabetes , self-reported  
45  
46 66 habitual consumers of DBs who were willing to introduce a dietary change to lose  
47  
48 67 weight which might include changing beverage consumption.  
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51  
52 68 All participants were required to be nonsmokers, free of established cardiovascular  
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54 69 diseases, stroke, liver diseases, kidney diseases, depression, cancer or autoimmune  
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3 70 disease. Subjects included those who were able to keep an adequate 4- day food  
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5 71 record and who demonstrated readiness to participate safely in daily physical activity  
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7  
8 72 (PA).  
9

10 73 Exclusion criteria were pregnancy or lactation during the previous 6 months or planned  
11  
12 74 pregnancy in the next 6 months, weight loss  $\geq 10\%$  of body weight within the 6 month  
13  
14 75 before enrollment in the study, taking medication to lower lipids/ cholesterol or that  
15  
16 76 could affect metabolism or change body weight.  
17

18  
19  
20 77 The study was approved by the Ethical Committee of The Digestive Research Institute,  
21  
22 78 Tehran University of Medical Science. All subjects provided their signed consent prior to  
23  
24 79 study enrollment. This trial was registered at <http://www.clinicaltrials.gov/> as  
25  
26  
27 80 NCT02412774.  
28

### 29 81 **Randomization and Intervention**

30  
31 82 The study was a 2-arm, **single-blind**, randomized clinical trial. Eligible participants were  
32  
33 83 randomly assigned after baseline measures by using a computer-generated random-  
34  
35 84 numbers method by the project coordinator with allocation concealed from the  
36  
37 85 participants and dietitians until randomization was revealed to the study participants at  
38  
39 86 the initial intervention clinic appointment.  
40  
41

42  
43 87 **Eighty-one participants who were eligible for the study were randomly assigned to one**  
44  
45 88 **of the 2 groups. All had a 2-wk any artificial sweetener products including diet**  
46  
47 89 **beverages washout period before intervention.** The groups were the Water group in  
48  
49 90 which subjects replaced habitual post lunch (main meal) intake of DBs with a glass of  
50  
51 91 water (250 ml) and in the DBs group subjects were instructed to continue to drink DBs  
52  
53 92 once a day (250ml), after their main meal (lunch) 5 times a week. Both groups were free  
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3 93 to drink water as beverage at other times, but were not allowed to have DBs  
4  
5 94 consumption. In addition, both groups were asked not to drink DBs or water during the  
6  
7  
8 95 lunch meal and also not to add low calorie sweeteners to beverages such as tea or  
9  
10 96 coffee. To control the effects of menstrual cycle on measurements, participants started  
11  
12 97 the study at the same phase of their menstrual cycle. Bi-weekly visits to the dietitian  
13  
14  
15 98 were required in order to promote adherence to the hypo-energetic diet and beverage  
16  
17  
18 99 substitution.

### 100 **Dietary and activity programs**

101 NovinDiet Clinic is a private weight loss clinic which uses an integrated approach  
102 (dietary, behavioural, exercise and medical treatments). Subjects who participated in  
103 this study did not pay clinic fees, were provided the diet beverages for DBs group and  
104 water for the Water group over the study. In this study the program was designed to  
105 enable weight loss of 7-10% of starting body weight, at a rate of 0.5-1 kg/week over 24  
106 weeks. The individual diet programs were based on the individual's food diary records,  
107 with gradual adjustment to bring their diet in line with the NovinDiet protocol. PA was  
108 encouraged; the objective was to gradually increase activity levels to achieve 60  
109 minutes of moderate activity on five days/ week. Predominant behavior change  
110 strategies applied included stages of change, goal setting, self-monitoring with food  
111 diaries and PA (17, 18).

112 At bi-weekly sessions, resources were provided as home booklets for each subject to  
113 record adherence to the diet protocol. During the intervention period, subjects  
114 completed the feedback form regarding their adherence to the diet. Subjects also had

1  
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3 115 access to a website, weekly internet magazines, and one to one telephone/ online  
4  
5  
6 116 support from a consultant, if needed.  
7

### 8 117 **Outcomes**

9  
10 118 To assess the effect of replacing DBs with water outcomes were collected at the  
11  
12 119 baseline, 12 weeks and 24 weeks (except height which was taken only at the screening  
13  
14  
15 120 visit).  
16

### 17 121 **Anthropometric measurements**

18  
19  
20 122 Body weight was taken to the nearest 0.1 kg using a digital calibrated scale (Omron  
21  
22 123 Health Care, Hoofdorp, Netherland), whilst subjects wore light clothing, without shoes.  
23  
24 124 Body height was measured to the nearest 0.1 cm by using a wall mounted stadiometer  
25  
26  
27 125 (SECA, Hamburg, Germany) while participants were barefoot and in a free-standing  
28  
29 126 position. Waist circumference (WC) was measured with a rigid measuring tape and  
30  
31 127 recorded to the nearest 0.5 cm. WC was measured at the smallest horizontal  
32  
33 128 circumference between the ribs and iliac crest (the natural waist), or, in case of an  
34  
35  
36 129 indeterminable waist narrowing, halfway between the lower rib and the iliac crest (19).  
37  
38  
39 130 BMI was calculated from measured weight in kilogram divided by the square of height in  
40  
41 131 meters.  
42

### 43 132 **Blood sample measurements**

44  
45  
46 133 Blood samples of all subjects were taken after overnight (8-10 h) fasting, between 07:00  
47  
48 134 and 09:00, at baseline, 12 and 24 weeks for biochemical, cellular and hormonal  
49  
50 135 measurements. Fasting blood samples were collected by venipuncture according to a  
51  
52  
53 136 standard protocol. Blood samples were taken while the subjects were in a sitting  
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55  
56 137 position, according to the standard protocol, and were centrifuged at 2000g at room  
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3 138 temperature within 30–45 min. Antecubital venous blood samples for **two-hour**  
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5  
6 139 **postprandial plasma (2hpp)** glucose were taken 2 hours after ingesting 75g of glucose  
7  
8 140 according to the standard method(20). Fasting plasma glucose (FPG) and 2hpp plasma  
9  
10 141 glucose levels were measured using the enzymatic colorimetric method. Insulin was  
11  
12 142 measured by using a radioimmunoassay with <sup>125</sup>I-labeled human insulin and a human  
13  
14 143 insulin antiserum in an immunoradiometric assay (IRMA) (Biosource, Dorest, Belgium)  
15  
16 144 with a gamma-counter system (Gamma I; Genesys). Insulin resistance was evaluated  
17  
18 145 by homeostasis model assessment of insulin resistance (HOMA-IR) (21).  
19  
20

21  
22 146 Glycated hemoglobin (Hb A<sub>1c</sub>) was measured by a colorimetric method after an initial  
23  
24 147 separation by ion exchange chromatography (Biosystem, Barcelona, Spain).  
25  
26

27 148 Biochemical analysis of the serum total cholesterol (TC), triglyceride (TG), and high-  
28  
29 149 density lipoprotein (HDL) cholesterol was carried out on a Selectra E auto analyzer (Vita  
30  
31 150 Laboratory, Netherlands) following standard procedures of the Pars Azmoon diagnostic  
32  
33 151 kits (Iran). The LDL cholesterol was calculated using the Friedewald formula(22).  
34  
35

36 152  $LDL\ cholesterol = TC - HDL\ cholesterol + (TG \div 2.2)$   
37  
38

### 39 153 **Self-reported dietary assessment**

40  
41 154 Energy and macronutrient intake at baseline, weeks 11 and week 23 was analyzed by  
42  
43 155 Nutritionist IV software (version 4.1; Hearst).  
44  
45

### 46 156 **Statistical analyses**

47  
48 157 Baseline values of cardiovascular risk factors (including weight, waist circumference,  
49  
50 158 LDL-c, HDL-c, TC, FPG, TG, fasting insulin, HOMA IR, Hb<sub>A1c</sub>, 2hpp glucose data) were  
51  
52 159 compared between the Water and DBs groups using unpaired *t*-tests.  
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3 160 At baseline, distribution was normal for all variables. All participants who were randomly  
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5 161 assigned and completed an initial assessment were included in the final results by using  
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7  
8 162 an intention-to-treat analysis. Multiple imputations with the use of linear regression were  
9  
10  
11 163 used to impute missing values from 24 wk and were based on the assumption that data  
12  
13 164 were missing at random.

14  
15 165 The primary analysis was an intent to treat linear mixed effect, which assessed at 12  
16  
17 166 and 24 weeks. These models, which included time, treatment, a time by group  
18  
19  
20 167 interaction and the respective baseline value as principal explanatory variables for all 81  
21  
22 168 participants. The per-protocol analysis was also done for the outcomes .the results from  
23  
24 169 per-protocol analysis were also similar to those of the intent to treat analysis in direction  
25  
26  
27 170 and significance. Statistical significance was set at  $p \leq 0.05$ . All data are presented as  
28  
29 171 mean  $\pm$  SD unless otherwise stated. Associations between variables were assessed by  
30  
31 172 simple correlational analyses (Pearson's  $r$ ). All statistical analyses were performed  
32  
33  
34 173 using SPSS 22.0 for Windows (SPSS Inc., USA).

35  
36 174 The primary outcome addressed in this study was the difference in body weight loss  
37  
38 175 during the 24 week weight loss program. The power calculation was based on the  
39  
40  
41 176 previous studies (16, 23) ( $\alpha = 0.05$ , power = 0.85), which were performed based upon  
42  
43 177 expected differences in weight loss between weight loss diet groups ( $2.0 \pm 2.5$  kg) to  
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46 178 determine the targeted final sample size ( $n = 56$ ). Anticipating a dropout rate of 30% the  
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48 179 sample size required was 80.

## 50 **Results**

### 51 **Results**

#### 52 **Sample characteristics**

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3 182 124 patients with type 2 diabetes, who believed that they were eligible and expressed  
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6 183 an interest in participating in the study, were evaluated for eligibility by a physician. After  
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8 184 evaluation, 81 subjects were recruited and 65 subjects completed the 24-week  
9  
10 185 intervention (with 80% retention rate, **Figure 1**). The remaining 81 subjects gave  
11  
12 186 written consent and then randomly 41 subjects were allocated to the water and 40 to the  
13  
14  
15 187 DBs group. After starting the intervention, a total of 11 subjects dropped out because  
16  
17 188 they did not wish to continue or they moved away from the area. 2 subjects left the  
18  
19  
20 189 study as they became pregnant. The remaining 3 subjects did not give any reason for  
21  
22 190 their withdrawal.

23  
24  
25 191 At baseline, there were no statistically significant differences in age, physical  
26  
27 192 characteristics or biochemical measurements between the groups or between those  
28  
29 193 who completed or did not complete the study once recruited (**Table 1**).

### 30 31 32 194 **Body weight**

33  
34 195 As shown in **Table-2**, there was a significant weight reduction in each group after 24  
35  
36 196 weeks ( $P < 0.001$ ). There was also a significant difference in weight reduction between  
37  
38 197 the two groups after 24 weeks ( $P = 0.006$ , **Figure 2**).

### 39 40 41 198 **BMI and Waist circumference**

42  
43 199 BMI reduction in each group was in the expected direction with significant effects over  
44  
45 200 24 weeks for both groups ( $P < 0.001$ ). However, the decline in BMI was greater in the  
46  
47 201 water group than the DBs group after 24 weeks ( $P = 0.006$ ).

48  
49  
50 202 In both groups, waist circumference had decreased after 24 weeks of intervention  
51  
52 203 ( $P < 0.001$ ) with no significant difference in WC effects between the two groups after the  
53  
54  
55 204 intervention ( $P = 0.833$ ).

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3 205 ***Glucose metabolism measurement***  
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5 206 Fasting plasma glucose, fasting serum insulin, 2 hour postprandial (2hpp) glucose, Hb  
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8 207 A<sub>1C</sub> and HOMA-IR all decreased over time in both groups ( $P < 0.001$ ). Also between  
9  
10 208 group differences were significant for all variables (Table 2).

11  
12 209 There was a significant difference in fasting plasma glucose level changes between the  
13  
14  
15 210 two groups after 24 weeks ( $P=0.005$ ). In terms of 2hpp, during the 24 weeks of  
16  
17 211 intervention between group changes was significant ( $P=0.027$ ).

18  
19  
20 212 There was a significant difference in insulin resistance between the two groups over 24  
21  
22 213 weeks ( $P =0.003$ ) but no significant improvement in HbA<sub>1C</sub> in the water group compared  
23  
24 214 with the DBs group over the 24 weeks ( $P =0.149$ ).

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26  
27 215 Furthermore, Fasting serum insulin concentration decreased significantly over time, with  
28  
29 216 significant differences between the two groups after 24 weeks ( $P=0.011$ ).

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32 217 ***Food intake measurement***  
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34 218 At baseline, there was no significant difference in energy intake. Estimated energy  
35  
36 219 intake measurements showed a significant reduction over time in both groups ( $P <$   
37  
38 220  $0.001$  for time effect). As shown in Table 3, there was a significant group\*time  
39  
40 221 interaction for total energy intake over 24 wk ( $P = 0.005$ ).

41  
42  
43 222 In addition, macronutrient intake measurements showed no significant differences  
44  
45 223 between the 2 groups at baseline. However, there was a greater carbohydrate deficit in  
46  
47 224 the water group than in the DB group during the 24 wk of intervention (group \*  
48  
49 225 time interaction,  $P < 0.001$ , Table 3)

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53 226 ***Discussion***  
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3 227 The purpose of the present study was to compare the effects of DBs and water  
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6 228 consumption after lunch, as a main meal, on weight loss and also characteristics of  
7  
8 229 carbohydrate and lipid metabolism in overweight and obese women with type 2 diabetes  
9  
10 230 attending a weight loss program for 24 weeks. The results of present study showed that  
11  
12 231 drinking water may lead to more weight loss, a greater improvement in fasting plasma  
13  
14 232 glucose, insulin sensitivity, measured by HOMA IR and 2hpp glucose levels compared  
15  
16 233 with consumption of DBs in women with Type 2 diabetes.  
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18  
19  
20 234 To our knowledge, this study was the first randomized controlled trial in women with  
21  
22 235 Type 2 diabetes which has assessed the impact of excluding DBs consumption on  
23  
24 236 weight loss, during a voluntary weight reduction program, for 24 weeks.  
25

26  
27 237 Weight gain and obesity are strongly related to the increased risk of type 2 diabetes  
28  
29 238 while moderate weight loss improves glycaemic control (1). All of the subjects in our  
30  
31 239 weight loss plan had a significant weight loss. This would have been predicted given the  
32  
33 240 characteristics of the prescribed treatment plan which included energy restriction, PA  
34  
35 241 instruction and regular patient visit and consultation in the clinic. In other rigorous clinic-  
36  
37 242 based behavioral lifestyle adjustment programs, 5–10% weight losses have been  
38  
39 243 reported at 6 months (24-26) which is similar to the weight losses reported in our study.  
40  
41 244 These comprehensive weight loss methods are more constantly effective in comparison  
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43 245 with others recommending small but theoretically sustainable lifestyle changes that can  
44  
45 246 be made to improve health (27). Furthermore, the present study showed a major  
46  
47 247 reduction in waist circumference and significant improvements in cardio metabolic risk  
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49 248 characteristics in both groups over 24 weeks, as would be predictable given the weight  
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51 249 loss observed. **Although the results indicated a significant effect of replacing DBs with**  
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3 250 water on weight loss during 24 weeks, it seems that the 24 weeks of intervention was  
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5  
6 251 not enough to reveal any significant effects on waist circumference (WC) as a related  
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8 252 metabolic variable. Further longer term studies measuring metabolic effects, including  
9  
10 253 WC, and more accurate assessment of body fat change using DEXA Scanning would  
11  
12 254 be required. Previous intervention studies have attempted to investigate the effects of  
13  
14  
15 255 water and DBs consumption on weight loss with inconsistent results. In a recent study,  
16  
17 256 the effects of either water or DBs consumption in comparison to SSBs, without any  
18  
19 257 hypoenergetic diet, and only having group behavioural counselling to promote  
20  
21 258 adherence to beverage substitution were compared(28). The authors failed to find any  
22  
23 259 significant differences in weight loss between water and DBs. In another study(29),  
24  
25 260 drinking water and diet beverage was compared in subjects undergoing cognitive  
26  
27 261 behavior therapy only, with no specific dietary restrictions. The result of this study  
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29 262 showed a greater impact on weight loss with DBs compared with water. On the other  
30  
31 263 hand, in a study by Dennis et al. (30), subjects who were randomly assigned to drink  
32  
33 264 pre-meal water lost about 2 kg more weight than subjects on an hypoenergetic diet  
34  
35 265 alone. It should be noted that the protocol of the last study (30) was not similar to our  
36  
37 266 study in that subjects in both groups had either water or DBs after their meal rather than  
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39 267 before the meal, which is more representative of normal behaviour in this group.  
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41 268 Furthermore, none of these studies involved obese or overweight subjects with Type 2  
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43 269 diabetes. Following our recent study (16) indicating the beneficial effects of replacing  
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45 270 diet beverages with water on weight loss and insulin sensitivity of obese and overweight  
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47 271 adults, our goal was to investigate whether these effects may be seen in women with  
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49 272 Type 2 diabetes.  
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3 273 In our current study, participants drinking water after their lunch over 24 weeks lost 1.16  
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6 274 kg more than those in the DBs group, which is in agreement with the result of our  
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8 275 previous study(16) where the overweight/ obese but otherwise healthy women in the  
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10 276 water group lost 1.2 kg more than the DBs group. In contrast, our results are  
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12 277 inconsistent with other studies which indicated either no significant change in effects on  
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14 278 weight loss between water and DBs (28) or reported greater impact on weight loss with  
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16 279 DBs compared with water(29). Nevertheless, it should be mentioned that these studies  
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18 280 had different experimental designs, for example not including any weight loss plan(28)  
19  
20 281 or have cognitive behavioral therapy alone for weight loss during a shorter period of 12  
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22 282 weeks(29). Also, the volume of beverage, the time of drinking and the type of  
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24 283 participants were different in these studies.  
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29 284 The results of our latest study may have arisen because the effect of replacement of  
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31 285 DBs with water may lead to better adherence to the weight loss diet in the Water group.  
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33 286 It has been hypothesized that artificial sweeteners may raise the hedonic desire for  
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35 287 sweetened and more energy dense foods (31-33). Also in our current study, the effect  
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37 288 of replacement of DBs with water on weight loss reflected better adherence to the  
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39 289 weight-loss diet in the water group. The greater reduction in energy intake in water  
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41 290 group compared with DBs group resulted in more weight loss in this group than DBs  
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43 291 group. Moreover, more reduction of carbohydrate consumption in the water group than  
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45 292 in the DBs group might support greater weight loss in the water group. However, in  
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47 293 order to elucidate the mechanism that might explain the better weight loss in the Water  
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49 294 group compared with the DBs group, longer term studies are required.  
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3 295 Like our study on healthy overweight/obese women (16), our present study in women  
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6 296 with Type 2 diabetes revealed a better improvement in fasting insulin sensitivity, (  
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8 297 HOMA IR), in the Water group over the 24 weeks. there was also a beneficial impact of  
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10 298 on fasting glucose and Hb<sub>A1C</sub> in the Water group, although our previous study in  
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12 299 women without diabetes(16) did not show any effects on these carbohydrate  
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14 300 metabolism characteristics. But these outcomes seen on diabetic patients were  
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16 301 consistent with the results of the recent epidemiological study indicating daily diet  
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18 302 beverage consumption was associated with impaired glucose control(32).  
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20 303 These results may have clinical implications, showing that if overweight/ obese people  
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22 304 with Type2 diabetes use a weight loss plan, they may have better improvements in  
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24 305 glycemic characteristics and weight loss if they drink water instead of DBs. These  
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26 306 findings would reinforce the recommendations given in popular weight loss programs  
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28 307 that the obese and overweight patients who are keen to lose weight should increase  
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30 308 their water intake (10, 11). On the other hand, most obese people consider that they  
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32 309 can drink diet beverages during a low- energy diet without any harmful effects on their  
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34 310 weight management, and whilst they do still lose weight, the magnitude of the weight  
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36 311 loss may be greater if they avoid DBs completely. Whilst the present study is consistent  
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38 312 with the current guideline for increasing water consumption for better diabetes control,  
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40 313 our results do not entirely support the recommendations indicating no deleterious  
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42 314 effects of diet beverage on diabetes control(34). Since the consumption of diet soda is  
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44 315 higher among people with diabetes than those without (35), the potential implications of  
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46 316 studies such as ours needs further investigation.  
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3 317 The main strength of this study is that it was a randomized, outpatient clinical trial, whilst  
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5 318 participants were selected from participants wished to lose weight and control their  
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8 319 blood sugar and included middle-aged overweight and obese women who were able to  
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10 320 comply with weight-loss plan; hence, they demonstrated that they were motivated to  
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12 321 adhere to the weight-loss diet protocol (36). Thirdly Subjects who participated in this  
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14 322 study did not pay clinic fees and were provided the diet beverages for DBs group and  
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16 323 water for the Water group which were incentive for regular by-weekly visits with the  
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18 324 dietitian when compliance could be encouraged in both groups.  
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22 325 On the other hand, there are some limitations. First of all, even though the sample size  
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24 326 providing sufficient power to distinguish statistically significant effects in the key  
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26 327 outcome variables, the sample was not representative of the general population,  
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28 328 mainly as it did not include men. In addition, due to the possible effects of the time of  
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30 329 the beverage consumption, we only asked the participants to drink either water or diet  
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32 330 beverages after the lunch in order to cover this confounding factor. Also we did not  
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34 331 record the fluid intake of participants as it may influence satiety. Moreover the energy  
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36 332 expenditure was not verified which would affect weight loss. Lastly, although our  
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38 333 weekly follow up by phone call and fortnight clinic visit to measure dietary compliance of  
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40 334 the subjects, the present study  
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42 335 only relied upon subjective report of storing and consuming the water and DBs which is  
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44 336 not as accurate as objective methods for measuring their compliance.  
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50 337 In conclusion, replacing DBs with water consumption would appear to impact  
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52 338 beneficially on weight loss, BMI, FPG and insulin sensitivity in overweight and obese  
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3 339 women with Type 2 diabetes following a weight loss diet. However, longer term studies  
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6 340 are essential to see what would happen in long term in such patients.  
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For Review Only

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3 342 **Author contributions:**  
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5 343 Experiments in this study were conducted in NovinDiet Clinic, Tehran. AM: contributed  
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8 344 to the initial study design, study protocol setup, data collection, data analysis, and  
9  
10 345 writing of the first draft of the manuscript; HRF: designed the research, conducted the  
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12 346 research, contribution to data interpretation, revision of the manuscript and provided  
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14 347 medical supervision; MAT, IAM: refined the study design and contributed to data  
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16 348 interpretation and redrafting of the manuscript. RM and AD: provided advice and  
17  
18 349 consultation for the study design, conducted the research. All authors read and  
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20 350 approved the final manuscript. HRF is the guarantor of this work and, as such, had full  
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22 351 access to all the data in the study and takes responsibility for the integrity of the data  
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54 364 reported.  
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**Table 1. Baseline characteristics before the intervention\***

	<b>water group(n=41)</b>	<b>DBs Group(n=40)</b>
<b>Age (y)</b>	34.15 (6.99)	35.45 (7.45)
<b>Body wt (kg)</b>	83.92 (4.42)	84.70 (7.43)
<b>Height (cm)</b>	159.83 (2.83)	159.65 (3.08)
<b>BMI (kg/m<sup>2</sup>)</b>	32.86 (1.67)	33.19 (2.25)
<b>WC (cm)</b>	103 (5)	102 (7)
<b>Married</b>	78%	82%
<b>TC ( mmol/l)</b>	4.78 (0.43)	4.75 (0.37)
<b>HDL-C (mmol/l)</b>	1.13 (0.19)	1.13 (0.17)
<b>LDL-C (mmol/l)</b>	2.73 (0.51)	2.71 (0.38)
<b>TG (mmol/l)</b>	2.02 (0.27)	1.97 (0.25)
<b>FPG (mmol/l)</b>	8.49 (0.90)	8.48 (1.03)
<b>2hppG (mmol/l)</b>	8.82 (1.14)	8.76 (1.22)
<b>HA1C (%)</b>	6.97 (0.77)	6.95 (0.20)
<b>Insulin ( mU/l)</b>	19.99 (4.07)	19.84 (4.07)
<b>HOMA-IR</b>	7.59 (1.93)	7.50 (1.89)

\* Group difference, P > 0.05.

Data are presented as mean ( SD)

Diet beverages: DBs, Waist circumference: WC, Total cholesterol: TC,  
Triglyceride: TG, Fasting plasma Glucose: FPG, 2 hour post prandial glucose:  
Glycated haemoglobin: HA1C,  
Homeostasis model assessment of insulin resistance: HOMA-IR

**Table 2. Anthropometric and blood measurement characteristics in Water and DBs Groups at baseline, 12 and 24-week interventions\***

	<u>Water Group(n=41)</u>			<u>DBs Group(n=40)</u>			<u>P for time × group<sup>†</sup></u>
	<u>Baseline</u>	<u>week 12</u>	<u>week 24</u>	<u>Baseline</u>	<u>week 12</u>	<u>week 24</u>	
<b>Weight, kg</b>	83.92 (4.42)	79.96 (4.86)	77.52 (4.95)	84.70 (7.43)	81.25 (7.03)	79.45(6.99)	0.006
<b>BMI, kg/m<sup>2</sup></b>	32.86 (1.67)	31.32 (2)	30.36( 2.06)	33.19 (2.25)	31.84 (2.13)	31.14(2.12)	0.006
<b>WC, cm <sup>‡</sup></b>	103 (5)	99 (7)	97(7)	103 (7)	99 (7)	97(6)	0.832
<b>TC, mmol/l <sup>‡</sup></b>	4.78 (0.43)	4.52 (0.45)	4.29(0.41)	4.75 (0.37)	4.49 (0.37)	4.31 (0.33)	0.119
<b>HDL-C, mmol/l <sup>‡</sup></b>	1.13 (0.19)	1.23 (0.18)	1.33( 0.17)	1.13 (0.17)	1.25 (0.18)	1.33(0.16)	0.319
<b>LDL-C, mmol/l <sup>‡</sup></b>	2.73 (0.51)	2.49 (0.49)	2.22(0.46)	2.71 (0.38)	2.44 (0.40)	2.24(0.35)	0.07
<b>TG, mmol/l <sup>‡</sup></b>	2.02 (0.27)	1.77 (0.28)	1.63(0.27)	1.97 (0.25)	1.75 (0.24)	1.62(0.19)	0.639
<b>FPG, mmol/l</b>	8.49 (0.90)	7.76 (0.82)	6.86(0.77)	8.48 (1.03)	7.85 (0.96)	7.19(0.81)	0.005
<b>2hpp, mmol/l</b>	8.82 (1.14)	7.91 (0.87)	7.15(0.70)	8.76 (1.22)	8.03 (1.06)	7.40(1.01)	0.027
<b>Hb A1C, % <sup>‡</sup></b>	6.97 (0.77)	6.16 (0.99)	5.80(0.82)	6.95 (0.20)	6.81 (0.17)	6.53(0.16)	0.149
<b>Insulin, m U/l</b>	19.99 (4.07)	16.75 (4.03)	14.27(3.81)	19.84 (4.07)	17.36 (3.43)	17.36(3.43)	0.011
<b>HOMA-IR</b>	7.59(1.93)	5.80(1.62)	4.39 ( 1.37)	7.50 (1.89)	6.05 (1.39)	5.01(1.20)	0.003

\* Data are presented as mean (SD) for the 81 participants

<sup>†</sup> P values are for Water relative to DBs group (time × Group interaction) by a linear mixed model analysis with repeated measures.

<sup>‡</sup> Significant main effect of time, P < 0.001

Diet beverages: DBs, Waist circumference :WC, Total cholesterol: TC, Triglyceride: TG, Fasting plasma glucose: FPG

Glycated hemoglobin: Hb A1C, 2 hour post prandial: 2hpp, Homeostasis model assessment of insulin resistance: HOMA-IR

**Table 3. Self-reported dietary intake in Water and DBs Groups before and after the 24-week interventions\***

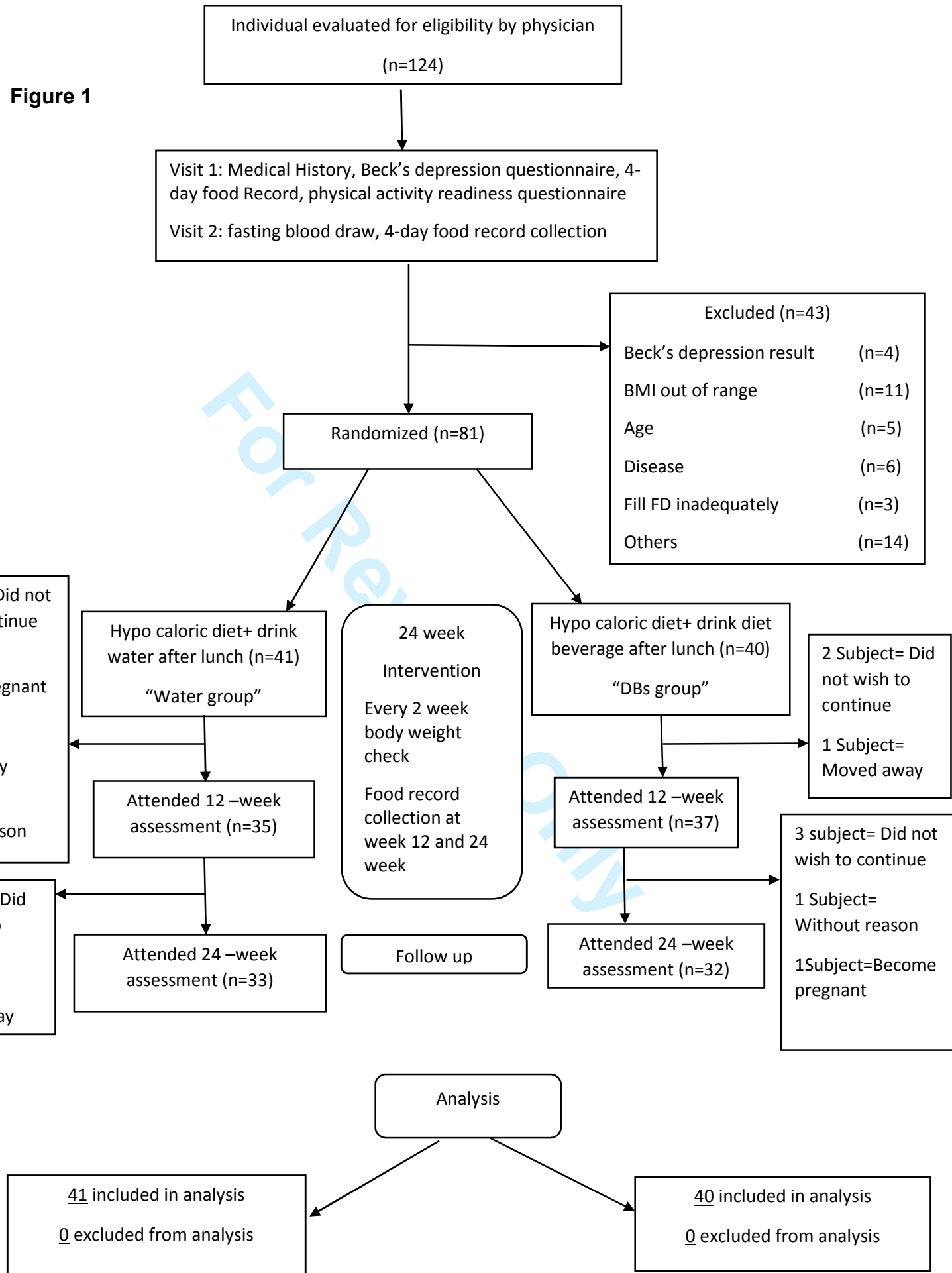
Intake	Water Group(n=41)		DBs Group(n=40)		<u>P for time × group</u> <sup>†</sup>
	Baseline	week 24	Baseline	week 24	
<b>Total Energy (kcal)</b>	2202(173)	1785(146)	2157(275)	1827(302)	0.005
<b>Protein (g)</b>	81.2(8.7)	79.6(9.4)	80.4(13.9)	80(15.6)	0.240
<b>Protein (%)</b>	14.8(2)	17.9(1.6)	14.9(2.1)	17.5(1.8)	
<b>Fat (g)</b>	86.2(11.7)	63.8(8.1)	82.6(16.6)	61.1(12)	0.675
<b>Fat (%)</b>	35.1(2.8)	32.1(2.3)	34.4(4.3)	30.1(2.4)	
<b>Carbohydrate (g)</b>	275.4(20.9)	223(17.6)	273.1(34.5)	239.1(38.6)	<0.001
<b>Carbohydrate (%)</b>	50.1(1.7)	50(2.5)	50.7(3.2)	52.4(2.4)	
<b>Fiber(g)</b>	20.7(5.3)	22.2(5.3)	20.8(3.1)	22.2(3.2)	0.280

\* Data are presented as mean (SD) for the 81 participants

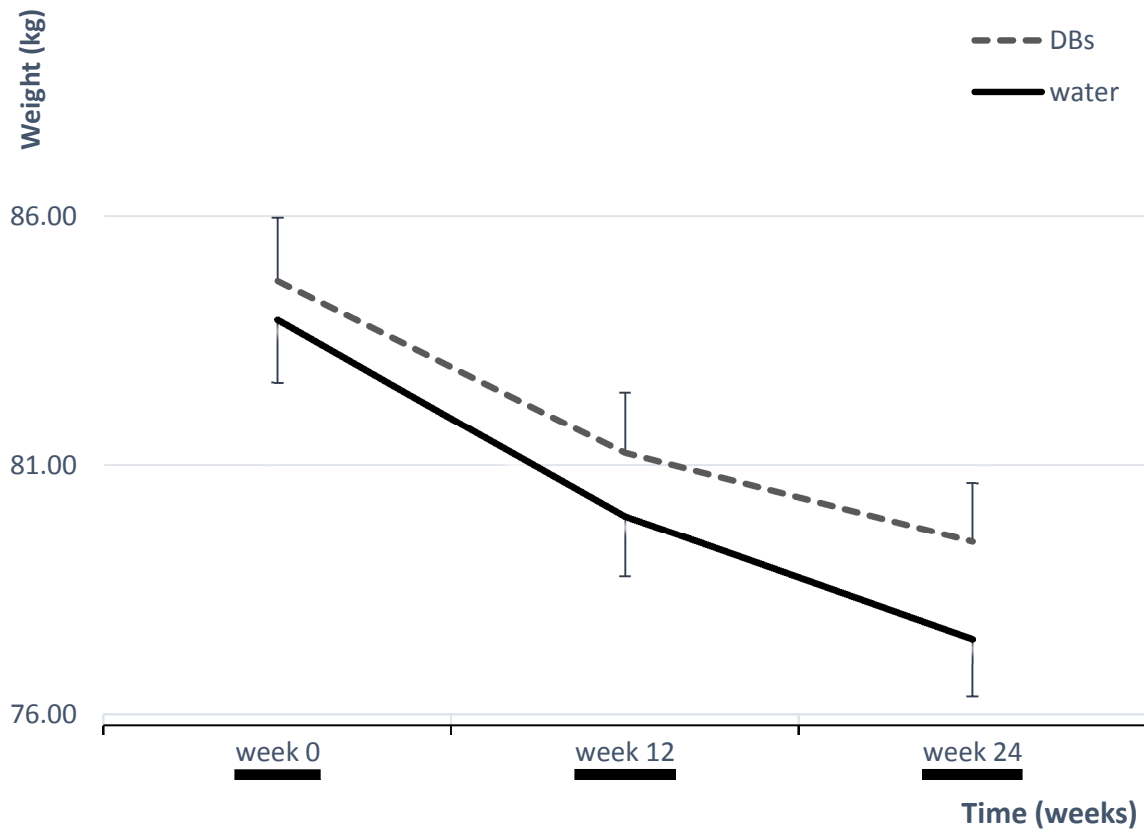
† P values are for Water relative to DBs group (time × Group interaction) by repeated-measures two way ANOVA

Figure 1

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**Figure 2** Mean (SE) weight at baseline, 12 and 24 wk of energy restriction with either drinking water (Water;  $n = 41$ ) or diet beverages (DBs;  $n = 40$ ) in all participants, regardless of attrition.  $P < 0.001$  for the main effect of time. There was also a significant difference in weight reduction between the two groups after 24 weeks ( $P=0.006$ ), based on linear mixed effects models.