Is Increased Water Consumption Among Older Adults Associated with Improvements in Glycemia?

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ABSTRACT

The high rates of obesity and impaired glycemia in older adults place these individuals at risk for developing diabetes. Dehydration, glucose tolerance, and insulin resistance are related. Many older adults do not achieve the Dietary Reference Intake (DRI) for water, and aging and dehydration are both associated with decreased glucose tolerance. Conversely, weight loss is associated with improvements in glucose tolerance. For older adults following a hypocaloric diet, additional water consumption may lead to greater weight loss. Furthermore, research suggests an association between insulin resistance and arginine vasopressin (AVP), the hormone responsible for regulating body water retention. Analysis of the association between plasma copeptin (an AVP derivative) and fasting glucose, insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) may provide further insight into the relationship between dehydration and diabetes risk.

To our knowledge, few investigations have addressed this relationship between dehydration, impaired glycemia, and insulin resistance and how increasing water consumption may influence diabetes risk. Our purpose was to investigate the possibility that increased water consumption among older adults (n=29, BMI=31$\pm$1 kg/m^2, age=62$\pm$1 years) could improve glycemia beyond that observed with weight loss, as well as associations between plasma copeptin and diabetes risk. Analysis of diabetes-related variables for subjects grouped according to study intervention group, amount of drinking water consumed, or pair-matched for weight loss and gender did not reveal significant differences between groups. Improvements in fasting insulin for water group participants, as well as correlations between hydration and insulin resistance support the need for future investigations.

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CHAPTER 1: Introduction

Water Intake in Older Adults

Water is a vital nutrient necessary for life. Water plays many significant roles within the human body and because humans cannot obtain adequate water via metabolism or food ingestion alone, beverage consumption is critical for maintaining hydration status (1). Oftentimes recommendations on daily water consumption are forgotten (1), thus many individuals may not understand the importance of drinking enough water. For the elderly population, adequate fluid intake and hydration status become especially important. Decreased renal function with aging leads to impairments in renal-concentrating and sodium-conserving ability, conditions that are associated with volume depletion and hypernatremia in the elderly (2). In healthy individuals, depleted volume and elevated sodium levels will prompt thirst and subsequent fluid intake to restore hydration status. It is important to note that fluid intake is the only method in which to replenish water deficits, so the thirst sensation is imperative for fluid and electrolyte homeostasis (3). However, thirst is often blunted in elderly subjects and inadequate fluid intake may increase risk of dehydration and hypernatremia (2).

Hypodipsia (abnormally diminished thirst) in the elderly population is well established. A study that examined the effects of dehydration on thirst and urine and plasma markers in the elderly as compared to younger adults found that after fluid deprivation, the elderly subjects experienced significant increases in plasma sodium concentration (140.2$\pm$0.4 to 143.2$\pm$0.5 mmol/L) and osmolality (288.4$\pm$1.3 to 296.0$\pm$1.2 mOsm/kg of water) while the younger group had nonsignificant increases of both variables (3). The younger participants experienced a strong thirst response that prompted them to drink enough fluids to replenish their body fluids while the elderly did not (3). These results clearly indicated a deficit in thirst and subsequent water intake in the older adults following dehydration (3). A wealth of literature exists that further demonstrates hypodipsia in the elderly despite elevated plasma sodium levels and osmolality. However, the physiological mechanisms behind blunted thirst in the elderly remain unclear.

Under normal conditions, the feedback mechanisms of osmotic control pathways and baroreceptor pathways will maintain water balance and bring disturbed plasma osmolarity back to normal. The osmoreceptors located within the hypothalamus are responsible for stimulating thirst and sodium appetite, causing an individual to drink when plasma osmolarity increases.

Additionally, peripheral osmoreceptors in the oropharyngeal area are stimulated by the dryness of the oral and esophageal mucosa that occurs in a dehydrated state. These osmoreceptors are responsible for stimulating secretion of arginine vasopressin (AVP), which causes an antidiuretic effect in the kidneys and retention of water under conditions of negative water balance and elevated plasma osmolarity (4). A less sensitive system responds to decreases in plasma volume or arterial pressure that occur with negative water balance. Baroreceptors within blood vessels and the heart are stimulated when hypervolemia occurs, causing suppression of AVP secretion. Conversely, AVP secretion increases in hypovolemia, leading to water retention (4). Dysfunctions within these systems are among the proposed mechanisms for decreased thirst in the elderly. Impairments in osmoreceptors that respond to elevated plasma osmolarity and baroreceptors that respond to decreased plasma volume may occur in older adults (3). Alterations in oropharyngeal factors (like dry mouth and taste), central nervous system dysfunction, and alterations in neuroendocrine function that accompany age (specifically the activity of the renin-angiotensin-aldosterone system and levels of atrial natriuretic peptide) may also contribute to hypodipsia and dehydration in the elderly (3). However, additional research is needed to clearly demonstrate causes for blunted thirst in the elderly.

Associations Between Copeptin, Hydration, and Diabetes Risk

Arginine vasopressin is a principal regulator of body water balance. It acts upon the renal collecting ducts by increasing water permeability of the apical membrane and promoting free water reabsorption (5). AVP is synthesized as prepro-hormone with four constituent parts: a signal peptide, the AVP hormone, a carrier protein, and the glycoprotein copeptin (5). Plasma AVP is unstable, is largely bound to platelets, and is rapidly cleared from the bloodstream. These factors combined with a lack of reliable AVP assays have limited the use of circulating AVP levels in clinical diagnostics (6). Alternatively, copeptin is stable *ex vivo* in plasma and sensitive sandwich immunoassays are available for detecting copeptin in human plasma or serum. Researchers believe that copeptin should represent the release of AVP (similar to the situation of C-peptide and insulin) (5), and correlations found between copeptin and AVP indicate that copeptin analysis is an acceptable alternative to AVP assays (6). Furthermore, recent research suggests that the AVP system plays a role in glucose homeostasis, insulin resistance, and diabetes mellitus (7). A large population-based prospective study found higher copeptin

concentrations among individuals with diabetes compared to those without diabetes, positive associations between copeptin, fasting blood glucose, and plasma insulin in those without diabetes, and significantly higher copeptin concentrations at baseline for those normoglycemic subjects who subsequently developed new-onset diabetes (7). Additionally, a cross-sectional study reports a positive correlation of plasma copeptin with components of metabolic syndrome (BMI, waist circumference, fasting serum glucose and insulin levels, HOMA-IR, presence of diabetes, and serum triglycerides) when adjusted for age and sex (8). These findings imply that copeptin is associated with the presence of metabolic syndrome and may be a predictor for diabetes development (independent of renal function, and diabetes risk factors such as fasting blood glucose and insulin). Proposed underlying mechanisms for the role of the AVP system in the pathophysiology of diabetes include action upon AVP receptors and stress-induced elevation of AVP levels (7, 8). An additional relationship may exist between copeptin, aging, and renal function. Older subjects experienced the most pronounced association between low copeptin levels, lower urine volume and higher urine osmolarity (9). Elevated copeptin in the elderly may indicate decline in renal function and/or reduced sensitivity to AVP, and researchers suggest that this population is likely to profit from interventions geared toward increasing water intake (9).

Effects of Inadequate Water Consumption

The current Adequate Intake (AI) for total water (from drinking water, beverages, and food) for adults over 50 years is 3.7 L/day and 2.7 L/day for males and females, respectively (10). Of this total water intake, it is normally assumed that 70-80% comes from beverages, and 20-30% comes from food (1). Thus, total daily beverage intake (including drinking water) should amount to 3.0 L/day for males and 2.2 L/day for females over 50 years of age (2). Data obtained from national health surveys on patterns of daily beverage consumption in the United States show that older adults are not meeting these recommendations. Trends for total beverage intake by age indicate a sharp decrease for adults over 60 years of age (11). Researchers suggest that the very low intake of only 2.1 L/day in this age bracket may be a potential health concern (11). Rates of plain water consumption also decrease with age. Data obtained from the National Health and Nutrition Examination Survey (NHANES) 2005-2008 show that adults aged 40-59 years drink about 1.1 L of plain water per day. Persons over 60 drink even less plain water,

averaging only 0.73 L/day and 0.83 L/day for males and females, respectively (12). These data show that the older adult population is clearly not drinking enough water.

Inadequate water consumption can lead to disruptions in hydration status, placing older individuals at risk for numerous health complications. Dehydration may result in impaired cognitive function and motor control, increased resting heart rate, increased risk of infection (i.e. urinary tract infections), kidney and gall stone formation, higher incidence of colon and bladder cancer, heart arrhythmias, blood clots, and mitral valve prolapse (2). Furthermore, both women and men who experienced mild dehydration (a loss of only 1.39% and 1.59% of body mass, respectively) demonstrated cognitive impairment and mood changes (13, 14). Regrettably, research has found that as many as 40% of older adults are dehydrated as evidenced by having hypertonic plasma (15). This hypertonicity is also associated with aging, decreased glucose tolerance, diabetes, and obesity (15, 16). For individuals who have diabetes, dehydration worsens diabetes control (2). Furthermore, adults with normal baseline fasting glucose who participated in a 9-year follow up study experienced an inverse association between water intake and the development of hyperglycemia (17). Odds ratios were calculated to determine the relationship between volume of self-reported daily water consumption (categorized as <0.5 L, 0.5 to <1.0 L, and >1.0 L) and onset of hyperglycemia. The results (odds ratios of 1.00, 0.64, and 0.73 respectively) indicated that subjects who consumed the least water had the highest occurrence of hyperglycemia (17). While future studies are warranted to determine whether increased water intake may be protective against development of hyperglycemia, these results demonstrate positive benefits of water consumption on blood glucose regulation.

The combination of blunted thirst, inadequate fluid intake, and impaired glucose homeostasis in older adults places these individuals at risk for numerous health complications. Thus, increasing water consumption to maintain hydration is critical for preventing illness induced by fluid deficits, as well as preventing impairments in blood glucose control.

CHAPTER 2: Is Increased Water Consumption Among Older Adults Associated with Improvements in Glycemia?

I. Introduction

It is known that increasing water consumption (17, 18), or reducing body weight (19-22), will lead to improvements in glucose tolerance in older adults. Additional research has shown that drinking more water may optimize weight loss in this population (23-26), as well. If it is found that older adults who lose weight while increasing water consumption experience greater improvements in glycemia than that observed with weight loss alone, this may be a method for reducing diabetes risk factors in this population (Figure 1). Additionally, the negative consequences of dehydration including impaired cognitive function and motor control, increased resting heart rate, infections, and kidney and gall stone formation (2) may be avoided in older adults through increased water consumption.

If weight loss coupled with improved hydration status leads to improvements in fasting glucose concentration and insulin resistance in older adults, this dietary strategy could be recommended by dietitians counseling individuals at risk for diabetes. Current clinical practice guidelines do not place emphasis on increasing water consumption in older adults; therefore, the results of this investigation may have important clinical implications for health care providers. Elucidating a simple method for improving glycemia in this population could positively benefit the elderly patient by potentially limiting chronic illnesses resulting in a healthier and more rewarding life free from diabetes complications. Additionally, if clinicians are required to emphasize the importance of water consumption (as well as a healthy lifestyle) for all age groups, this preventative approach may lessen the high rates of diabetes seen later in life. Therefore, the purpose of this study is to determine if glycemia is improved with increased water consumption beyond that observed with weight loss among older adults.

II. Review of Literature

<u>The Effects of Weight Loss and Water Consumption on Glucose Control in Older Adults</u>

It is well established that decreased glucose tolerance and insulin resistance are often present in obese individuals and may develop with aging (19). The changes in body composition, namely increased body weight, fat mass, and fat distribution (abdominal and visceral adiposity) that occur with aging are associated with hyperinsulinemia (which is tethered to insulin resistance) and elevated plasma glucose (19, 27). Impaired fasting glucose (IFG) and impaired

glucose tolerance (IGT) are states of abnormal glucose regulation that fall between the conditions of normal glucose homeostasis and diabetes (28). An elevated fasting plasma glucose (FPG) reading between 100-126 mg/dl indicates IFG, and a reading between 140-200 mg/dl following a 75 g glucose load on the oral glucose tolerance test (OGTT) indicates IGT (28). Both IFG and IGT are indicators of abnormal glucose regulation; individuals with impaired glycemia in addition to hyperinsulinemia and/or insulin resistance often develop diabetes and other associated metabolic disorders (27, 28).

Individuals with obesity, impaired glucose tolerance, or type 2 diabetes mellitus experience increases in insulin sensitivity and improvements in glucose tolerance with weight loss (19). Two long-term randomized clinical trials (the Diabetes Prevention Program and Look AHEAD) present strong evidence for the positive impact of lifestyle interventions aimed at weight loss on development of diabetes (29). Participants enrolled in the Diabetes Prevention Program (DPP) (n=3234) were overweight adults (mean BMI=34.0 kg/m^2, mean age=51 years) at an elevated risk for the development of type 2 diabetes (FPG: 95-125 mg/dl; IGT after OGTT: 140-199 mg/dl) (22). Goals for participants assigned to the intensive lifestyle intervention group included a 7% loss and maintenance of body weight via healthy diet and 150 min/week of moderate intensity physical activity. The incidence of diabetes was 58% lower in the intensive lifestyle intervention group than in the placebo group, and FPG concentration was significantly lower for participants in the lifestyle-intervention group at the end of the follow-up period (22). The results of this large trial show that lifestyle modification (resulting in weight loss) is a highly effective means for delaying or preventing type 2 diabetes in the susceptible older adult population.

In addition, middle-aged and older obese men who lost an average of 19% of their body fat mass experienced a decrease in the prevalence of IGT from 57% of subjects to 40%. Fasting insulin levels decreased by 20% (90 to 72 pmol/L) with weight loss in these individuals (20). Other studies show that the incidence of diabetes can be reduced through lifestyle interventions, namely improved diet and increased physical activity that lead to reductions in body weight (21). Middle-aged overweight subjects (n=522, mean age=55 years, mean BMI=31 kg/m^2) with impaired glucose homeostasis who received personalized dietary and physical activity counseling lost significantly more weight than the control group (3.5 ± 5 vs. 0.8 ± 4.4 kg) and

experienced significant improvements in glucose tolerance (FPG: -0.1 ±0.7 vs. +0.2±0.8 mmol/L, $P<0.001$; 2 hours after OGTT: -0.8±2.1 vs. +0±2.5 mmol/L, $P<0.001$) at the end of the 2-year intervention (21). Participants in the intervention group also experienced significantly greater reductions in serum insulin concentration following the 2-hr OGTT (21).

We have previously mentioned the inverse association found among water consumption and development of hyperglycemia (17). Most solutes found within plasma are dissociated sodium salts, but ions (like potassium and calcium), urea, and glucose also contribute to plasma osmolality. In conditions of dehydration, total body water decreases below normal levels without a reduction in solutes, which most notably leads to hypernatremia, but may also raise plasma glucose (30). Therefore, decreased glucose tolerance may be related to increased solute concentration resulting from dehydration, and increasing water consumption may have preventative effects on elevations in plasma glucose. Furthermore, selecting water over caloric beverages may be a tool for improving both hydration and glycemia. Non-diabetic overweight and obese adults who participated in the 6 month CHOICE weight loss trial used noncaloric beverage substitution alone as a primary weight loss strategy (18). Compared to the attention control (AC) group, participants who replaced caloric beverages with water (WA) significantly improved fasting glucose (WA: -3.21 vs. AC: 0.59 mg/dl) and hydration (urine osmolality WA: -93.83 vs. AC: 32.76 mOsmol/kg) despite similar or smaller weight loss in the water group (mean % weight loss: 2.03% vs. 1.76%) (18). The results of this weight loss intervention indicate that drinking more water (as opposed to calorie-containing beverages) may contribute to improved hydration and fasting glucose in the overweight older adult population, even without modest weight loss. Although fasting glucose was a parameter measured in this study, blood glucose regulation was not specifically targeted by the beverage replacement weight loss intervention. Most current research concerning improved glucose tolerance focuses on the positive effects of weight loss, and not water consumption exclusively, on blood glucose control.

Water Consumption May Enhance Weight Loss

We have explained that 1) proper hydration is important for many health outcomes including blood glucose regulation and 2) body weight loss can improve glucose tolerance. Recent studies have demonstrated an additional benefit of increased water consumption: the ability to enhance weight loss in older adults.

A secondary analysis of the Stanford A to Z clinical weight loss trial (in which overweight pre-menopausal women were assigned to four popular weight loss diets) focused on those subjects who consumed less than 1 liter of drinking water per day at baseline. This subset of individuals (n=173) had significantly greater weight loss once water intake increased to >1 L/day compared to those with continual intake of <1 L/day (24). Potential mechanisms for the ability of water to promote weight loss include an increase in energy expenditure and/or rates of lipolysis, due to the thermogenic effect from warming the water to body temperature (24, 26). Researchers have found that drinking 500 ml of water increases metabolic rate by 30% in healthy, normal weight adults (mean age=28 years) when the ingested water is warmed from 22 to 37^{o}C (26). Furthermore, an increase in lipid metabolism was found among the male participants (respiratory quotient changed from 0.841 to 0.79) (26). It is estimated that increasing water consumption by 1.5 L/day would result in an additional energy expenditure of about 48 kcal (26), allowing for augmented weight loss for those drinking more water.

Additional studies have targeted increased water consumption as an effective weight-control strategy in overweight and obese older adults due to a reduction in meal energy intake. Individuals (n=24, mean BMI=34.3$\pm$1.2 kg/m^2, age=55-75 years) who consumed a 500 ml water preload prior to meal consumption had a significantly lower meal energy intake (EI) compared with a control condition in which no pre-meal water was consumed (74$\pm$23 kcal difference between the two conditions) (23). This approximate 13% reduction in EI following a water preload may be due to delayed gastric emptying resulting in sensations of fullness and reduced hunger in the older adult population (23).

A follow-up investigation of the aforementioned water preload study sought to determine if premeal water consumption would facilitate weight loss in overweight/obese older adults (BMI=25-40 kg/m^2, age=55-75 years), and if a resulting reduced meal EI was sustained after 12 weeks (25). At the end of the 12-week weight-loss intervention, participants assigned to the water preload condition (hypocaloric diet + 500 ml H_2O before each of 3 daily meals) showed a 44% greater rate of weight loss than did those in the non-water group (hypocaloric diet only) (25). This approximate 2 kg greater weight loss in the water group may be attributed to delayed gastric emptying seen with advancing age and increased sensations of fullness that lead to

reduced meal EI. However, the exact mechanisms by which the reduced energy intake occurs, as well as the long-term effects of this intervention strategy, are still being investigated.

These findings suggest that including increased water consumption as part of a weight loss regimen for overweight older adults may lead to greater reductions in body weight, thus resulting in even better improvements in glycemia and insulin sensitivity than with weight loss alone (Figure 1). Augmenting weight loss with increased water consumption may have the potential to reduce the incidence of and progression to type 2 diabetes for overweight adults with diminished glucose control. To our knowledge, there are no studies to date that have directly addressed the possibility that increasing water intake in combination with weight loss in the overweight older adult population will lead to considerable improvements in fasting glucose and reductions in diabetes risk factors, or the exact mechanisms behind this additive effect. Available research has suggested beneficial effects on glucose tolerance, but has not directly targeted diabetes risk factors, such as IFG, IGT, and insulin resistance.

III. Materials and Methods

This retrospective analysis utilized data collected at Virginia Tech (25). The purpose of the original study was to determine if premeal water consumption of 500 ml would facilitate weight loss in a population of obese and overweight older adults over 12 weeks. Additionally, the study sought to determine if the reduction of meal energy intake observed with premeal water consumption would be sustained after a 12-week period. Participants who were eligible for the study were overweight or obese (BMI=25-40 kg/m^2), between the ages of 55-75 years, weight stable ($\pm$2 kg, >1 year), and non-smokers. Assessments included height, measured in meters without shoes using a wall mounted stadiometer; weight, measured in light clothing and no shoes to the nearest 0.1 kg on a digital scale (Scale-Tronix model 5002, Wheaton, IL); urine, collected over 24 hours for assessment of total volume, and specific gravity using a refractometer (Fisher UriSystem; Fisher Scientific, Hampton, NH). Although not reported in the original published article, venous blood drawn in a fasted state was used to determine fasting plasma glucose and insulin concentration. Plasma glucose concentration was measured using a YSI glucose analyzer (model 2300, Yellow Springs Instruments) and plasma insulin concentration was quantified using a commercially available ELISA (Linco Research, Inc.). Insulin resistance (previously unreported) was estimated using homeostasis model assessment (HOMA) and an insulin

resistance score (HOMA-IR) was computed with the following formula: fasting plasma glucose (mmol/L) times fasting serum insulin (mU/L) divided by 22.5 (31). High HOMA-IR values indicate low insulin sensitivity (insulin resistance), and low HOMA-IR values indicate high sensitivity to insulin (31). Following completion of baseline assessments, participants were randomly assigned to one of two diet groups for 12 weeks: (i) hypocaloric diet + 500 ml water prior to each daily meal (water group), or (ii) hypocaloric diet alone (non-water group). Participants' body weight was measured weekly in the laboratory, and daily premeal water consumption logs were submitted by the water group at this time to monitor compliance. For the present investigation, plasma copeptin was assessed at baseline and at week 12 of the weight loss intervention, using an enzyme immunoassay (EIA) kit from Phoenix Pharmaceuticals (Cat #EK-065-32).

Statistical Analysis

Statistical analyses were performed using SPSS statistical analysis software (versions 12.0 and 20.0 for Windows, 2003, 2011 SPSS, Inc., Chicago, IL). Independent sample t-tests were used to assess group differences at baseline, as well as differences in intervention outcomes including BMI, body weight, drinking water consumed, urinary specific gravity (USG), fasting glucose, fasting insulin, HOMA-IR, and plasma copeptin. One-sample t-tests revealed pre-to-post change values within groups. Pearson correlation coefficients (r) measured the strength of association between variables at both baseline and 12 weeks, as well as correlations between changes in variables over the course of the intervention.

All study subjects (n=29) were classified into three water consumption categories (i) <500 g/day, (ii) 500-1,000 g/day, and (iii) >1,000 g/day to determine if any differences were detected depending upon amount of drinking water consumed. One-way Analysis of Variance examined differences in water consumption categories at 12 weeks and corresponding changes in weight loss, BMI, body fat, fasting glucose, fasting insulin, HOMA-IR, and plasma copeptin. One-sample t-tests revealed pre-to-post changes for these variables within the water categories.

Finally, subjects were paired according to both gender and total kilograms of weight lost to eliminate these variables as potential confounding factors. Six subjects from the water group (4 females, 2 males) were matched to subjects in the non-water group who were of the same

gender and had lost a similar amount of weight ($\leq$0.6 kg difference between paired subjects). Subjects selected for pair-matching lost between 1.8 and 8.4 kg of total body weight. Paired samples t-tests were performed to determine paired differences for fasting glucose, insulin, HOMA-IR, and copeptin.

IV. Results

A total of 48 individuals completed the original study. Of these, 29 had glucose, insulin, and HOMA-IR data available, and only these participants were included in the present investigation. This subset consisted of overweight adults (BMI=31$\pm$1 kg/m^2, age=62$\pm$1 years) with 13 individuals assigned to the water and hypocaloric diet group and 16 assigned to the hypocaloric diet group.

There were no baseline differences between groups with respect to age, BMI, body weight, drinking water consumed, USG, fasting glucose, fasting insulin, HOMA-IR, or plasma copeptin. Water group participants significantly reduced BMI, body weight, USG, and fasting insulin with a significant increase in water consumption at the end of the intervention period (all P<0.05). Non-water group subjects significantly reduced BMI, body weight, and plasma copeptin at the conclusion of the intervention (all P<0.05). No group differences were noted in pre-to-post changes in BMI, body weight, USG, fasting glucose, fasting insulin, HOMA-IR score, or plasma copeptin (Table 1).

Several notable correlations between variables were detected. At baseline, body weight correlated with drinking water consumed (r=-0.512, P<0.01); plasma copeptin correlated with USG (r=0.424) and total grams of beverages consumed (r=-0.403) (P<0.05); fasting insulin correlated with body weight (r=0.628, P<0.01) and grams of drinking water consumed (r=-0.378, P<0.05); and HOMA-IR score correlated with body weight (r=0.658, P<0.01), USG (r=0.394, P<0.05), and drinking water consumed (r=-0.373, P<0.05). At week-12, plasma insulin correlated with body weight (r=0.542, P<0.01), USG (r=0.512, P<0.01), and copeptin (r=0.389, P<0.05); and HOMA-IR score correlated with USG (r=0.530, P<0.01). Interestingly, change in BMI correlated with change in USG (r=0.443, P=0.021) at the conclusion of the intervention.

Categorization of subjects into three water-consuming categories did not reveal significant differences between groups with regard to changes in weight, BMI, kilograms of total body fat, fasting glucose, fasting insulin, HOMA-IR, or plasma copeptin. In a secondary

analysis, subjects in the lowest water consuming category (<500 g/day) were compared to the highest category (>1,000 g/day) to analyze differences in the same variables. No significant differences were detected despite seemingly large differences in the means for fasting insulin (-0.3±5 vs. -9.2±3 pmol/L, P=0.142) (Table 2). Notably, participants in the highest drinking water category (>1,000 g/day), significantly reduced body weight, BMI, body fat, fasting insulin, and HOMA-IR score from baseline to 12-weeks (all P<0.05). Participants in the lowest drinking water category (<500 g/day) also experienced significant reductions in body weight, BMI, and total body fat at the conclusion of the intervention (all P<0.05).

Furthermore, no paired differences were detected for fasting glucose, plasma insulin, HOMA-IR, or plasma copeptin at the conclusion of the intervention. The ranges and means for these variables among the participants pair-matched for gender and kilograms of weight lost are displayed in Table 3.

V. Discussion

Despite a wealth of literature supporting the positive impact of increased water consumption and weight loss on diabetes risk in older adults, our analyses did not clearly demonstrate these benefits. The small sample size (n=29) likely contributed to the lack of significant differences between water and non-water participants with regard to weight loss, glucose, insulin, HOMA-IR, and copeptin.

Although pre-to-post changes in diabetes risk factors were not significantly different between groups, important within-group changes were detected. All subjects successfully reduced BMI and body weight at the conclusion of the hypocaloric diet intervention, regardless of intervention group. However, those assigned to the water group also experienced improvements in hydration status (demonstrated by decreased USG) and reductions in plasma insulin concentration. Furthermore, several notable correlations between variables were detected. At baseline, the amount of drinking water consumed correlated negatively with body weight and fasting insulin, supporting the findings of previous research regarding the benefits of water consumption. At the conclusion of the intervention, plasma insulin had a positive correlation with copeptin and USG, and insulin resistance (HOMA-IR) increased as USG increased. Furthermore, change in BMI correlated positively with change in USG, suggesting a possible association between body composition and hydration status. These results support previous

research findings of positive correlations of plasma copeptin with components of metabolic syndrome (which included fasting insulin levels and HOMA-IR). Positive correlations among USG and insulin resistance, as well as positive change correlations among USG and BMI, may further demonstrate associations between hydration status and diabetes risk.

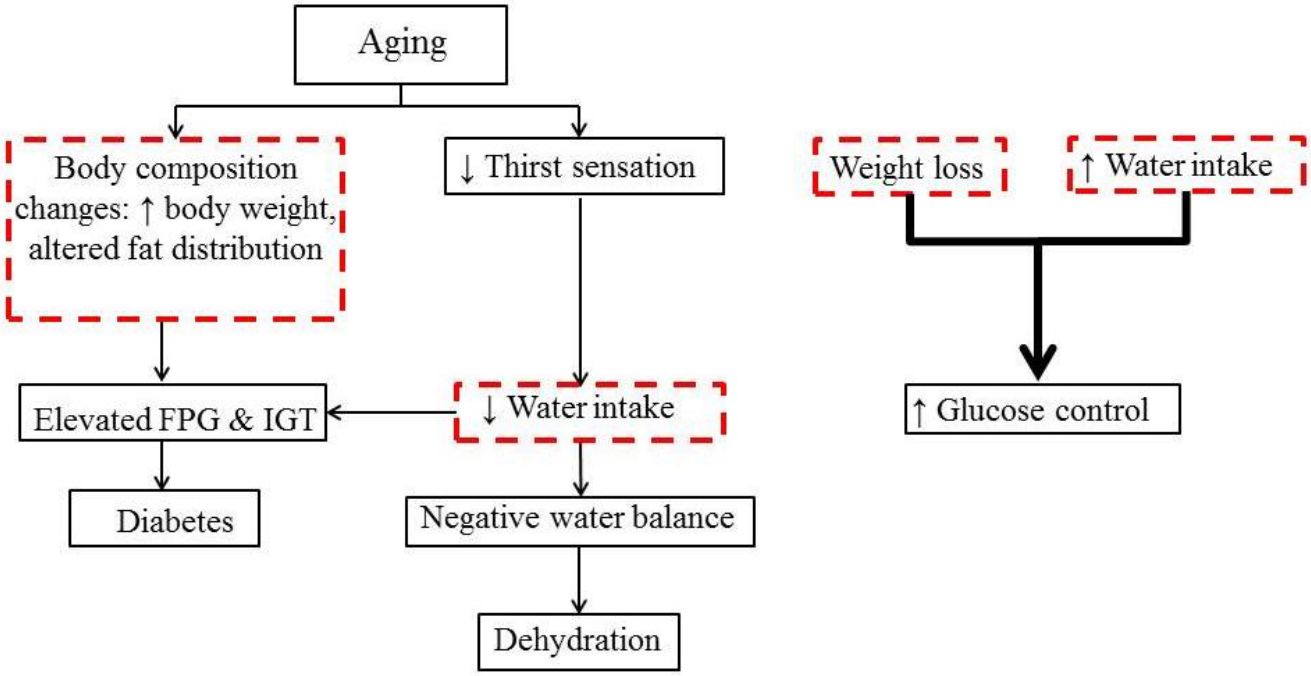
According to current available literature, plasma copeptin concentrations in healthy adults range from 0.44-44.3 pmol/L with a median value of 3.8 pmol/L (32). Additionally, men tend to have higher plasma copeptin levels than women (6, 33, 34). For the entire sample included in our investigation, plasma copeptin values ranged from 0.28-4.57 pmol/L with a median value of 0.69 pmol/L. No gender differences were detected among the entire sample for plasma copeptin at baseline, week 12, or pre-to-post changes, which led to our pair-match based upon both weight loss and gender. Limitations exist with regard to our copeptin analysis. Copeptin is greatly influenced by recent water consumption and fasting and therefore may not reflect chronic hydration status. Furthermore, copeptin may be influenced by dietary habits. Higher sodium intake may prompt AVP secretion, subsequently elevating plasma copeptin levels (9, 35). Because copeptin analysis was not a component of the original investigation, participants were not given specific instructions for fluid or sodium consumption prior to the overnight fast before blood was drawn, potentially impacting our results. The clinical significance of plasma copeptin as a diagnostic tool is still under investigation, and further research into its relevance is warranted.

While analysis of diabetes risk factors according to levels of drinking water consumption did not reveal significant differences between groups, those subjects who drank the most water (>1,000 g/day) experienced reductions in body weight, BMI, body fat, insulin, and HOMA-IR, indicating that increasing water consumption does have positive benefits for this population.

While the small sample size likely limited the statistical power to detect differences in diabetes risk factors between groups, this preliminary study may be used to determine sample sizes needed for future investigations. Using findings of this investigation (group mean differences, standard deviations), it is estimated that future investigations would require a sample size of at least 104 participants (52/group) in order to detect significant group differences in weight loss, insulin, and HOMA-IR scores given the small-medium average effect size of 0.28 for these factors.

The increasing prevalence of overweight, obesity, and type 2 diabetes in older adults is a public health concern. Successful approaches to loss and maintenance of body weight are essential for lowering risk factors for diabetes. Although results of this investigation did not clearly support the hypothesis, future studies are warranted to determine if health messages and clinical practice should be altered to include recommendations on increasing water consumption in conjunction with weight loss for the older adult population.

Figure 1. Associations between aging, water consumption, and diabetes risk; and areas to target for intervention.



Aging is associated with changes in body composition that lead to impairments in glycemia that place older individuals at an increased risk for type 2 diabetes. A diminished sense of thirst and reduced water intake in older adults also lead to impairments in glucose regulation. Weight loss and increased water intake are two intervention strategies that improve glucose tolerance and reduce diabetes risk factors. Using these two methods in combination may lead to even greater improvements in glycemia.

Table 1. Results: Summary table of participant characteristics and variables associated with weight loss, water consumption, and diabetes risk (n=29).*

Variables	Water Group (n=13)			Non-water Group (n=16)		
	Baseline	**Week12**	**Change**	**Baseline**	**Week12**	**Change**
Age, years	62±1	-----	-----	62±1	-----	-----
BMI, kg/m^{2a}	31.3±1	28.9±1	-2.4±0.4	29.9±1	28.4±1	-1.4±0.3
Weight, kg[a]	89.7±4	82.8±4	-7.0±1	86.1±4	81.9±4	-4.2±1
Drinking Water Consumed, g[b]	359±87	1307±154	949±171[a]	501±142	361±110	-140±145
Urinary Specific Gravity, UG	1±.001	1±.002	-.003±.001[a]	1±.001	1±.002	-.0002±.001
Fasting Glucose, mg/dl	87.8±4	86.2±4	-1.5±3	88.7±4	87.2±4	-1.5±2
Fasting Insulin, pmol/L	39.0±4	30.5±4	-8.5±4[a]	35.2±5	34.6±6	-0.6±3
HOMA-IR Score	1.2±0.1	0.9±0.1	-0.3±0.1	1.1±0.1	1.1±0.2	-0.01±0.1
Plasma Copeptin, ng/ml	3.7±0.5	3.9±1	0.2±0.8	4.5±1	3.5±0.9	-1±0.4[a]

*Presented as mean ± SEM, for continuous variables.
[a]Significant differences detected from baseline to week 12 within groups (P<0.05).
[b]Significant differences detected from baseline to week 12 between groups (P<0.05).

Table 2. Results: Group differences according to two drinking water categories at week 12 of the intervention (n=25).*

Variables	Drinking Water Categories at Week 12	
	<500 g/day (n=13)	**>1,000 g/day (n=12)**
Weight Lost, kg	-4.7±1	-7.3±1
Change BMI, kg/m^2	-1.6±0.4	-2.6±0.5
Change Body Fat, kg	-3.5±0.8	-4.6±0.9
Change Fasting Glucose, mg/dl	-1.7±3	-2.9±2
Change Fasting Insulin, pmol/L	-0.3±5	-9.2±3
Change HOMA-IR Score	-0.01±0.2	-0.3±0.1
Change Plasma Copeptin, ng/ml	-0.5±0.8	-0.2±0.5

*Presented as mean ± SEM, for continuous variables. No significant differences were detected.

Table 3. Results: Ranges and means for variables related to diabetes risk among participants pair-matched for gender and kilograms of weight lost (n=12)*.

	Intervention Group	Minimum	Maximum	Mean ±SEM
FPG, mg/dl	Water	54.3	100.9	83.9±7
	Non-water	68.6	95.9	85.7±4
Insulin, pmol/L	Water	15.7	48.6	29.2±6
	Non-water	9.6	79.3	28.2±10
HOMA-IR	Water	0.42	1.3	0.84±0.1
	Non-water	0.28	2.6	0.88±0.3
Copeptin, ng/ml	Water	1.4	9.7	3.8±1
	Non-water	2.5	15.8	5.3±2

*No significant differences were detected.

CHAPTER 3: Conclusions and Implications for Future Research

The prevalence of diabetes for Americans over 65 years is a staggering 26.9%, and 50% of this age group is considered prediabetic (having IFG, IGT, and/or hemoglobin A1c 5.7% to 6.4%) (36, 37). Diabetes and prediabetes are major risk factors for cardiovascular and kidney diseases, thus intervention strategies aimed at reducing diabetes risk factors in this population are critical. Weight loss and increasing water consumption are two effective methods for improving glucose tolerance and insulin resistance (17-22). The purpose of this study was to determine the effects of weight loss in combination with increased water consumption on diabetes risk factors in older adults. The water group significantly reduced their body weight, BMI, and fasting insulin over the course of the 12-week intervention, while those in the non-water group did not experience reductions in insulin. These findings indicate that weight loss in combination with increased water consumption can have a beneficial impact on elevated insulin production. However, the differences between groups with regard to diabetes risk factors (fasting glucose, insulin, and HOMA-IR) were not significant. Investigations with larger sample sizes may detect these differences.

Additional research is needed to address the possible role of the AVP system in glucose homeostasis, insulin resistance, and diabetes mellitus. Standardization of hydration status and dietary sodium intake at the time of copeptin measurement may be a necessary component of future research designs. Participants in this investigation were not standardized with regard to hydration or sodium intake, and copeptin analysis was not an aim of the original study, potentially resulting in limitations for our analyses.

Despite a lack of statistical support for our hypothesis, future research should be conducted to further explore this association between drinking water and improved glycemia. Increasing water consumption, or replacement of caloric beverages with water are simple and cost-effective strategies for body weight loss and maintenance. The addition of drinking water recommendations to common healthcare practice may result in improved health outcomes with relation to hydration, as well as diabetes risk for older adults. In conclusion, this type of intervention may represent a feasible and potentially effective approach for reducing the prevalence and progression to diabetes for at risk older adults.

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