Vasopressin and diabetic nephropathy

Ronan Roussel, Gilberto Velho, Lise Bankir

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Ronan ROUSSEL (1, 2, 3)
Gilberto VELHO (1)
Lise BANKIR (1,4)

(1) INSERM, UMRS 1138, Centre de Recherche des Cordeliers, 15 rue de l'Ecole de Médecine, 75006 Paris, France;
(2) Assistance Publique Hôpitaux de Paris, Bichat Hospital, DHU FIRE, Department of Diabetology, Endocrinology and Nutrition, Paris, France;
(3) Université Paris Diderot, Sorbonne Paris Cité, UFR de Médecine, Paris, France;
(4) Université Pierre et Marie Curie, Centre de Recherche des Cordeliers, Paris, France

Correspondance to:

Prof. Ronan Roussel or Lise Bankir

INSERM UMRS 1138 (Équipe 2), Centre de Recherche des Cordeliers

15 rue de l'École de Médecine, 75006 Paris, France

Phone: +33 1 44 27 81 14, Fax: +33 1 44 27 64 21,

e-mail: ronan.roussel@gmail.com

e-mail : lise.bankir@inserm.fr

Abstract

Purpose of review: The prevalence of diabetic kidney disease (DKD) is increasing worldwide. Despite major therapeutic advances in the last decades in DKD, the current standard of care let many people progress to severe stages ~~an unmet need~~. Vasopressin secretion is increased in diabetes, and its potential role in the onset and progression of DKD is being re-investigated.

Recent findings: Recently, observational studies evidenced an association between surrogates of vasopressin secretion (daily fluid intake or urine volume, and plasma copeptin concentration) and chronic kidney disease in the community, but also specifically in type 1 and in type 2 diabetes. Causality is strongly supported by a series of studies in rats conducted more than a decade ago, and by additional recent experimental data.
The mechanism underlying these adverse effects likely involves the hyperfiltration induced indirectly as a consequence of the tubular effects of the hormone mediated by the V2 receptor.

Summary: If chronic vasopressin action on the kidney is detrimental in diabetes as suggested so far, intervention studies should be designed. Available tools include V2 receptor blockade, as well as changes in daily water intake in vulnerable patients. Safety and effectiveness should be tested, as it is currently done in patients with CKD (NCT01766687).

Keywords: albuminuria, hyperglycemia, renal failure, diabetic complication, anti-diuretic hormone

Introduction

Diabetic kidney disease (DKD) has become the most common cause of CKD (Chronic Kidney Disease) in the Western world, and the same trend is observed in developing countries. The human burden is huge because DKD may lead not only to ESRD, but also very often to cardiovascular events and premature death. Hyperfiltration at the single-nephron level is usually considered as an important feature of DKD that predisposes to progressive nephron damage by increasing intraglomerular hydraulic pressure, albeit other mechanisms of damage have also been evidenced [1].

Circulating levels of vasopressin are increased in people with type 1 or type 2 diabetes, and in animal models with spontaneous or streptozotocin-induced diabetes (see review in [2]). The causes of the increased level of vasopressin in diabetes are not fully elucidated, but it could result from a relative contraction of extracellular volume induced by glycosuria and/or from an increased sensitivity of hypothalamic osmoreceptor neurons to the plasma osmolarity [3]. From an adaptive perspective, high levels of vasopressin may be beneficial in the short term by limiting the water loss in urine induced by glycosuria [2]. However, in the long term, persistently high levels of vasopressin might be deleterious to renal function [4].

We will review the evidence available so far regarding plausible link between vasopressin and DKD. Most of the evidence in humans is related to surrogate markers of vasopressin secretion, like hydration markers and copeptin, and is very consistent in renal disease associated with diabetes or not. However, strong experimental data have been accumulated in the last decades supporting a direct causal role of vasopressin in the pathogenesis of CKD and DKD. This evidence is hypothesis-generating for potential preventive and therapeutic strategies in DKD.

Evidence supporting the beneficial effect of hydration in the prevention of CKD in the general population

Strippoli and coworkers observed an inverse linear relationship between fluid intake and prevalence of CKD (eGFR <60 ml/min/1.73 m^2) in two cohorts of over 5000 participants [5]. Those in the highest quintile of fluid intake (3.2 L/day) had a significantly lower risk of CKD. Sontrop and coworkers analyzed the 2005-2006 US National Health and Nutrition Examination Survey with consistent conclusions [6]. Clark and coworkers used urine volume as a surrogate for the hydration status in a population-based Canadian prospective cohort [7]. After a follow-up of 6 years, the risk of rapid decline of renal function (defined as a eGFR loss exceeding 5% per year) was twofold lower in participants with a urine volume over 3 L/day at baseline, compared to the reference group (urine volume in between 1 and 1.9 L/day) (Figure 1).

Plasma copeptin as a biomarker of CKD risk in the general population

Copeptin, the COOH-terminal portion of the pre-provasopressin molecule, is much more stable than vasopressin in vitro, and as such is an easily measurable surrogate marker of vasopressin. Several studies have shown plasma copeptin and vasopressin concentrations to correlate strongly over a wide range of osmolalities [8-10] Plasma copeptin has been shown to be positively associated with the prevalence of microalbuminuria in cross-sectional observational and long-term follow-up studies in the general population [11-13]. In the large Dutch population-based PREVEND

study, the prevalence of microalbuminuria (urinary albumin excretion ≥30 mg/24 hours) was twice higher in participants within the upper quintile of plasma copeptin distribution than in those in the lowest quintile, and the association was independent of confounding factors such as sex, age, blood pressure and eGFR (estimated Glomerular Filtration Rate) [11]. Enhörning and coworkers analysed data from 2064 participants from the Swedish prospective population-based Malmo Diet and Cancer Study - Cardiovascular Cohort [12]. They reported associations of baseline plasma copeptin with the incidence of microalbuminuria at re-examination after an average follow-up of 16 years. The association between copeptin and microalbuminuria was independent of incident diabetes and incident hypertension.

In a subset of 1234 participants from the DESIR study, a prospective cohort of the French general population, we assessed the association between plasma copeptin measured at baseline and the risk for progression towards CKD during a 9-year follow-up [14]. We considered two criteria of progression towards CKD. The first criterion was defined as eGFR below 60 ml/min/1.73m^2 (CKD stage 3 or worse) in at least one of the follow-up visits. The second criterion was a "Certain Drop in eGFR", as proposed by the Kidney Disease Improving Global Outcomes (KDIGO) group [15] . Baseline plasma copeptin was positively associated with both criteria of CKD progression, and the associations were independent of other classical risk factors for CKD, including age, sex, blood pressure and renal function at baseline.

Plasma copeptin and diabetic nephropathy

A few studies investigated the impact of high copeptin levels on renal function in people with diabetes [16-19]. Boertien and co-workers analysed data from 1328

patients with type 2 diabetes of relatively recent onset (4 years of median duration of diabetes) from the Dutch ZODIAC prospective study [16]. They reported the higher quartile of baseline plasma copeptin to be associated with a faster decline in eGFR during a follow-up of 6.5 years. In a Swedish study of people with newly diagnosed type 2 diabetes from the Skaraborg Diabetes Register, plasma copeptin was positively associated with eGFR decline at re-examination after 12 years of follow-up [17].

We studied the association of copeptin with the progression of diabetic nephropathy in 3101 French type 2 diabetic patients from the DIABHYCAR cohort, selected on the basis of persistent micro- or macroalbuminuria without renal failure at baseline [18]. The median duration of follow-up was 5 years and the main outcome was a renal event, defined as the doubling of the serum creatinine concentration, or the requirement of renal replacement therapy or renal transplantation during follow-up. The higher tertile of baseline plasma copeptin was associated with a faster decline in renal function during follow-up, both in subjects with micro- or macroalbuminuria (Figure 2A), and with a ~300% increase in the incidence of renal events (Figure 2B). These associations were independent of relevant covariates such as age, duration of diabetes, blood pressure, and baseline levels of HbA1c, albuminuria and eGFR. Analyses by ROC curves showed that plasma copeptin and albuminuria at baseline predicted similarly the incidence of renal outcomes (ROC area 0.73 and 0.77, respectively) and a 4% added effect was observed for the combined markers (ROC area 0.82) [18].

Recently, we assessed the association of plasma copeptin at baseline with the risk of subsequent kidney or coronary morbidity in ~1200 participants from 2 binational (Belgium and France) cohorts of people with long-standing type 1 diabetes [19] The

main outcomes during follow-up were ESRD (requirement of haemodialysis or renal transplantation), a coronary event (myocardial infarction or coronary revascularisation) and all-cause mortality. High levels of plasma copeptin were associated with the prevalence of established and advanced diabetic nephropathy at baseline, and with increased risk during follow-up of ESRD, coronary events and all-cause mortality. The association with the incidence of ESRD during follow-up remained significant following adjustment for relevant confounding factors (age, duration of diabetes, blood pressure, HbA1c, eGFR and albuminuria at baseline). On the other hand, the association of high plasma copeptin with increased risk of coronary events during follow-up could be accounted for by the higher blood pressure, eGFR and albuminuria observed in participants with higher plasma copeptin.

Experimental data supporting detrimental action of vasopressin on the kidney

The selective vasopressin V2 receptor agonist dDAVP (not inducing an increase in blood pressure) was shown to induce a marked increase in urinary albumin excretion both in rats and in healthy human subjects [20]. The involvement of the V2 receptor was confirmed by the fact that albuminuria also increased upon infusion of dDAVP in patients with nephrogenic diabetes insipidus (NDI) due to mutations of the AQP2 water channel, but failed to increase in patients with NDI due to mutations of the V2 receptor.

Involvement of vasopressin in experimental diabetic nephropathy

The previous experimental observation of vasopressin-induced hyperfiltration in normal rats [21], and the well-known increase in vasopressin secretion in diabetes (see review in [2]) led us to hypothesize a role for vasopressin in DKD [14]. Brattleboro vasopressin-deficient rats were a relevant model to study the possible influence of vasopressin on glomerular hyperfiltration, albuminuria and kidney hypertrophy, characteristics of early diabetic nephropathy,. In these animals, a spontaneous single point mutation in the vasopressin gene prevents normal vasopressin synthesis, resulting in central diabetes insipidus (CDI) in rats homozygous for the mutation. Diabetes mellitus was induced by streptozotocin injection in CDI rats and in their Long Evans controls [22]. After 4 weeks, glycemia was increased to the same extent in both groups. Creatinine clearance and albuminuria were increased in control rats but underwent no change in CDI Brattleboro rats, as shown in Figure 3. Kidney hypertrophy was much less intense in CDI rats lacking AVP. This shows that the well-known renal complications of diabetes require a normal vasopressin secretion. A mirror experiment was conducted in rats with normal vasopressin secretion in which diabetes mellitus was induced by streptozotocin [23]. Half of the rats were treated for 3 months with the highly selective, orally active, non-peptide vasopressin V2 receptor antagonist, SR 121463A (Sanofi Aventis), mixed daily with their powdered food (diab-treated). The dose of antagonist was adjusted once a week so that urine osmolality was kept around 400 mosm/L, as compared to about 1000 mosm/L observed in control diabetic rats (diab-control). The purpose was to markedly reduce the urine concentrating activity of the kidney without inducing the formation of dilute urine (which might represent a confounding factor) [4,23] . The rise in glycemia and in glucose excretion rate was similar in both groups (Figure 4A) but the V2 antagonist treatment totally prevented

the rise in albuminuria seen in diab-controls [23]. At the end of the experiment, albuminuria was twice lower in diab-treated rats than in diab-controls (Figure 4A) although creatinine excretion was similar in both groups. Kidney weight per 100g body weight was 10% lower in diab-treated than in diab-control rats while liver or heart weights were identical in the two groups.

An interesting observation was made among the 13 diabetic rats of the control group that did not receive any treatment. They exhibited a marked inter-individual variability in GFR (as estimated by creatine clearance) and albuminuria. Three months after streptozotocin injection, significant correlations were observed between creatinine clearance or albuminuria and the solute-free water reabsorption T^cH_2O (the best reflect of vasopressin action on water reabsorption) (Figure 4B). The early signs of diabetic nephropathy were more visible in rats that showed a stronger urine concentrating activity, an activity that essentially depends on the action of vasopressin. These studies show that the antidiuretic effects of vasopressin play a significant role in the early manifestations of diabetic nephropathy in type 1 diabetes.

Further studies were designed to evaluate if vasopressin also contributes to diabetic nephropathy in type 2 diabetes [24]. Experiments were conducted in an animal model, the obese db/db mouse. Obese db/db mice were treated for 8 weeks with the selective V2 receptor antagonist (30 mg /kg.d, mixed with the food, of SR 121463, Sanofi-Aventis, same as used above in rats) (= diab-treated) and compared to untreated obese db/db mice (diab-control). All mice were uninephrectomized 2 weeks before the start of the experiment to increase the susceptibility of the kidney to adverse events. As expected, the antagonist resulted in a significant increase in urine output, and decrease in urine osmolality. No difference was observed in body weight gain, glycaemia, hematocrit, and blood pressure between the two groups throughout

the study but, after 4 and 8 weeks of treatment, the urinary albumin/creatinine ratio was significantly lower in diab-treated mice than in diab-control. Creatinine clearance (in ml/d) was significantly increased over time in diab-control mice, but remained stable in diab-treated mice (530 ± 86 vs 437 ± 51, NS) [24].

Potential mechanism of vasopressin-associated renal damages

This mechanism is not fully understood. Of note, there is no reason to assume a role, in DKD, of the vasopressin-induced cyclic-AMP production in collecting duct cells, an effect involved directly in cyst enlargement in autosomic dominant polycystic kidney disease [25]. Vasopressin was shown to increase GFR in normal rats and humans [4,14,21]. It is well accepted that such "hyperfiltration" induces a vicious circle that leads to progressive renal damage, as proposed by Brenner and coworkers [26]. There are no V2 receptors in the glomerulus. The vasopressin-dependent hyperfiltration is likely due to a reduction in the tubulo-glomerular feedback control of GFR, secondary to a reduced sodium concentration at the macula densa. It has been proposed [14] that this reduction results from the complex vasopressin-dependent intrarenal handling of urea (secretion in the pars recta, reabsorption in the terminal collecting duct, recycling in the medullary circulation), leading to a greater flow and higher concentration of urea in the loops of Henle (Figure 5). Vasopressin-stimulated NaCl reabsorption in the thick ascending limb of Henle may also contribute to the lower sodium concentration at the macula densa [14,27].

Discussion

Altogether, these studies suggest that the V2 receptor dependent antidiuretic effects of vasopressin are strongly associated with albuminuria in humans, and have a

causal role in the early manifestations of nephropathy in animal models of both type 1 and type 2 diabetes.

The current recommendations of care to reduce the onset and progression of DKD are evidence-based and focused on the tight control of blood glucose and blood pressure. Particularly beneficial classes of drugs are identified, like renin-angiotensin system blockers, but also recently glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter type 2 inhibitors, two classes of antidiabetic agents. Recently, stabilization of the incidence rates for DKD-related ESRD was observed in North America, but the number of patients with less severe stages of renal impairment is high and still increasing. Therefore, there is an important and unmet therapeutic need to limit the progression of the disease in this population. Many drugs and therapeutic strategies have been tested, but many failed, often because of intolerable side effects. Of note, lifestyle changes have been proposed for a long time in renal care (reduction of daily intake of salt, phosphate, potassium, or proteins). The intake of water was more rarely addressed [28], except in advanced CKD with indication of reduced intake because of frequent hyperhydration. However, the KDIGO recommendations mention supplemental free water, but with a narrow scope, "for children with CKD and polyuria to avoid chronic intravascular depletion" [15].

Interestingly, the association mentioned above between fluid intake and prevalence of CKD was observed only for the intake of plain water, but not when considering other beverages such as energy drinks, sugar- or artificially-sweetened drinks, tea, coffee, alcoholic beverages, fruit and vegetable juice, and milk or other dairy drinks [6]. Thus, it seems reasonable to include a claim for appropriate hydration by drinking

plain water in future recommendations for the prevention of the onset of DKD, or against the progression of the disease in its early stages.

Conclusion

As described above, there is strong evidence from experimental studies in rodent models that vasopressin plays a significant role in albuminuria, CKD and DKD. However, only observational data are available sofar in humans. There is a tremendous need for interventional studies [29]. A randomized controlled trial with clinical outcomes is ongoing in a CKD population, not specifically in patients with diabetes [30]. Results are expected in the next future, but preliminary data already support the feasibility of an intervention based on increased water intake in this population, and the expected change in some parameters, including plasma copeptin concentrations. Next steps should include interventional studies in people with diabetes and early DKD, resistant to conventional care.

Key points

- The prevalence of diabetic kidney disease (DKD) is increasing sharply worldwide.

- Consistent clinical observational studies support an association between low fluid intake, other markers of vasopressin secretion, and chronic kidney disease in the community

- Consistent evidence is available regarding DKD

- Experimental data support causality in the association between vasopressin and chronic kidney damage

- In the context of the unmet therapeutic need in DKD, interventions to attenuate chronic vasopressin action on the kidney in diabetes should be designed and tested

Conflicts of interest

Dr Roussel has been a consultant or on the speakers' bureau for AstraZeneca, Boehringer-Ingelheim, Janssen, Eli Lilly, Sanofi, Merck Sharp and Dohme, Physiogenex, and Novo-Nordisk, and has received research funding from Amgen, Sanofi, and Danone Research.

Dr Velho has no conflict to declare

Dr Bankir is an occasional consultant for Danone Research, France

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Preliminary encouraging data on a first intervention randomized trial testing increased water intake in CKD

Figure legends

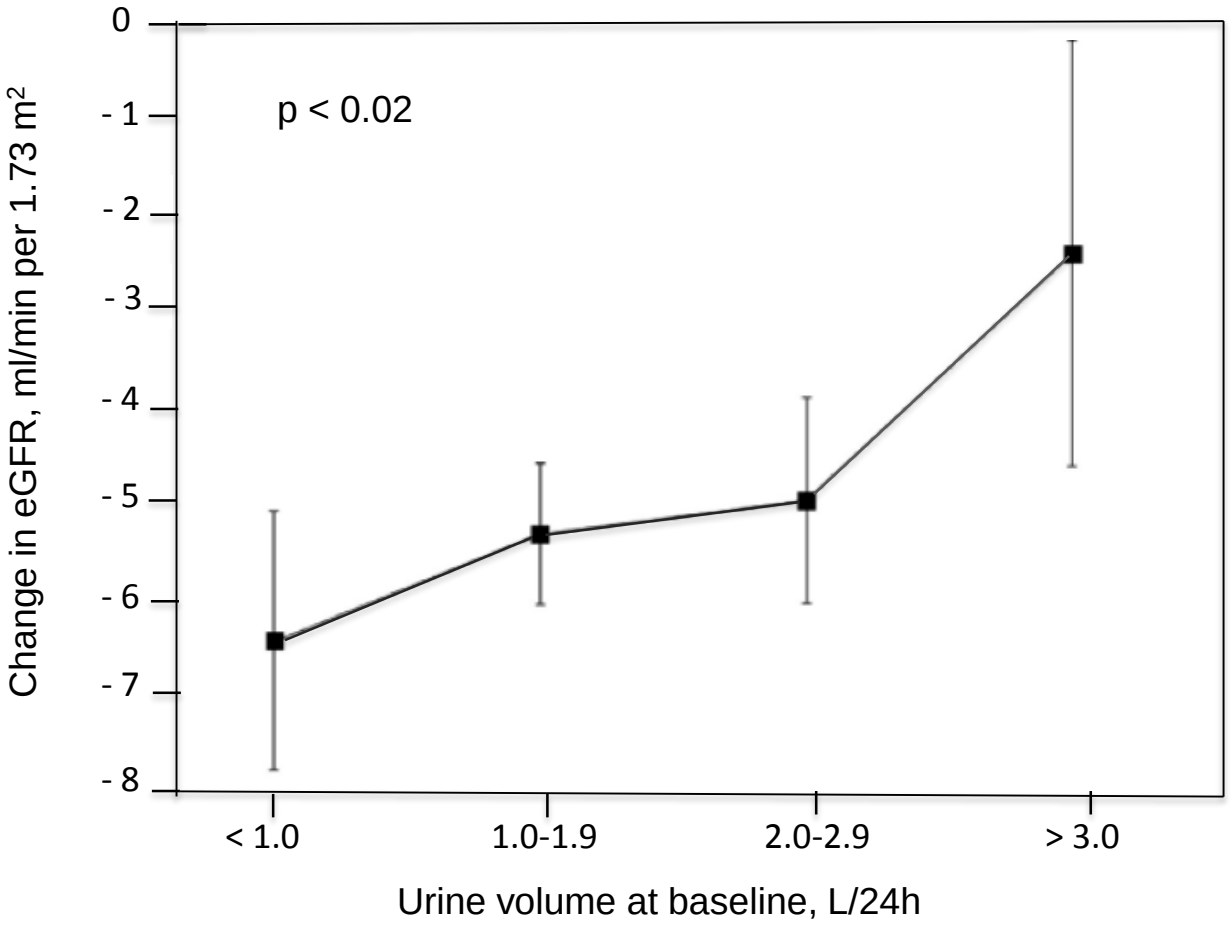
Figure 1. Decline in kidney function over a 5.7 year follow-up period, as a function of categories of daily urine volume at baseline (n=2148); eGFR = estimated GFR. The decline was much smaller in people with large urine volumes (and thus probably higher fluid intakes). Modified after data shown by Clark et al [7]

of baseline plasma copeptin. White bars: all subjects (n=3101, p=0.0001). Grey bars: subjects with macroalbuminuria at baseline (n=729, p=0.005). Results expressed as means ± SEM. Statistics are ANCOVA adjusted by sex, age and study treatment (randomization group in the original DIABHYCAR study: ramipril vs placebo). After G. Velho et al. [18]. B. Incidence of renal events during follow-up by tertiles of baseline plasma copeptin. Renal events were defined as the doubling of the serum creatinine levels or ESRD (requirement of hemodialysis or renal transplantation) during follow-up. Upper panel: all subjects (n=3101); log-rank p<0.0001. Lower panel: subjects with macroalbuminuria at baseline (n=729); log-rank p<0.0001. After G. Velho et al. [18] with permission.

Figure 3. Influence of urine concentration on the early manifestations of diabetic nephropathy. Diabetes mellitus was induced by an injection of streptozotocin in Brattleboro rats that cannot secrete vasopressin (no AVP) and in control Long Evans rats (normal AVP). Sham injected rats served as controls. Although glycemia rose to the same extent in the two strains of rats, the rise in creatinine clearance and urinary albumin excretion that were observed in control rats did not occur in the absence of AVP, and kidney hypertrophy was much less intense. Drawn after data shown in Bardoux et al [22].

Figure 4. A. Glycemia, urinary glucose excretion, and urinary albumin excretion in control rats (no DM) and in DM rats not treated (DM-Cont) or treated with a vasopressin V2 receptor antagonist (DM-SR). Open bars show results obtained in the basal period (before the anti-V2 treatment), and hatched bars show the results obtained after 9 weeks of treatment. Glycemia and glucose excretion were not affected by the treatment, but the rise in albuminuria seen in DM-Cont rats was totally prevented by the drug. B. Relationship between creatinine clearance (Ccreat) or urinary albumin excretion (UAE) and solute-free water reabsorption (TcH2O) during the last week of the study in control diabetic rats (receiving no treatment). Linear regressions and correlation coefficients are shown; (a) denotes two very high values excluded from the linear regression. Adapted from Bardoux et al. [23] with permission.

Figure 5. Sequence of events initiated by increased vasopressin secretion in diabetes mellitus and accounting for its action on water conservation and for its possible involvement in diabetic nephropathy. Only a role for V2-receptor- mediated actions is presented here. An additional contribution of V1a-receptor-mediated events cannot be excluded, but should be less important because of a partial desensitization of V1a receptors in diabetes mellitus. The protection against progression of diabetic nephropathy afforded by the chronic blockade of the renin-angiotensin system could, at least in part, be explained by the fact that they interrupt one of the pathways by which vasopressin might influence renal function. Reproduced from [2] with permission.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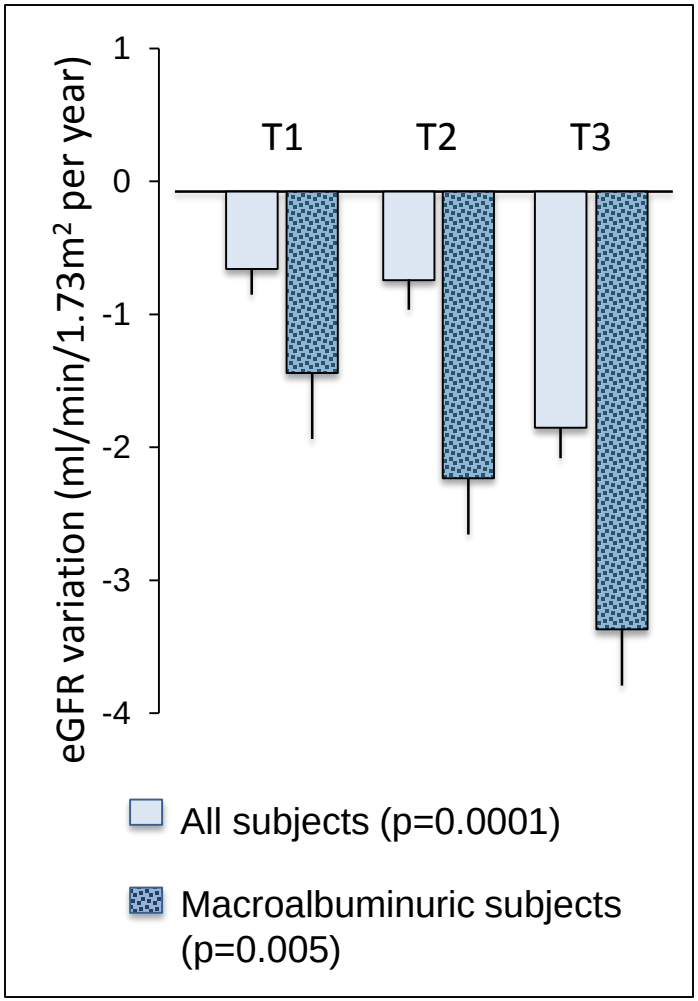
p < 0.02
Change in eGFR, ml/min per 1.73 m²
< 1.0
1.0-1.9
2.0-2.9
> 3.0
Urine volume at baseline, L/24h

A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eGFR variation (ml/min/1.73m² per year)
T1
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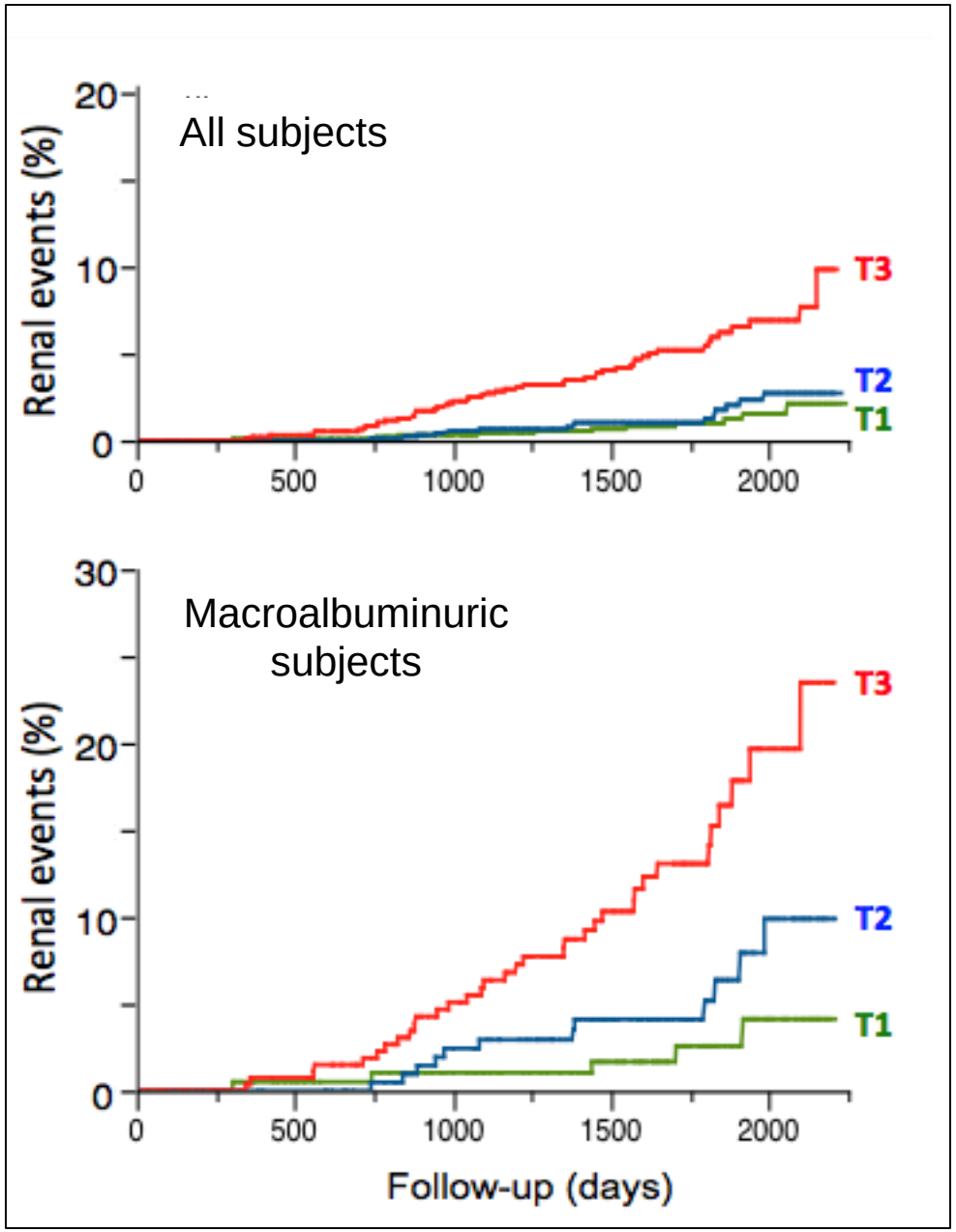
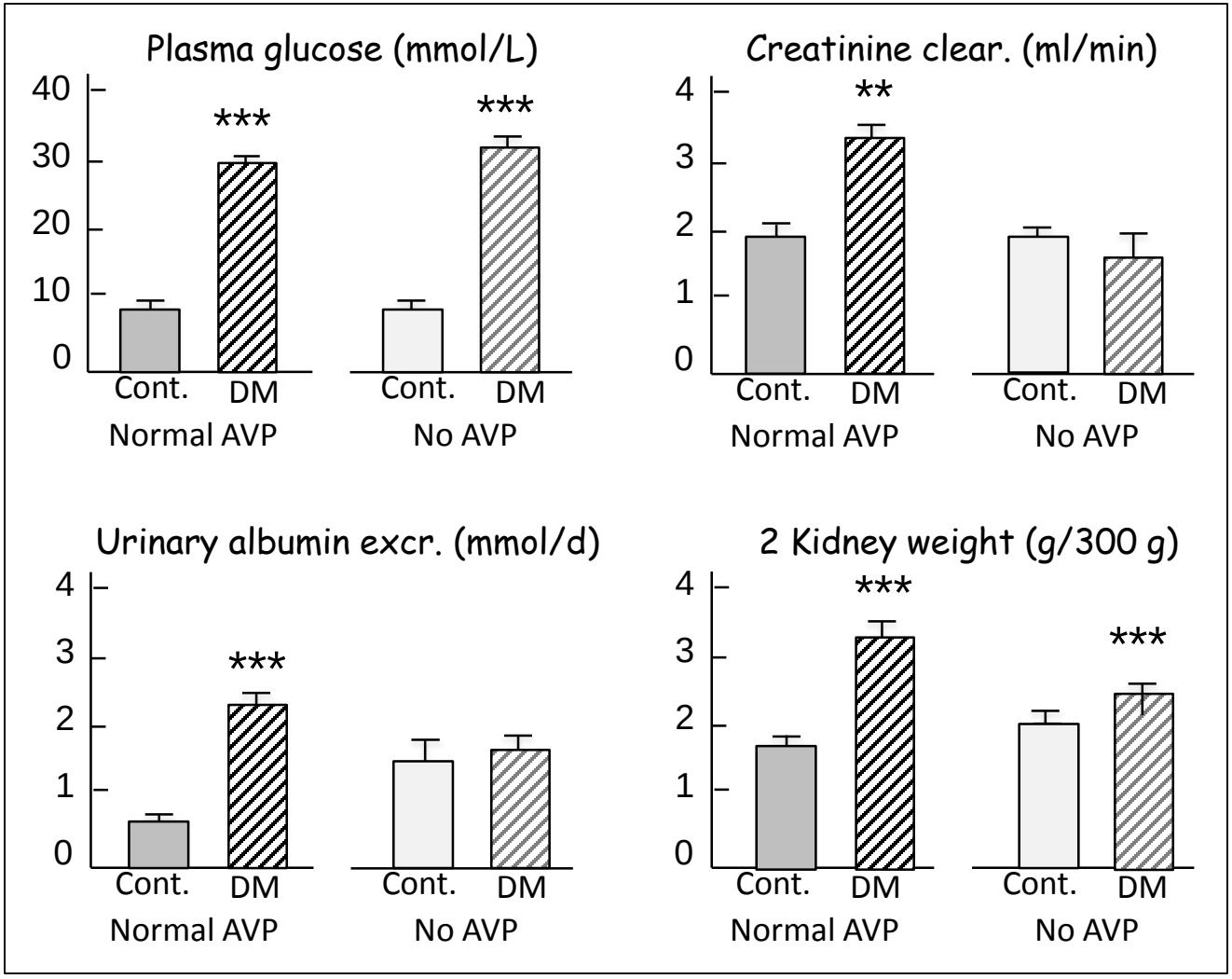
All subjects (p=0.0001)
Macroalbuminuric subjects (p=0.005)

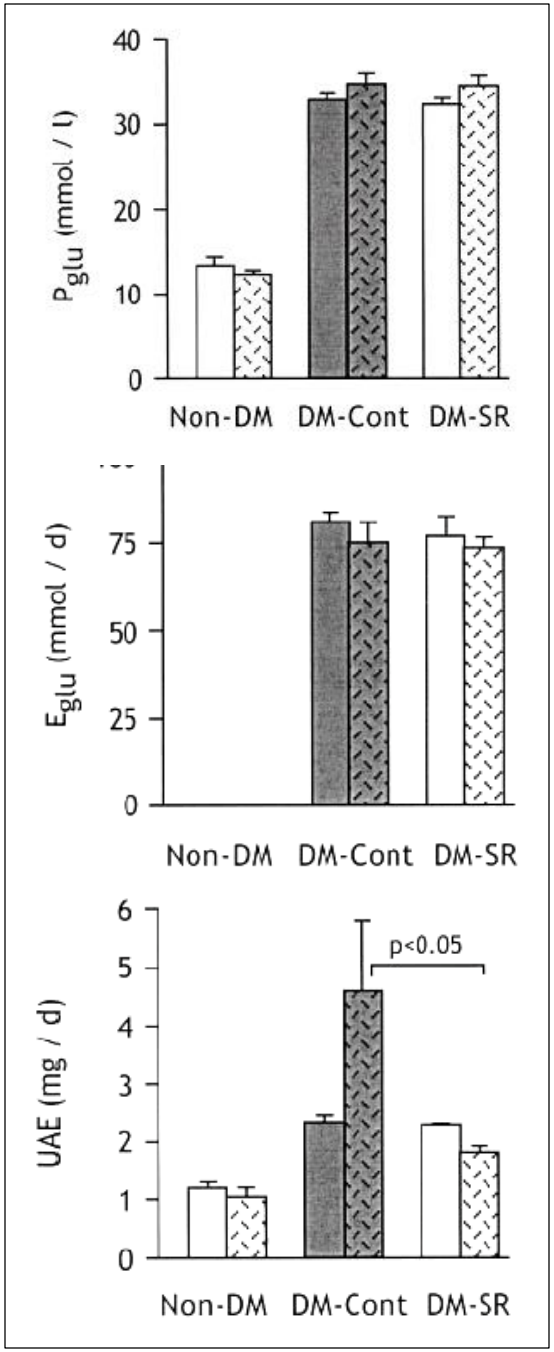
B

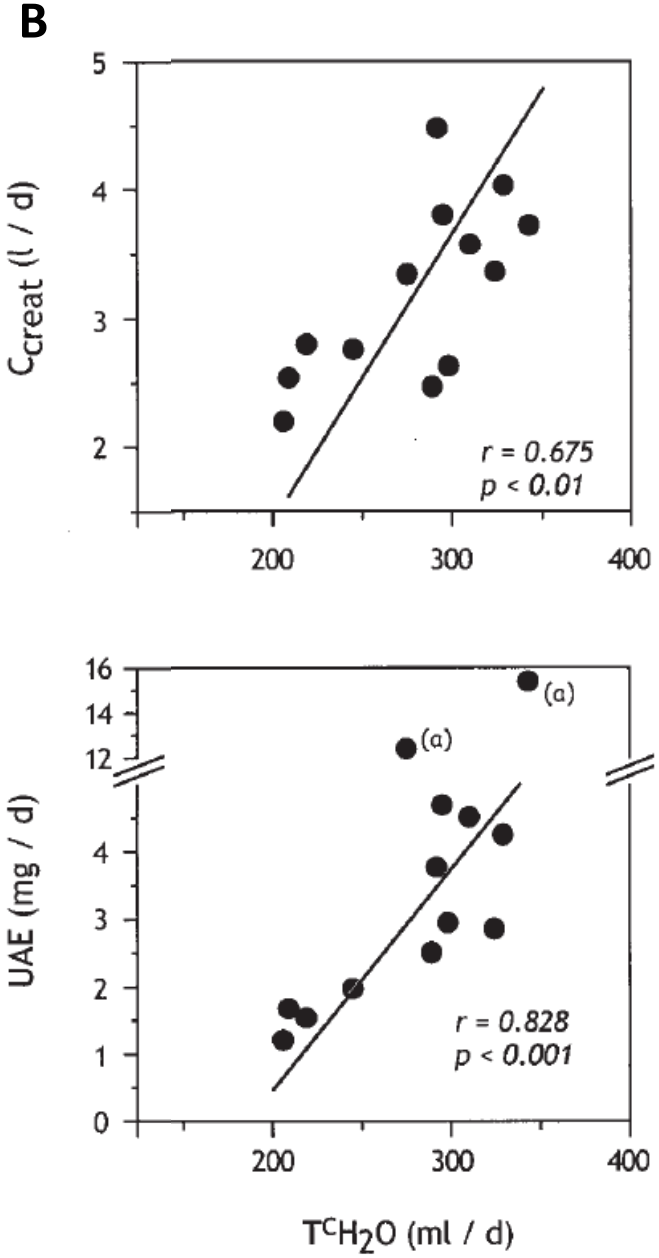

All subjects
Renal events (%)
20
10
0
T3
T2
T1
0
500
1000
1500
2000
Macroalbuminuric subjects
Renal events (%)
30
20
10
0
T3
T2
T1
0
500
1000
1500
2000
Follow-up (days)


Plasma glucose (mmol/L)
40
30
20
10
0
***
***
Cont.
DM
Cont.
DM
Normal AVP
No AVP
Creatinine clear. (ml/min)
4
3
2
1
0
**
Cont.
DM
Cont.
DM
Normal AVP
No AVP
Urinary albumin excr. (mmol/d)
4
3
2
1
0
***
Cont.
DM
Cont.
DM
Normal AVP
No AVP
2 Kidney weight (g/300 g)
4
3
2
1
0
***
***
Cont.
DM
Cont.
DM
Normal AVP
No AVP

Roussel et al, Vasopressin and diabetic nephropathy

Figure 4





Roussel et al, Figure 5