ATTENUATION OF VASOPRESSIN-INDUCED ANTIDIURESIS IN POORLY-CONTROLLED TYPE 2 DIABETES

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Abstract

Renal resistance to vasopressin has been demonstrated in type 1 diabetes, and in type 2 diabetes with nephropathy. However, renal response to vasopressin in type 2 diabetes without nephropathy, has not been studied.

We studied 10 subjects with poorly controlled type 2 diabetes (PCDS, HbA1c > 9 %), 10 subjects with well-controlled type 2 diabetes (WCDS, HbA1c < 7 %), and 10 matched non-diabetic control subjects (NDCS), during a euglycaemic 8-hour water deprivation test. None of the subjects had nephropathy or arterial hypertension.

Analysis of variance model (ANOVA) showed that water deprivation caused similar rises in plasma vasopressin concentrations in all three groups, but the rise in urine osmolality in PCDS (280.3 ± 49.7 to 594.4 ± 88.5 mOsm/kg) was lower than in WCDS (360.7 ± 142.8 to 794.1 ± 77.3 mOsm/kg, between groups p < 0.001), or NDCS (336.0 ± 123.3 to 786.5 ± 63.3 mOsm/kg, between groups p = 0.019). Total urine output was higher in the PCDS (794 ± 161 mls) than in WCDS (589 ± 138 mls, between groups p = 0.014), and NDCS (507 ± 224 mls, between groups p = 0.004). Linear regression analysis showed that in PCDS, the osmotic threshold for thirst (291.9 ± 4.6 mOsm/kg) and vasopressin release (291.1 ± 2.9 mOsm/kg) were higher compared to WCDS (286.6 ± 1.8 and 286 ± 3.6 mOsm/kg, respectively), and to NDCS (286.0 ± 2.4 and 284.1 ± 4.7 mOsm/kg, respectively); between groups p < 0.001 for both variables.
Under conditions of euglycaemia, PCDS have impaired renal response to vasopressin, and elevated osmotic threshold for thirst and vasopressin release in response to dehydration. Under conditions of chronic hyperglycaemia, these abnormalities may have significant contribution to the development of dehydration in PCDS.

**Abbreviations:** AVP, arginine vasopressin; PCDS, poorly-controlled diabetic subjects; WCDS, well-controlled diabetic subjects; NDCS, non-diabetic control subjects.

**Key words:** vasopressin, type-2 diabetes, osmoregulation
INTRODUCTION

The commonest clinical manifestations of poorly controlled diabetes mellitus are polyuria, leading to polydipsia. Although the polyuria in poorly controlled diabetes is traditionally attributed to an osmotic diuresis secondary to glycosuria, the underlying pathophysiology is complex (1). Renal resistance to the antidiuretic action of arginine vasopressin (vasopressin, AVP), with failure to recruit aquaporin-2, has been shown to be associated with impaired urine concentrating ability in type 1 diabetes without nephropathy (4), and type 2 diabetes with nephropathy (6). Marked elevation in plasma vasopressin concentration have been reported in diabetic ketoacidosis (15), acute insulin withdrawal (5), and non-ketotic hyperglycaemia (16), indicating that vasopressin does not exert an antidiuretic effect, under conditions of severe glycosuric diuresis. When patients with type 1 diabetes are infused with hypertonic sodium chloride solution, to elevate plasma osmolality, they exhibit similar elevation in plasma vasopressin to controls, but do not respond with similar increases in urine osmolality (11, 12). These results suggest that in type 1 diabetes, there is renal resistance to vasopressin. This hypothesis was tested in studies where vasopressin was infused intravenously into patients with type 1 diabetes, who failed to concentrate urine or reduce urine volume, compared with controls (4). Resistance to vasopressin was most marked in those patients with poor glycaemic control, and the resistance to vasopressin could be reversed with short-term improvements in control. Failure of urine concentration in these studies was associated with lower urinary concentration of aquaporin-2. Chronic hyperglycaemia, therefore, blunts the ability of vasopressin
to generate renal aquaporin-2 in type 1 diabetes, thereby attenuating the antidiuretic response to glycosuric diuresis.

Renal responses to vasopressin have not been studied in type 2 diabetes in the absence of nephropathy, though vasopressin secretion in response to dehydration has been shown to be normal (3). In this study, we have tested the hypothesis that the urine concentrating responses to the rise in plasma vasopressin concentrations during water deprivation would be blunted in poorly controlled patients with type 2 diabetes, compared with patients with good glycaemic control. Water deprivation was selected as the stimulus to endogenous vasopressin secretion in this study as it is the closest simulation of those physiological conditions, which promote vasopressin secretion.
METHODS

Subjects

Ten subjects with poorly controlled type 2 diabetes (PCDS), and ten with well-controlled type 2 diabetes (WCDS) were recruited from out-patient diabetic clinics. The diagnosis of type 2 diabetes was based on: absence of ketonuria, age over 40 years at diagnosis and insulin independence for at least one year following diagnosis. Good control was defined by a glycosylated haemoglobin (HbA1c) < 7% and poor control as HbA1c > 9%. The laboratory reference range for HbA1c, derived from the local non-diabetic population, was 3.7 – 5.7%. Exclusion criteria included the presence of diabetic nephropathy, defined by either serum creatinine outside of the laboratory reference range, or microalbuminuria, prostate disease or microscopic haematuria, frequent urinary tract infections, hypertension (office blood pressure > 140/90 mmHg), cardiac disease and treatment with diuretics, lithium, or angiotensin converting enzyme inhibitors. All patients had normal thyroid function, including three patients receiving maintenance thyroxine therapy. Three PCDS and two WCDS had background diabetic retinopathy, identified by dilated fundoscopy, but no other diabetes-related complications were present. Ten non-diabetic age-matched control subjects (NDCS) were recruited from hospital staff. Clinical characteristics are summarised in table 1.

Protocol

Subjects were admitted to the investigation unit at 0730h on the day of study. All subjects had been advised to avoid alcohol for 48 hours and nicotine and caffeine for 12 hours, prior to study. Subjects were encouraged to allow themselves free access to
tap water on the morning of study, but presented to the unit in a fasted state. Subjects with diabetes withheld their oral hypoglycaemic agents on the morning of therapy, but subjects taking thyroxine continued this treatment.

After resting recumbent for 30 minutes, subjects had intravenous cannulae inserted into the antecubital fossa for venesection. Diabetic subjects had intravenous cannulae sited in the contralateral antecubital fossa via which they were attached to an intravenous infusion of soluble insulin (Actrapid, Novo Nordisk, Copenhagen, Denmark) constituted in the form of 50 I.U. insulin dissolved in 50 mls of 0.9% sodium chloride, in a 50 ml syringe, in a syringe driver. The insulin infusion was commenced if the blood glucose concentration rose above 6.0 mmol/l (110 mg/dl) and the rate of infusion was adjusted to maintain blood glucose concentrations between 4-6 mmol/l (70-110 mg/dl) for the duration of the study. Blood glucose was monitored at the bedside at 15-minute intervals throughout the study. Blood pressure was measured using a mercury sphygmomanometer.

Once stable euglycaemia (plasma glucose concentration 4-6 mmol/l) had been achieved, patients voided their bladders; an aliquot of urine was set aside for measurement of baseline urine osmolality, and the remainder discarded. Baseline blood samples were withdrawn, and thirst was measured on a well-validated visual analogue scale (10), which has been shown to be reproducible within an individual (13). Each subject then commenced a standard 8-hour water deprivation test. Blood samples were taken at 2-hour intervals during the study and, at blood sampling times, thirst was assessed using the visual analogue scale, urine volume was measured and an aliquot retained for measurement of urine osmolality.
At the end of the water deprivation period, patients were allowed free access to tap water at room temperature and the volume drunk in a 30-minute period was noted.

Blood samples were taken through free running intravenous cannulae into chilled syringes and transferred immediately into heparinised tubes, in ice, and centrifuged immediately at 4°C for 15 minutes at 2000G; the plasma supernatant was separated and divided into aliquots. One aliquot was used immediately for the measurement of plasma osmolality and plasma sodium concentration, and the other was frozen at –70°C for later measurement of plasma vasopressin. Blood was also taken into EDTA tubes and after centrifugation the plasma supernatant was stored for measurement of plasma renin.

All studies were medically supervised and subjects were weighed at 2-hour intervals, with the intention that studies would be stopped if subjects lost >5% of their body weight, as per standard protocols for the conduct of water deprivation testing.

**Analyses**

Plasma and urine osmolalities were measured by the depression of freezing point method (Fiske 2400 Osmometer, Massachusetts, USA) and plasma sodium by the ion-selective electrode method (Olympus 2700, Tokyo, Japan). Plasma AVP was measured by a sensitive and specific radioimmunoassay after extraction from plasma by adsorption onto magnesium silicate (Florisil) (9). The limit of detection of the assay is 0.3 pmol/l, with intra- and inter-assay coefficients of variation of 9.7% and 15.3% respectively. Blood glucose was measured by the glucose oxidase method.
(Yellow Springs autoanalyser, Clandon Scientifics, London, England). Plasma renin activity was measured by commercial antibody (Soten, Milan, Italy).

**Statistical Analysis**

Data are expressed as mean ± standard deviations (SD). Univariate analysis was done using the Student’s t test.

Repeated measures Analysis of variance (ANOVA) models were used to compare Plasma and urine osmolalities, plasma AVP, plasma sodium, urine volume and thirst, between groups. Multiple comparison tests, using a Bonferroni correction factor, were used to determine if results reached significance at the 5% level. Stata (version 8, Texas, USA) was used for the statistical analysis.

Linear regression analysis was applied to define the relationship between plasma osmolality and plasma vasopressin, and between plasma osmolality and thirst.

**Ethical Considerations**

The studies were approved by the local ethics committee and all patients signed informed consent prior to study.
Disclosure

During this study, Dr Agha was in receipt of a Pfizer International Research Fellowship.
RESULTS

The studies were well tolerated in all volunteers. Blood glucose remained unchanged throughout the study (figure 1), in NDCS (4.5 ± 0.5 to 4.5 ± 0.3 mmol/l, p = 0.74), WCDS (5.0 ± 0.9 to 4.5 ± 0.5 mmol/l, p = 0.74) and PCDS (4.5 ± 0.9 to 4.5 ± 0.7 mmol/l, p = 0.84). There were no differences in blood glucose concentration between the groups, p >0.05. Baseline plasma renin activity was higher in PCDS (1.0 ± 0.8 ng/ml/hr) than in NDCS (0.3 ± 0.2 ng/ml/hr, p = 0.017) and WCDS (0.4 ± 0.3 ng/ml/hr, p = 0.038). There was no difference in basal plasma renin activity between NDCS and WCDS (p = 1.0). Water deprivation caused a significant rise in plasma renin activity in NDCS, from 0.3 ± 0.2 to 0.9 ± 0.8 ng/ml/hr (p < 0.001), WCDS from 0.4 ± 0.3 to 0.9 ± 1.0 ng/ml/hr (p < 0.001) and in PCDS from 1.0 ± 0.8 to 2.1 ± 1.6 ng/ml/hr (p < 0.001).

Water deprivation caused an elevation in plasma osmolality in the NDCS from 287.5 ± 2.4 to 296.6 ± 2.8 mOsm/kg (p < 0.001), in WCDS from 287.7 ± 2.6 to 295.1 ± 2.1 mOsm/kg (p < 0.001) and, in PCDS from 294.0 ± 2.9 to 300.7 ± 3.1 mOsm/kg (p < 0.001) (figure 1). Plasma osmolality was consistently higher throughout the study period in the PCDS than in the NDCS (p < 0.001) or the WCDS (p < 0.001). There was no difference in plasma osmolality between the NDCS and the WCDS.

The elevation in plasma osmolality caused a rise in plasma AVP concentrations (figure 2), in NDCS from 0.6 ± 0.4 to 2.1 ± 1.3 pmol/l (p < 0.001), in WCDS from 0.5 ± 0.2 to 2.9 ± 2.0 pmol/l (p < 0.001) and, in PCDS from 0.7 ± 0.5 pmol/l to 3.0 ± 2.6
pmol/l (p < 0.01). There were no differences in plasma AVP between the groups during the study (p > 0.05 between groups).

The elevation in plasma osmolality also stimulated an elevation in thirst ratings (figure 2); in NDCS, from 1.4 ± 0.8 to 8.0 ± 1.3 cm (p < 0.001); in WCDS, from 1.0 ± 0.9 to 7.5 ± 1.6 cm (p < 0.001); and in PCDS, from 2.3 ± 1.6 to 8.4 ± 1.6 cm (p < 0.001). The elevation in thirst was not different between the PCDS and the NDCS (p = 0.09) or the WCDS (p = 0.059). However, the volume of water drunk in 30 minutes following water deprivation was higher in PCDS (915 ± 153 mls) than in the NDCS (751 ± 205 mls, p = 0.011), or the WCDS (631 ± 251 mls, p = 0.012).

The elevation of plasma AVP concentration caused a fall in urine flow (figure 3), in NDCS from 79.3 ± 27.2 to 19.2 ± 11.2 mls/h (p < 0.001), in WCDS from 104.5 ± 37.5 to 26.3 ± 7.8 mls/h (p < 0.001), and in PCDS from 105.4 ± 41.9 to 52.6 ± 12.9 mls/h (p < 0.001). The change in urine flow was not different between the NDCS and the WCDS (p = 0.1), but the decrease in urine flow rate in response to vasopressin was higher in NDCS (p < 0.001) and WCDS (p = 0.046) than in PCDS. The total urine volume passed during the eight hours of water deprivation was higher in the PCDS (794 ± 161 mls) than either the NDCS (507 ± 224 mls, p = 0.004) or the WCDS (589 ± 138 mls, p = 0.014), but was not different between the NDCS and the WCDS (p = 0.37).

Urine osmolality rose in response to vasopressin (figure 3), in the NDCS from 336.0 ± 123.3 to 786.5 ± 63.3 mOsm/kg (p < 0.001), in WCDS from 360.7 ± 142.8 to 794.1 ± 77.3 mOsm/kg (p < 0.001) and in PCDS from 280.3 ± 49.7 to 594.4 ± 88.5
mOsm/kg (p < 0.001). The rise in urine osmolality was less in the PCDS than in the NDCS (p = 0.019) or the WCDS (p < 0.001). There was no difference in urine osmolality between NDCS and WCDS (p = 0.39).

Linear regression analysis was applied to define the relationship between plasma osmolality and plasma vasopressin, and between plasma osmolality and thirst. This mathematical model defines two important characteristics of the relationships between plasma osmolality and plasma vasopressin, and between plasma osmolality and thirst. The slope of the regression line reflects the sensitivity of the relationship, whereas the intercept corresponds to the osmotic threshold at which vasopressin and thirst begin. The results are shown in table 2. Linear regression analysis demonstrated that the characteristics of osmotically stimulated thirst and vasopressin release were similar in WCDS to NDCS, in that the slopes and intercepts were similar in the two groups.

In contrast, the osmotic thresholds (intercepts) for both thirst and vasopressin secretion were set at a higher plasma osmolality in PCDS than in either NDCS (thirst, p = 0.005; vasopressin, p < 0.001) or WCDS (thirst, p = 0.007; vasopressin, p < 0.001). The slope of the mean lines relating plasma osmolality and plasma vasopressin, and plasma osmolality and thirst, were similar in PCDS to NDCS and WCDS (table 2).
DISCUSSION

Our data show that patients with poorly controlled type 2 diabetes respond to dehydration with two distinct abnormalities of osmoregulation. First, the osmotic set point at which vasopressin secretion and thirst begin is reset at a plasma osmolality threshold 5-6 mOsm/kg above that for non-diabetic controls and patients with well-controlled type 2 diabetes. This means that the homeostatic responses to dehydration are not activated in PCDS until they are significantly more hyperosmolar than non-diabetic controls or well-controlled diabetic subjects. Secondly, in response to equivalent plasma vasopressin concentrations, PCDS are less able to concentrate urine or limit urine flow, in comparison to non-diabetic controls or WCDS. This is the first time that these abnormalities have been demonstrated experimentally in type 2 diabetes.

The demonstration that the osmotic thresholds for thirst and vasopressin release were higher in PCDS was unexpected. Given that the PCDS were relatively volume deplete prior to commencement of water deprivation, as shown by the higher baseline plasma osmolality and the higher baseline plasma renin activity, one would expect a lowering of the osmotic thresholds for thirst and vasopressin secretion. In other experimental models, acute volume depletion has been shown to lower the osmotic threshold and increase the sensitivity of osmotically stimulated vasopressin release (8). In type 2 diabetic, subjects who have biochemical evidence of volume depletion but good glycaemic control, have elevated plasma vasopressin concentrations in comparison to euvalaemic patients (2). Previous studies have demonstrated normal characteristics of osmotically stimulated thirst and vasopressin release in patients with well-controlled type 1 (11) and type 2 diabetes (3). In the light of published data
therefore, it seems that the results of our study indicate normal osmoregulation is in WCDS, but that chronic hyperglycaemia causes upward resetting of the osmotic threshold for thirst and vasopressin secretion, rather than the downward resetting which acute volume depletion would ordinarily cause (2). This specific effect of chronic poor glycaemic control on osmoregulation has not been reported in type 2 diabetes.

Chronic poor glycaemic control may directly attenuate the vasopressin response to dehydration. Early studies, which established the solute specificity of the osmoreceptors for vasopressin release, suggested that hyperglycaemia lowered plasma vasopressin secretion (17). Although we have previously shown that acute hyperglycaemia, over 12-24 hours, does not impair the osmoregulation of thirst or vasopressin release, it may be that chronic hyperglycaemia blunts the osmoreceptor response to elevation in plasma sodium such that the osmotic thresholds for thirst and vasopressin secretion are reset above the normal levels. If this hypothesis is true, it is clearly a maladaptive response, as it would be more useful to lower the thresholds for thirst and vasopressin release in the situation of hypovolaemia.

The counter-productive effect of the elevated osmotic threshold for thirst and vasopressin release in PCDS is compounded by the impaired renal response to vasopressin. At the end of the period of water deprivation, plasma vasopressin concentrations were similar in all three groups. However, although the WCDS concentrated urine appropriately in response to vasopressin, with a similar rise in urine osmolality to controls, the PCDS neither concentrated urine nor reduced urine flow to the same extent as controls. This indicates renal resistance to vasopressin in
PCDS, a situation analogous to that which we have already reported in type I diabetes (4). The pathophysiology behind renal resistance to vasopressin action in poorly controlled diabetes remains speculative. Although the traditional view has been that interstitial solute is the key determinant of renal concentrating ability, we have shown that in human type 1 diabetes, impaired renal response to vasopressin is caused by failure to generate aquaporin-2, the renal water channel (4). The ability to generate aquaporin-2 and concentrate urine was restored after short-term (7 days) improvement in glycaemic control, suggesting that hyperglycaemia per se attenuated the recruitment of aquaporin-2 in response to vasopressin. In contrast to our human data, studies in animal models of diabetes have shown no convincing evidence of impaired generation of aquaporin-2. Rat studies have suggested that the density and affinity of renal V2 receptors are unchanged in diabetic rats in comparison to controls, yet the poorly controlled animals were clearly polyuric (14). These studies, however, did not rule out impaired generation of aquaporin-2 by the V2 receptors. In acute streptozotocin-induced diabetic rats, semiquantitative immunoblotting revealed higher concentrations of inner medullary aquaporin-2 than in non-diabetic rats (7). Diabetic rats had marked hyperglycaemia, with evidence of increased water intake and urine excretion, but the changes in renal aquaporins in relation to plasma vasopressin concentrations were not reported in this study. Thus, although this study showed that volume depletion caused the generation of renal aquaporin-2 in diabetic rats, it could not comment on whether the recruitment of aquaporin-2 was appropriate to ambient plasma vasopressin concentrations. In addition, control rats were not in an equivalent state of hypovolaemic diuresis, so that comparisons between the aquaporin response to equivalent vasopressin concentrations in diabetic rats and control rats could not be made.
Impaired renal generation of aquaporin-2 in response to dehydration has also been shown in one other study of human type 2 diabetes (6). Diabetic patients with significant nephropathy, characterised by elevated serum creatinine, were shown to have lower urinary excretion of aquaporin-2 in response to dehydration than control subjects. We were careful to exclude patients with diabetic nephropathy, as manifested by either elevated serum creatinine or by the presence of microalbuminuria. Our data shows that even in the absence of nephropathy, urine concentration is blunted in response to vasopressin in the setting of poor glycaemic control.

Over the eight hours of water deprivation, PCDS excreted a mean of 200-300 mls more urine than WCDS or controls. The PCDS drank a mean of 200-3000mls more than either WCDS or controls in the 30 minutes after dehydration, indicating appropriate thirst responses to the greater degree of fluid loss in the PCDS group. However the failure to concentrate urine and limit urine flow in response to dehydration would correspond to an extra 0.75 litres of fluid loss per 24-hour in situations where fluid intake is limited, such as during serious intercurrent illness, or if drinking was not possible due to vomiting or lack of availability. Our studies were performed with the blood glucose maintained in the euglycaemic range. However, it would seem reasonable to speculate that the degree of dehydration may be greater still if dehydration occurred against the background of hyperglycaemia, which is a common clinical scenario. We would hypothesize that the inability to respond to the antidiuretic action of vasopressin may worsen dehydration during intercurrent illness in PCDS.
One additional clinical point should be noted. One of ten of the WCDS and nine out of ten of the PCDS “failed” the water deprivation test, with peak urine osmolality < 700 mOsm/kg, the standard criterion used in our laboratory to indicate a normal response. Poor glycaemic control should therefore be corrected before people with diabetes undergo a water deprivation test to investigate polyuria (for example, investigation for diabetes insipidus following pituitary surgery or head trauma).

In summary, therefore, we have shown that type 2 diabetic patients with poor glycaemic control, confirmed by HbA1c concentrations > 9%, have the following osmoregulatory abnormalities;

1. elevated osmotic thresholds for thirst and vasopressin release.
2. Impaired renal concentrating ability in response to vasopressin.
3. excess urine excretion in response to dehydration, with a consequent reliance on increased water intake to prevent dehydration.

These abnormalities are likely to contribute significantly to the development of dehydration in poorly controlled diabetes.
REFERENCES


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**Table 1**: Demographic characteristics of non-diabetic control subjects (NDCS), well controlled type 2 diabetic subjects (WCDS) and poorly controlled diabetic subjects (PCDS). N/A, not applicable. * Between groups p value = 0.2. Non-diabetic reference range for HbA1c: 3.7 – 5.7%, derived from local population.
Table 2: Mean linear regression lines for non-diabetic control subjects (NDCS), well controlled type 2 diabetic subjects (WCDS), and poorly controlled diabetic subjects (PCDS). Results expressed as mean ± SD. * = p < 0.001 compared with PCDS. pAVP = plasma arginine vasopressin concentration
LEGENDS TO FIGURES

Figure 1. Changes in plasma osmolality, plasma sodium and blood glucose concentration during water deprivation. T2D, type 2 diabetic subjects.

Figure 2. Changes in plasma vasopressin concentration, and thirst ratings (cm), during water deprivation. LD = assay limit of detection for vasopressin (0.3 pmol/l). T2D, type 2 diabetic subjects.

Figure 3. Changes in urine osmolality and two-hour urine volumes during water deprivation. T2D, type 2 diabetic subjects.