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Hypohydration and Glucose Regulation in Adult Males with Type II Diabetes Mellitus

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Hypohydration and Glucose Regulation in Adult Males with Type II Diabetes Mellitus

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Abstract

Daily total water intake (TWI) has been linked to a number of chronic diseases, such as urolithiasis and chronic kidney disease. Additionally, epidemiological and animal model data have tied low TWI to impaired blood glucose regulation. However, the effect of a fluid intake intervention on blood glucose regulation has not yet been observed in humans.

PURPOSE: Thus, the purpose of the current investigation is to determine if the response to an oral glucose tolerance test (OGTT) is altered by manipulation of hydration status in people with diabetes. **METHODS:** Nine men (53±9 y, 94.9± 23.8 kg, 1.75± 0.11 m, 30.0± 4.3 $m \cdot kg^{-2}$, 31.5± 6.5 %BF) who had previously been diagnosed with type II diabetes mellitus (T2DM) (hemoglobin A1C; 6.8±0.9 %) were recruited to take part. Participants completed two OGTTs in a euhydrated and hypohydrated state one week apart in a counterbalanced order. Euhydration was achieved by standard water prescription in line with the dietary reference intakes for water, and hypohydration was achieved through progressive water restriction over three days leading up to the OGTT. Blood samples were taken at time points 0, 15, 30, 45, 60, 90, 120 min of the OGTT. **RESULTS:** The changes in TWI in the three days before each trial resulted in significantly lower body mass (-1.5±1.5 kg; $p = 0.017$) and increased urine specific gravity (0.017±0.009; $p = 0.001$), and plasma osmolality (10±8 $mmol \cdot kg^{-1}$). Repeated measures analysis of variance identified a main effect of condition for blood glucose concentration $F[1,48] = 10.772$, $p = 0.011$, but not for insulin concentration $F[1,48] = .657$, $p = 0.441$. Insulin sensitivity calculated with the Matsuda index revealed attenuated insulin sensitivity during the hypohydrated trial (3.4±3.2) versus the euhydrated trial

(3.8±3.7; *t*[8] = 2.834, p = 0.022) **CONCLUSION:** Hypohydration elicits an acute, negative effect on the blood glucose response to OGTT in men with T2DM. Although, blood insulin did not change, blood glucose and insulin sensitivity were reduced during the euhydrated trial. This suggests that inadequate TWI can negatively impact blood glucose regulation via decreased insulin sensitivity.

INTRODUCTION

Type II diabetes mellitus (T2DM) is a costly disease that greatly reduces the quality of life. Estimated total cost of diabetes in the United States is $245 billion (17). T2DM results from a combination of resistance to insulin and/or a deficiency in insulin production (17). During a person's lifetime, the risk that someone will develop type II diabetes is 1 in 3 for males and 2 in 5 for females (17). T2DM increases the risk of developing many chronic diseases. There were 4.2 million people diagnosed with T2DM who subsequently developed diabetic retinopathy (7). A total of 228,924 people with diabetes had kidney failure (7). A person with diabetes was found to be 1.8 times more likely to have a heart attack than those without diabetes (7). These are only some of many complications that can occur in people with type II diabetes mellitus.

Excessive thirst is a common comorbidity with T2DM. Glucose multiplies in the bloodstream which causes the kidneys to lose their ability to reuptake glucose from water. The osmotic pressure then becomes high and stops water from being absorbed back into the bloodstream. This results in major dehydration and thirst. The normal thirst mechanism includes intracellular and extracellular components. Intracellularly, when the body is dehydrated, there is an increase in plasma osmotic pressure (20). This causes stimulation of both pituitary release of ADH and brain thirst centers (20). The release of ADH results in the reabsorption of water in the kidneys, while the stimulation of brain thirst centers causes the urge to drink (20). The body should then return to a normal hydration state (20). Extracellularly, when the body is dehydrated, there is a decrease in plasma volume (and in blood pressure) (20). This causes stimulation of specialized volume receptors that leads to an increase in blood levels of angiotensin II, which leads to

the stimulation of pituitary release of ADH, brain thirst centers, and aldosterone release (20). The release of ADH and angiotensin II results in temporary vasoconstriction (20). Reabsorption of sodium in the kidney occurs after aldosterone is released (20). Ideally, the body will then return to a normal hydration state (20).

The renin-angiotensin system has become an important focus in the treatment of hypertension (13). Although vasopressin is not directly part of the renin-angiotensin system, it acts indirectly by inhibiting the release of renin by the kidney (19). Serious depletions in water volume can effect secretions of vasopressin by the renin-angiotensin (3). Vasopressin, the fluid regulatory hormone, has been experimentally linked to blood glucose regulation in animal models (5). Furthermore, previous research has shown an association between vasopressin and diabetes (18). Vasopressin has also been observed to be linked to kidney dysfunction in type II diabetic mellitus patients (21). Measuring copeptin, the stable COOH-terminal portion of the precursor of vasopressin, is effective in determining vasopressin levels (16). As expected, elevated amounts of copeptin are associated with heightened risk for diabetes mellitus (9). Hydration status is known to determine the amount of vasopressin and copeptin secretion (16).

Low insulin sensitivity, also known as insulin resistance, is a characteristic of people with type II diabetes mellitus (8). Many different techniques can be used to predict insulin sensitivity. One effective way of measuring insulin resistance is by using the homeostasis model assessment-insulin resistant (HOMA-IR) (11). HOMA-IR predicts homeostatic concentrations that emerge from differing degrees of insulin resistance (15). The Matsuda index of insulin sensitivity predicts whole body insulin sensitivity during an oral glucose tolerance test (14). QUICKI is a reliable index of insulin sensitivity to

determine hepatic insulin resistance (12). While, the Abdul-Ghani index of insulin sensitivity predicts muscular insulin resistance (1).

Therefore, the purpose of the present investigation was to determine the effects of mild hypohydration on glucose tolerance within individuals diagnosed with type II diabetes mellitus (T2DM). Subsequently, our aim was to evaluate blood glucose levels over two 120 minute time periods while in euhydrated and hypohydrated states. Hypohydration must not be confused with dehydration. Hypohydration refers to a status with maximum (minimum) urine osmolality, while dehydration refers to an acute process of loss (gain) of total body water (10). We hypothesized that individuals in a hypohydrated state would achieve blood sugar homeostasis for a longer period of time than those in a euhydrated state after an oral glucose tolerance test. The current protocol systematically modified fluid intake in order to investigate the hypothesis.

RESEARCH DESIGN AND METHODS

Participants

We studied nine males, previously diagnosed with type II diabetes from Northwest Arkansas. Participation of the study was based on a certain criteria. The inclusion criteria included: (a) males of ages 18-65 years old, (b) signed informed consent prior to the initiation of any trial procedure, (c) sedentary lifestyle, (d) previously diagnosed as having T2DM (confirmation of diabetic status during screening visit by glycosylated hemoglobin concentration (HbA1c) $\geq$ 6.5%). The exclusion criteria included: (a) BMI greater than 35 kg/m^2 , (b) inability to participate in the entire study, (c) changes in diet during the last month, (d) drastic change in weight in the last month (more than 3 kg), (e)

inability or lack of desire to discontinue glucose regulating, diuretics, and/or renal (ACE inhibitor) medications for the three days prior to, and the day of each experimental visit, (f) serotonin re-uptake inhibitors (i.e. Prozac), (g) diabetic medication other than Metformin or sulfonylureas, (h) impaired kidney or liver function, and (i) insulin therapy.

Procedures

Each participant had four visits to the Human Performance Laboratory at the University of Arkansas over a period of two weeks. These visits included one screening/familiarization visit, two experimental days, and one pre-dehydration visit. One experimental day consisted of the participant coming to the lab in a euhydrated state and the other experimental day in a hypohydrated state. The pre-dehydration visit occurred exactly one day before the hypohydrated experimental day.

Screening and Consent

A certified nurse initially met with each participant to ensure qualification to participate in the study. The nurse confirmed each participant was able to withdraw from any medications for three days prior to both experimental days. The participants read the consent form and were able to have their questions answered by the nurse. Next, the participants completed a medical history form. Anthropomorphic measurements (i.e., height, weight, waist & hip circumference and body composition via DXA) were recorded after receiving consent. To determine glycosylated hemoglobin (HbA1c) and creatinine, a blood sample from a finger stick was performed and analyzed. The participants were required to possess a value ≥6.5% to be involved in the study. The criteria for diagnosis of T2DM is a value ≥6.5% (2). After qualification was confirmed,

each participant was familiarized with the perceptual scales, filled out a water frequency questionnaire, and practiced the static balance assessment (SBA) protocol.

Dietary control 3 days prior to experimental days

Each participant's diet was controlled 3 days before the experimental days. A list was provided to the participants for them to choose acceptable low water foods while consuming 150 grams of carbohydrates each day (6). The participants were asked to record their diet 3 days before the first experimental day and to replicate their diet for the second experimental day. Thus, the fluid intake was the only difference between the experimental days. Approximately 45 mL/kg of water were provided for the euhydrated trial, while approximately 5 mL/kg of water were prescribed for the hypohydrated trial. Participants were told to refrain from alcohol and caffeine for 24 hours prior to each experimental day in order to elicit approximately 1-2% dehydration while controlling for food within participants.

Experimental days

Participants reported to the lab on two days, separated by at least a week, in a fasted state (i.e. no consumption of calories from food or beverage for the previous 9 hours) for the main experimental visits. Typically for the first visit, the participant arrived in a euhydrated state, while for the second visit, the participant arrived in a hypohydrated state. However, this was not always the case. Some of the participants arrived in a hypohydrated state for the first visit and a euhydrated state for the second visit. This allowed for the experiment to be counterbalanced. As the participant entered the lab, a urine sample was provided. Secondly, body weight was recorded to ensure hydration status.

Following, the patient settled in a specialized reclining chair designed for blood draws. An oral glucose tolerance test (OGGT) was administered to evoke the classical insulin and glucose responses following ingestion of dietary carbohydrates in a standardized process. After 15 minutes of resting, a baseline blood sample was taken. Within 10 minutes of the initial draw, the patient consumed a standardized glucose beverage that contained 75 grams of glucose. The patients then remained seated for the next 2 hours. Blood samples of 15 mL were collected from the catheter at +15, +30, +45, +60, +90, and +120 minutes from the time the standardized glucose beverage was consumed. The total blood drawn equaled 90 mL, which is approximately 2.0% total blood volume.. The remaining blood was centrifuged to separate the plasma. Plasma osmolality was determined with freezing point depression. Further, electrolytes (Na+, K+, & Cl-) were analyzed. The leftover blood plasma was stored in the freezer for later testing. After observing differences between euhydrated and hypohydrated trials, analyses of secondary markers were performed. These secondary analyses included renin, aldosterone, arginine, vasopressin, and copeptin.

RESULTS

During this investigation, 9 men with T2DM were observed across a euhydrated trail and a hypohydrated trial. Each participant was given a certain amount of water for the euhydrated trial (3.5 $L \cdot d^{-1}$) and hypohydrated trial (0.83 $L \cdot d^{-1}$) (Table 1). To measure glucose and insulin responses, fasting glucose, fasting insulin, HOMA-IR, Matsuda, QUICKI, and Abdul-Ghani were recorded for each participant for both the euhydrated and hypohydrated trials. Body mass, urine osmolality, and plasma osmolality were

measured in each participant for both the euhydrated and hypohydrated trials to determine hydration status before they started the OGTT. For the euhydration trial, the average body mass was 95.1±23.8 kg, the average urine osmolality was 512±185 $mmol \cdot kg^{-1}$, and the average plasma osmolality was 289±4 $mmol \cdot kg^{-1}$ (Table 1). For the hypohydration trial, the average body mass was 93.6±23.0 kg, the average urine osmolality was 994±115 $mmol \cdot kg^{-1}$, and the average plasma osmolality was 298±6 $mmol \cdot kg^{-1}$ (Table 1).

Euhydration

Fasting glucose in the participants resulted in 9.9±4.1 $mmol \cdot L^{-1}$. Fasting insulin in the participants were 59.2±67.8 $pmol \cdot L^{-1}$. HOMA-IR, ((fasting glucose×fasting insulin)/22.5), predicted 5.7±5.2 for resting insulin resistance (15). Matsuda, (10,000 / $\sqrt{}$ fasting glucose×fasting insulin) × (mean OGTT glucose×mean OGTT insulin), predicted 3.8±3.7 for whole body insulin sensitivity during OGTT (14). QUICKI, (1/(*log*(fasting insulin) + *log*(fasting glucose)), predicted 0.33±0.06 for hepatic insulin resistance (12). Abdul-Ghani, ($Glucose_{0\text{-}30}$(AUC) × $Insulin_{0\text{-}30}$(AUC)), predicted 279±203 for muscular insulin resistance (1) (Table 2). The area under the glucose curve was shown to be 1765±540 $mmol \cdot L^{-1} \cdot min^{-1}$ (Figure 1).

Hypohydration

Fasting glucose in the participants resulted in 10.4±4.2 $mmol \cdot L^{-1}$. Fasting insulin in the participants were 67.8±48.9. HOMA-IR, ((fasting glucose×fasting insulin)/22.5), predicted 6.1±6.6 for resting insulin resistance (15). Matsuda, (10,000 / $\sqrt{}$ fasting glucose×fasting insulin) × (mean OGTT glucose×mean OGTT insulin), predicted 3.4±3.2 for whole body insulin sensitivity during OGTT (14). QUICKI, (1/(*log*(fasting insulin) +

log(fasting glucose)), predicted 0.32±.05 for hepatic insulin resistance. Abdul-Ghani, ($Glucose_{0\text{-}30}$(AUC) × $Insulin_{0\text{-}30}$(AUC)), predicted 282±203 for muscular insulin resistance (1) (Table 2). The area under the glucose curve was shown to be 1862±560 $mmol \cdot L^{-1} \cdot min^{-1}$ (Figure 1).

Effect of Hydration Markers, Blood Glucose, and Insulin

The changes in total water intake in the three days before each trial resulted in significantly lower body mass (-1.5±1.5 kg; p = 0.017), increased urine specific gravity (0.017±0.009; p = 0.001), and plasma osmolality (10±8 $mmol \cdot kg^{-1}$; p=0.003). Repeated measures analysis of variance identified a main effect of condition for blood glucose concentration F[1,48] = 10.772, p = 0.011, but not for insulin concentration F[1,48] = .657, p = 0.441. Insulin sensitivity calculated with the Matsuda index revealed attenuated insulin sensitivity during the hypohydrated trial (3.4±3.2) versus the euhydrated trial (3.8±3.7; *t*[8] = 2.834, p = 0.022). A significant effect occurred with the QUICKI index (p=0.007) but not for the Abdul-Ghani index (p=0.596).

DISCUSSION

This investigation sought to differentiate between euhydrated and hypohydrated states and the effect each state has on glucose regulation of adult men with type II diabetes mellitus. The primary findings were: 1) that reduced water consumption resulted in increased glucose concentration before and during oral glucose tolerance testing, 2) no changes in fasting or stimulated insulin occurred between trials, 3) glucose kinetic calculations revealed that reduced water intake effected insulin sensitivity only during the

OGTT, and 4) glucose regulation impairment appears to take place in the liver rather than in the muscle tissue.

We expected a significant difference for urine osmolality (0.017±0.009; p = 0.001) and urine specific gravity (0.017±0.009; p = 0.001) as markers of hydration status. Previous studies have shown that urine osmolality and urine specific gravity are reliable in order to determine hydration status (4). We also expected the area under the glucose curve for the euhydrated trial (1765±540 $mmol \cdot L^{-1} \cdot min^{-1}$) to be significantly different than the hypohydrated trial (1862±560 $mmol \cdot L^{-1} \cdot min^{-1}$). Comparable research suggests that hydration status can prevent the onset of T2DM (18). However, in our study, we found there to be no significant difference between the areas of the glucose curves. A significant difference occurred as expected for the QUICKI index (p=0.007). Earlier studies have linked hepatic insulin resistance with T2DM (8).

This study has several limiting factors. The current investigation applies specifically to men with T2DM. Also, no males under the age of 18 were allowed to participate. Another limitation was having a small sample size. Having a larger sample size would ensure a better representation of the target population.

Based on the information we know now, future research opportunities could help determine the relationship between hydration state and glucose regulation in people with T2DM. Future research should look to investigate glucose regulation in females with T2DM in a euhydrated and hypohydrated state. This could potentially yield differing results that could lead to positive repercussions in the long run for females with T2DM. Also, future research should aim to establish if longer periods of fluid restriction results in larger disturbances to blood glucose regulation.

TABLES AND FIGURES

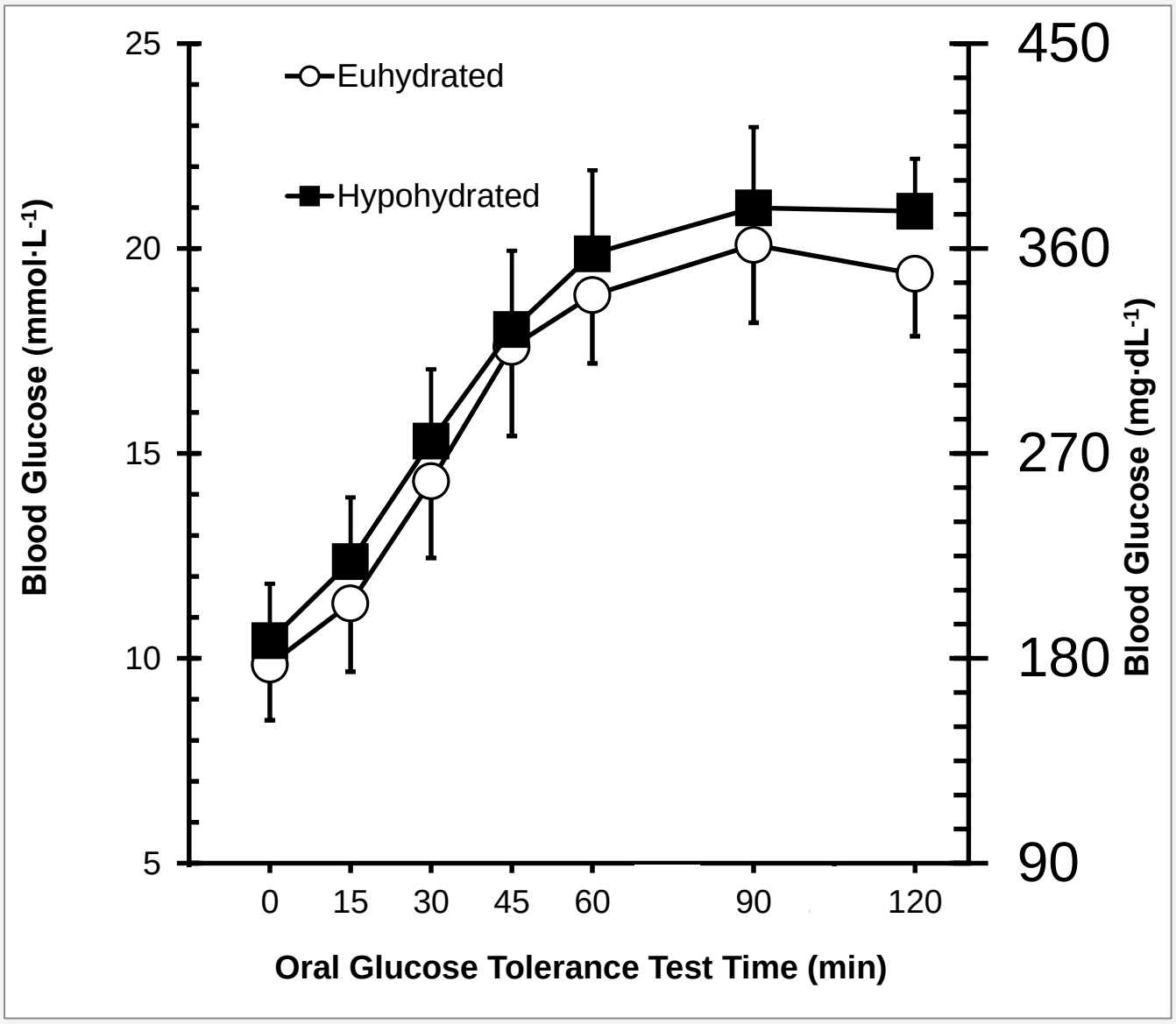

Figure 1. Plasma glucose (mean ± SE) during OGTTs.

	Euhydrated	Hypohydrated	P-Value
Water prescription* ($L \cdot d^{-1}$)	3.5	0.83	**<0.001**
Body mass (kg)	95.1 ± 23.8	93.6 ± 23.0	**0.017**
Urine Osmolality ($mmol \cdot kg^{-1}$)	512 ± 185	944 ± 115	**0.002**
Plasma Osmolality ($mmol \cdot kg^{-1}$)	289 ± 4	298 ± 6	**0.003**

Table 1. Markers of hydration between euhydrated and hypohydrated conditions.

* – Average of prescribed bottled water intake on the three days leading up to the oral glucose tolerance test.

Variable	Predicts	Euhydrated	Hypohydrated	P-Value
Fasting glucose ($mmol \cdot L^{-1}$)		9.9 ± 4.1	10.4 ± 4.2	**0.037**
Fasting Insulin ($pmol \cdot L^{-1}$)		59.2 ± 67.8	67.8 ± 48.9	0.155
HOMA-IR	Resting insulin resistance	5.7 ± 5.2	6.1 ± 6.6	0.750
Matsuda	Whole body insulin sensitivity during OGTT	3.8 ± 3.7	3.4 ± 3.2	**0.022**
QUICKI	Hepatic insulin resistance	0.33 ± 0.06	0.32 ± 0.05	**0.007**
Abdul-Ghani (in thousands)	Muscular insulin resistance	279 ± 203	282 ± 203	0.596

Table 2. Fasting plasma glucose, insulin, and calculated indexes of insulin sensitivity.

- HOMA-IR = (fasting glucose × fasting insulin) / 22.5
- Matsuda = 10,000 / $\sqrt{}$(fasting glucose × fasting insulin) × (mean OGTT glucose × mean OGTT insulin)
- QUICKI = 1/(*log*(fasting insulin) + *log*(fasting glucose)
- Abdul-Ghani[5] = $Glucose_{0\text{-}30}$(AUC) × $Insulin_{0\text{-}30}$(AUC)

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