Low Water Intake and Risk for New-Onset Hyperglycemia

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OBJECTIVE—Water intake alters vasopressin secretion. Recent findings reveal an independent association between plasma copeptin, a surrogate for vasopressin, and risk of diabetes.

RESEARCH DESIGN AND METHODS—Participants were 3,615 middle-aged men and women, with normal baseline fasting glycemia (FG), who were recruited in a 9-year follow-up study. Odds ratios (ORs) and 95% CIs for the incidence of hyperglycemia (FG ≥6.1 mmol/L or treatment for diabetes) were calculated according to daily water intake classes based on a self-administered questionnaire.

RESULTS—During follow-up, there were 565 incident cases of hyperglycemia. After adjustment for confounding factors, ORs (95% CIs) for hyperglycemia associated with classes of water intake (<0.5 L, *n* = 677; 0.5 to <1.0 L, *n* = 1,754; and >1.0 L, *n* = 1,184) were 1.00, 0.68 (0.52–0.89), and 0.79 (0.59–1.05), respectively ($P = 0.016$).

CONCLUSIONS—Self-reported water intake was inversely and independently associated with the risk of developing hyperglycemia.

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Copeptin, a stable glycopeptide comprising the COOH-terminal portion of the preprovasopressin, released in equimolar amounts as vasopressin, recently has been shown to represent an independent risk factor for diabetes (1). A causal link between vasopressin and glucose homeostasis is plausible because vasopressin induces gluconeogenesis in the rat liver and transiently increases glycemia in healthy humans and because vasopressin receptors are expressed in hepatocytes and pancreatic islets (2–9).

Vasopressin and copeptin secretion is known to depend on the level of hydration (10). Thus, we tested in initially normoglycemic participants of a large French cohort, whether water intake (W-Intake) was associated with the subsequent development of hyperglycemia or diabetes over a 9-year follow-up.

RESEARCH DESIGN AND METHODS

Study population

We included 3,615 French men and women, aged 30–65 years, with baseline fasting glycemia (FG) <6.1 mmol/L, who participated in the 9-year follow-up D.E.S.I.R. study (Data from Epidemiological Study on Insulin Resistance Syndrome). Volunteers were recruited and offered extensive health examinations every 3 years in western France. Participants provided written informed consent, and the protocol was approved by the ethics committee of Bicêtre Hospital, Kremlin-Bicêtre, France.

Incident hyperglycemia was identified by an FG ≥6.1 mmol/L or treatment for diabetes, and incident diabetes was identified by an FG ≥7.0 mmol/L or treatment of diabetes during at least one of the three follow-up examinations (years 3, 6, and 9).

Clinical and biochemical measures

Detailed methods have been reported previously (11–13). Smoking, dietary habits, degree of physical activity, and alcohol consumption were assessed using a self-administered questionnaire. Mean daily intake of water, wine, beer or cider, and sweet beverages was categorized in the questionnaire into six mutually exclusive levels: none, <0.5, 0.5 to 1, 1 to 1.5, 1.5 to 2.0, and >2 L. In the present analyses, the levels were grouped into three classes: <0.5, 0.5 to 1, and >1 L. Other clinical and biological measurements are presented in the Supplementary Methods.

Statistical analyses

Skewed variables were log transformed. Results are presented as means (SD) or median (25th–75th percentiles) for quantitative variables and as percentages for qualitative variables. Baseline means and percentages were compared between the three W-Intake classes using ANOVA or χ^2 tests. Logistic regression models were used to determine odds ratios (ORs) and 95% CIs corresponding to the comparison of incident hyperglycemia in middle and high classes of W-Intake in comparison with the lowest class. Adjustment variables were either known risk factors for type 2 diabetes or factors associated ($P < 0.10$) with hyperglycemia and W-Intake in our population.

RESULTS—Baseline characteristics of the 3,615 normoglycemic participants

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Table 1—*Baseline characteristics of the study population and risk for new-onset hyperglycemia during follow-up, by classes of mean daily W-Intake*

	Daily W-Intake (L)			
	<0.5	0.5 to 1.0	>1.0	*P* for difference
General				
n	677	1,754	1,184	
Men (%)	48.6	47.9	45.4	0.31
Age (years)	46.4 (9.9)	47.3 (10.0)	46.3 (9.9)	**0.001**
BMI(kg/m^2)	24.1 (3.5)	24.4 (3.5)	24.7 (3.8)	**0.001**
Waist circumference (cm)	81.6 (10.7)	82.3 (11.0)	82.7 (11.6)	**0.026**
Physical activity (%)				**0.0001**
Low	28.7	25.7	19.4	
Medium	56.1	54.6	52.6	
High	15.2	19.8	28.0	
Tobacco smoking (%)				**0.0001**
Never smokers	47.7	55.9	57.8	
Ex-smokers	26.3	26.6	24.1	
Current smokers	26.0	17.5	18.2	
Alcohol consumption (g/day) (%)				**0.0001**
Nonconsumers	22.0	23.0	30.7	
1–10	24.7	27.2	31.2	
10–20	8.1	8.4	6.7	
>20	45.2	41.3	31.4	
Creatininemia (μmol/L)	81.2 (13.0)	81.6 (13.0)	81.0 (12.9)	0.39
C-reactive protein*	1.00 (0.85–2.64)	0.87 (0.85–2.00)	0.85 (0.85–2.00)	0.49
Blood pressure				
Systolic (mmHg)	129 (15)	131 (15)	130 (15)	0.32
Diastolic (mmHg)	79 (10)	80 (9)	79 (9)	0.21
Hypertension (%)	32.5	34.3	32.4	0.50
Treated THZD/Furo (%)	3.7	2.2	3.2	0.07
Metabolic data				
Family history diabetes (%)	20.6	19.0	19.3	0.67
Fasting plasma glucose (mmol/L)	5.21 (0.45)	5.22 (0.44)	5.17 (0.44)	0.72
Fasting insulinemia (pmol/L)	42.7 (23.3)	45.0 (24.7)	44.1 (27.6)	0.08
HOMA-IR	1.40 (0.80)	1.48 (0.87)	1.43 (0.96)	0.10
HOMA-B	63 (46–89)	66 (46–92)	65 (47–91)	0.15
Total cholesterol (mmol/L)	5.76 (0.97)	5.72 (0.97)	5.66 (0.98)	**0.007**
Triglycerides (mmol/L)	1.14 (0.85)	1.09 (0.66)	1.09 (0.65)	0.15
HDL cholesterol (mmol/L)**	1.64 (0.41)	1.66 (0.43)	1.64 (0.44)	0.44
LDL cholesterol (mmol/L)**	3.39 (0.83)	3.35 (0.89)	3.32 (0.90)	**0.032**
Other drinks				
Mean volume of sweet drinks (L) (%)				**0.0001**
<0.5	92.0	95.5	97.0	
0.5 to 1.0	6.9	4.3	1.9	
>1.0	1.0	0.2	1.1	
Mean volume of wine/day (L) (%)				**0.0001**
<0.5	89.1	93.9	96.4	
0.5 to 1.0	9.9	6.1	3.6	
>1.0	1.0	0.0	0.1	
Mean volume of beer or cider (L) (%)				0.056
<0.5	96.9	98.1	98.7	
0.5 to 1.0	2.7	1.8	1.1	
Urine				
Urine density (× 1,000)	1,019.6 (8.0)	1,019.3 (9.1)	1,017.9 (9.6)	**0.0001**
ORs for new-onset hyperglycemia				
Model 1	1.00 (reference)	0.64 (0.49–0.83)	0.73 (0.55–0.97)	**0.003**
Model 2	1.00 (reference)	0.68 (0.52–0.89)	0.79 (0.59–1.05)	**0.016**

Data are means (SD) or medians (25th–75th percentiles) for continuous variables and percentages of patients for categorical variables. THZD, thiazidic diuretics; Furo, furosemide; HOMA-IR, homeostatic model assessment index of insulin resistance; HOMA-B, homeostatic model assessment index of insulin secretion. Hypertension was defined as systolic or diastolic blood pressure >140 or 90, respectively, or treated with antihypertensive drugs. ORs (95% CIs) for the association between daily W-Intake at baseline and the risk of incident hyperglycemia (fasting plasma glucose ≥6.1 mmol/L or treatment for diabetes) are presented according to two statistical models; variables for adjustment were either known risk factors for type 2 diabetes or factors associated ($P < 0.10$) with hyperglycemia and W-Intake in our population. Model 1: Adjusted for age, sex, BMI, baseline FG, physical activity, smoking status, triglycerides, HOMA-IR, and total cholesterol. Model 2: Further adjusted on self-reported intake of other fluids (i.e., volumes of beer or cider, sweet drinks, and wine consumed per day). Significant *P* values (<0.05) are in boldface. *The C-reactive protein was available for only 181, 466, and 333 subjects in the three classes of W-Intake, respectively. **HDL cholesterol and LDL cholesterol were not available for 28 and 26 subjects, respectively.

are presented according to their class of W-Intake (Table 1). Among them, during follow-up, 565 subjects became hyperglycemic and 202 developed diabetes. The daily W-Intake was negatively associated with the risk of new-onset hyperglycemia, even after adjustment for multiple metabolic risk factors. Compared with daily W-Intake of <0.5 L, ORs were 0.64 (95% CI 0.49–0.83) and 0.73 (0.55–0.97) for classes of 0.5–1.0 L and >1.0 L, respectively ($P = 0.003$). After further adjustments for intake of other beverages, the ORs were slightly attenuated: 0.68 (0.52–0.89) and 0.79 (0.59–1.05) for classes of 0.5–1.0 L and >1.0 L, respectively ($P = 0.016$) (Table 1). The relation was not linear (data not shown). With the two upper classes combined, the OR was 0.72 (0.56–0.92) (Supplementary Fig. 1). There was no interaction with several important characteristics, including those related to self-reported alcohol or tobacco consumption (Supplementary Table 1).

The same trend, although nonsignificant, was observed for the association with new-onset diabetes: compared with participants with a daily W-Intake <0.5 L, ORs for those drinking 0.5–1.0 L and >1.0 L water per day were 0.68 (95% CI 0.41–1.15) and 0.75 (0.43–1.32), respectively, $P = 0.36$.

CONCLUSIONS—Risk for hyperglycemia was negatively and independently related with self-reported W-Intake in normoglycemic middle-aged individuals from the French general population. This observational study does not establish causality. However, the association was moderately attenuated when important metabolic risk factors and potential confounders were introduced as covariables in the analysis, including intake of other classes of beverages with known adverse long-term effects (sweet and alcohol-containing drinks). Our data support the novel idea that vasopressin, besides its role in urine concentration, is also an important actor in glucose homeostasis (1).

The negative association of W-Intake and risk for hyperglycemia was relevant among many subsets of participants, and those reporting a low W-Intake (<0.5 L) had a higher risk for hyperglycemia (for example, participants in the high physical activity group) (Supplementary Table 1). This indicates that identification of individuals with a W-Intake of <0.5 L may be widely relevant to target preventive interventions regarding the metabolic risk.

Our study has several limitations. Diabetes incidence was low and statistical power was thus limited; 24-h urine volume was not measured, but the urinary density was inversely associated with self-reported W-Intake, arguing for the validity of the questionnaire (Table 1). In addition, we cannot exclude residual confounding: healthier behaviors correlating with higher water drinking could account for the observed association. Finally, only volunteers were included and the results may not be extrapolated to the general population.

Knowing the rise of vasopressin in diabetes, its effect on glycemia, gluconeogenesis, and glucagon release, it is surprising that no attention had been given to vasopressin as a possible risk factor for hyperglycemia and diabetes until a recent report of an association between copeptin and the incidence of diabetes (1,4,5,14). Our study extends this observation, drawing attention to a low W-Intake as a possible new risk factor for impaired glycemia. It suggests that an increase in W-Intake, an easy and costless intervention, could prevent or delay the onset of hyperglycemia and subsequent diabetes. Hopefully, our study will serve as a benchmark to design appropriate clinical trials testing the efficacy of this intervention in people who report drinking <0.5 L of water per day, as did almost 20% of the participants in this cohort.

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R.R., L.F., and L.B. researched data, contributed to discussion, and wrote, reviewed, and edited the manuscript. N.B. and F.A.-G. contributed to discussion and reviewed and edited the manuscript. B.B., O.L., and M.M. researched data, contributed to discussion, and reviewed and edited the manuscript.

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