SEX DIFFERENCE IN URINE CONCENTRATION ACROSS DIFFERING AGES, SODIUM INTAKE AND LEVEL OF KIDNEY DISEASE

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Short title: Sex difference in urine concentration

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ABSTRACT

Men are known to be at greater risk of urolithiasis and cardiovascular and renal diseases than women. Previous studies suggest that greater urine concentration is associated with acceleration of progression of chronic kidney disease (CKD), increased urinary albumin excretion and delayed renal sodium excretion. The present review addresses possible sex-related differences in urine volume and osmolality ($U_{\text{osm}}$) which could participate in this male risk predominance. Because of the scarcity of information, we reanalyzed 24h urine data collected previously by different investigators for other purposes. In nine studies concerning healthy subjects (six studies) or patients with CKD or diabetes mellitus, $U_{\text{osm}}$ (or another index of urine concentration based on the urine/plasma creatinine concentration ratio) was 21 - 39 % higher (i.e., about a 150 mosm/kg $H_2O$ difference) in men than in women. Urine volume was not statistically different. Thus, the larger osmolar load of men (related to their higher food intake) is excreted in a more concentrated urine with no difference in urine volume. This sex difference was not influenced by the level of sodium excretion and was still present in CKD patients. Sex differences in thirst threshold, AVP level, and other regulatory mediators may all contribute to the higher male $U_{\text{osm}}$. Because of the previously demonstrated adverse effects of vasopressin and/or high urine concentrating activity, the greater tendency of men to concentrate urine could participate in their greater susceptibility to urolithiasis and hypertension and to the faster progression towards end-stage renal failure.

KEY WORDS

Lithiasis, Sodium intake, Vasopressin, Thirst, Urine volume
There is a sex-related difference in susceptibility to renal and cardiovascular diseases which includes a higher male prevalence of urolithiasis (24, 46), hypertension and chronic kidney disease (CKD) as well as a faster rate of progression of CKD (40, 48, 51, 66). A similar sex difference is found in rats (13, 47, 58). Several experimental studies have revealed adverse effects of vasopressin, through its V2 receptor-mediated effects and/or the resulting urine concentration on progression of CKD (17, 18), albuminuria of diabetes mellitus (DM) (11) and hypertension (28). It is thus interesting to evaluate if sex differences in urine concentration could contribute to the greater male susceptibility to vascular and renal diseases. The amount of information in this field is surprisingly small. Urine osmolality is rarely measured in clinical investigations and urine volume, even when used for calculation of 24h excretions, is rarely reported. This prompted us to gather and reanalyze data obtained for other purposes in previous clinical investigations to characterize possible sex differences in urine concentration which could play a role in the male predominance of lithiasis, hypertension and progression of CKD.

DIRECT AND INDIRECT EVALUATION OF URINE CONCENTRATION

Studies A to G concerned healthy subjects of various ages (7, 15, 32, 36, 38, 50, 65) while studies R, S and T included patients with CKD or DM (4, 5, 36) (see Table 1). In all studies (except study G), 24h urine was collected in subjects of both sexes that were in steady state on an ad lib diet and fluid intake. Investigators from the initial studies provided demographic information (see Table 2) along with measurements of 24h urine volume and sodium and potassium concentrations (U\textsubscript{Na} and U\textsubscript{K}, respectively). In some studies, plasma and urine creatinine concentration (P\textsubscript{creat} and U\textsubscript{creat}, respectively), urine urea concentration (U\textsubscript{urea}), or urine osmolality (U\textsubscript{osm}) were also available.

The 24h urine volume was measured in all studies (except study G) but U\textsubscript{osm} was available only in studies A, B, G and S. In the others, the level of urine concentration was evaluated in two different ways. When U\textsubscript{Na}, U\textsubscript{K} and U\textsubscript{urea} were
available (studies C, D, and R), an estimated value of urine osmolality (eU_{osm}) was calculated according to the formula: eU_{osm} = (U_{Na}+U_{K})*2 + U_{urea}. Highly significant and similar correlation coefficients were found between U_{osm} and eU_{osm} for men and women in studies A+B (combined because they both concern French subjects of similar age) (r=0.95 and 0.97, respectively), and in study S (0.92 and 0.92, respectively) (p<0.001 for each). The slopes of the regression lines were about 8-12% lower than unity (with no significant sex difference) which indicates that eU_{osm} underestimates slightly true U_{osm}, likely because the formula for calculation of eU_{osm} does not take into account the minority solutes. In the remaining three studies (E, F and T), P_{creat} and U_{creat} allowed an indirect evaluation of the kidney’s tendency to concentrate urine. Because water but not creatinine is progressively reabsorbed along the successive nephron segments, tubular fluid creatinine concentration increases above the plasma value. Thus, the ratio U_{creat} / P_{creat} provides a relative index of urine concentration (UCI). In the two studies in which both U_{osm} and UCI were available, UCI was linearly and positively correlated with U_{osm} (r=0.86 and 0.89 in healthy men and women of study A and 0.82 and 0.82 in CKD patients of study S). The equations of the regression lines did not differ significantly between men and women in either study. Tubular secretion of creatinine could increase UCI and lead to an overestimation of the kidney’s tendency to concentrate urine, but this secretion becomes significant only when plasma creatinine is elevated (39), as in CKD or during infusion of exogenous creatinine (as used in older studies) (31, 42). A higher renal secretion of creatinine in males could induce a bias because testosterone has been shown to stimulate this secretion in rats (31). But, among the large number of more recent investigations that have explored 24h endogenous creatinine clearance and a more reliable marker of GFR, none has mentioned a greater discordance between the two variables in males than females (33, 35, 49).

**URINE CONCENTRATION IN MEN AND WOMEN**

The age and BMI were very close in men and women in all studies (Table 2). Food intake was likely higher in men than in women (men/women ratio for 24h osmolar excretion >1). In every case, whether involving healthy subjects or
patients with DM or CKD, $U_{osm}$, $eU_{osm}$ or UCI was higher in men than in women by 15-39% (significant except in studies with n<20 per sex). The male/female ratios obtained with UCI fell in the same range as those obtained with $U_{osm}$ or $eU_{osm}$, Table 2. In 5/9 studies, 24h urine volume was almost similar in men and women (within ±5%) and in the others, it was 10-14% lower in men. To our knowledge, only one prior study reported urine volume and osmolality in men and women separately (21). It shows similar differences as those observed here ($U_{osm} = 678±39$ and 493±34 mosm/kg H$_2$O in men and women respectively, p<0.05; urine volume =1.37±0.09 and 1.54±0.09 L/d, NS; male/female ratio =1.38 for $U_{osm}$ and 0.88 for volume). Rats and dogs also show male/female ratios of $U_{osm}$ of similar magnitude as humans (1.16 to 1.24) (27, 34, 44).

It is interesting to note the wide inter-individual variability in 24h urine concentration (Fig. 1) and volume (0.5 to 5.4 L/24h in all studies together, not shown) among healthy subjects, probably related to a parallel variability in thirst, fluid intake and plasma vasopressin ($P_{AVP}$) (67). Within the 24h cycle, $U_{osm}$ is highest at night and increases after a protein-rich meal (30). However, the sex difference in $U_{osm}$ does not result from a proportionately higher protein intake in men because we verified that the proportion of urea in the urine did not differ in the two sexes. Differences in sodium intake are not involved since selective changes in dietary sodium over a relatively wide range do not alter $U_{osm}$ in either sex, as shown in study D (Table 3). Two-way ANOVA showed a significant sex difference for $U_{osm}$ and volume (p<0.002 for each) but no influence of sodium itself and no interaction. Urine concentrating ability declines with age and linear regression of $U_{osm}$ vs. age in subjects of study D shows a decline (p<0.0003) by about 50 mosm/kg H$_2$O per decade, maintaining a significant sex difference across ages (p=0.005) (Fig. 2A).

Subjects with CKD or DM exhibited a sex difference in $U_{osm}$ similar to that in healthy subjects (Table 1). Fig. 2B illustrates the decline in $U_{osm}$ as a function of the degree of renal failure in study S. Two-way ANOVA revealed differences for sex and CKD class (p<0.0001 for each) with a significant interaction (p=0.001). $U_{osm}$ declined progressively in men and more abruptly in women. In the same study, a sample of early morning urine was about 50-100 mosm/kg H$_2$O higher than the 24h average, even in CKD stages III and IV, showing that
the concentrating activity of the kidney is still increasing at night throughout most of the disease progression.

POSSIBLE CAUSES OF THE SEX DIFFERENCE IN URINE OSMOLALITY

It is unlikely that sex hormones directly influence urine concentration since a higher $U_{\text{osm}}$ and similar urine volume were already present in boys compared to girls before puberty, and urine concentration did not vary with age in either sex from 4 to 15 y (26). Further, the difference in $U_{\text{osm}}$ remained significant in women after the age of menopause in study D (Fig. 2A) and C (all above 50 y). Finally, $U_{\text{osm}}$ was not altered 5 weeks after gonadectomy in male and female rats (27).

Because men excrete a higher osmolar load through an increase in urine concentration rather than in urine volume, it may be assumed that their thirst/vasopressin system has higher thresholds than those of women, and that they drink proportionally less. However, information is lacking to document these differences. One study reported of a higher water intake in female vs. male rats (62). Some studies (1, 22, 54), but not all (21), reported higher values for and/or urinary vasopressin in men than in women, a difference also observed in rats (54). Vasopressin secretion seems to be more sensitive to osmotic stimuli (e.g., hypertonic saline infusion) in males than in females in rats and humans (43, 56).

However, a higher plasma vasopressin is not sufficient to explain the sex difference in urine concentration because study G showed that the difference in $U_{\text{osm}}$ was not abolished during maximal stimulation of the urinary concentrating mechanism, at least in an acute situation. Six healthy subjects (3 of each sex) were infused with a high dose of dDAVP (a selective V2 receptor agonist of vasopressin) (7, 15). $U_{\text{osm}}$ rose from 835±150 to 955±10 mosm/kg H$_2$O in men and from 540±140 to 775±20 mosm/kg H$_2$O in women. This observation suggests that the higher urine concentration in men than women involves downstream events, probably in the kidney itself, although clearly more data is required. Animal studies support a sex difference in vasopressin actions (55).
The male kidney is more sensitive to vasopressin because the antidiuretic response to exogenous hormone was greater in male than female rats (61, 64). In addition, papillary collecting duct cells from male rats exhibit more V2 receptors and a greater vasopressin-induced cAMP accumulation than those from females (64). A higher male sensitivity to vasopressin in humans is also suggested by the higher $U_{osm}$ observed in men than women who exhibited similar $P_{AVP}$ (21).

Because prostaglandins or a high medullary blood flow are known to interfere with the antidiuretic effect of vasopressin and the ability to concentrate urine (14, 25, 37), known sex differences in the production of prostaglandins (45, 60, 63) and in medullary or papillary blood flow (27) could also play a role in the greater male urine concentration.

POSSIBLE CONSEQUENCES OF THE SEX DIFFERENCE IN URINE OSMOLALITY

The higher tendency of men to concentrate urine compared to women may participate in their higher susceptibility to several diseases or their more severe rate of progression, including urolithiasis, CKD and some forms of hypertension.

Urolithiasis is 2-3 times more frequent in men than in women (20, 23, 57) but to our knowledge, no study has considered the possibility that a difference in urine concentration could contribute to this sex difference. The higher $U_{osm}$ in men will obviously favor the occurrence of supersaturation which is responsible for crystallization of relatively insoluble compounds (24). In study C, almost half of the men but only 5% of the women had 24h urine exceeding 600 mosm/kg H$_2$O (Fig. 1A), illustrating the greater risk in men. Even if the concentration of relatively insoluble solutes does not reach supersaturation threshold in the pooled 24h urine, it may well exceed it during transient episodes of higher concentration occurring after protein-rich meals, at night or during intense physical exercise, especially in summer, a season during which men show a remarkable decrease in urine volume (46).
Vasopressin and/or the resulting rise in urine concentration, influence renal function in different ways. Chronic stimulation of urine concentrating activity by dDAVP in normal rats increases GFR (16) and urinary albumin excretion (10) and induces a hypertrophy of the kidney that resembles that induced by a high protein intake (6, 8). In rats with experimental CKD, detrimental effects of V2 receptor stimulation or beneficial effects of their inhibition were reported on proteinuria, glomerulosclerosis and tubulo-interstitial injury (17, 18, 59). V2 receptor activation also participates in the rise in albuminuria observed in rat models of DM and salt-sensitive hypertension (10-12, 28). Because of the sex difference in U_{osm}, all these effects may be more pronounced in males vs. females. The antidiuretic action of vasopressin probably adds its influence to that of the renin-angiotensin system (3, 10, 48, 51, 66) when the intensity of both systems is increased in response to their respective stimuli.

Another potentially adverse effect of vasopressin could result from the direct stimulation of sodium reabsorption in the collecting duct mediated by the activation of the epithelial sodium channel, ENaC (41, 52). This effect is most likely responsible for the diminished ability of healthy humans to excrete sodium (7, 19). It is detectable only above a certain threshold of ~ 500-600 mosm/kg H_{2}O (2, 7, 9) and thus, should affect males more than females. Interestingly, after an infusion of hypertonic saline (3 % NaCl), sodium excretion increased less in men than in women, and only men showed an increase in systolic and pulse pressures, suggesting a hypertensive shift in the pressure-natriuresis curve associated with an increase in extracellular fluid volume (56). These observations suggest that vasopressin could play a role in salt-sensitive hypertension as shown in rats (28).

In summary, the present investigation shows, in several independent studies performed in France and in the USA, that men concentrate urine more than women in free living conditions on their usual diet and spontaneous fluid intake. This difference does not seem to depend on direct effects of sex hormones and is not influenced by the level of sodium intake. It is still present during aging and in CKD. Whether this difference plays a role in the greater
prevalence of urolithiasis and hypertension in men and in their faster CKD progression remains to be evaluated. Hopefully, this review will stimulate further studies addressing this issue and including simultaneous measurements of thirst, fluid intake, $P_{AVP}$, $U_{osm}$ and $TH_2O$ in men and women. Newly developed vasopressin V2 receptor antagonists (29, 53) will also represent useful tools for evaluating in humans the possible adverse consequences of the concentrating activity of the kidney, with special attention to sex differences.
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- Marie-Marchelle TRINH-TRANG-TAN (INSERM, Unité 665, INTS, Paris, France) (study B);
- Paul R. CONLIN (Department of Medicine, Brigham and Women's Hospital, Boston, M, USA) (study D);
- Myron H. WEINBERGER (Department of Medicine, Indiana University School of Medicine, Indianapolis, USA) (study E);
- Susie Q. LEW (Department of Medicine, Renal Division, George Washington University Medical Center, Washington D.C., USA) (studies F and T);
- Daniel G. BICHET (Research Center and Nephrology Service, Hopital du Sacre-Cœur, Montreal, Quebec, Canada) (study G);
- Bernard BAUDUCEAU (Service d'Endocrinologie, Hôpital Begin, Saint-Mandé, France) (study R);
- Paul JUNGERS (Service de Néphrologie, Hôpital Necker, Paris, France) (study S);

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REFERENCES


FIGURE LEGENDS

Fig. 1. Individual values and means ± SE of urine osmolality (eUosm) or concentration index (UCI) in men and women of studies C and E. Note the wide dispersion of individual values over a 5-fold range.

Fig. 2. A. Urine osmolality in men and women in the different age categories in subjects of study D during the run-in period. B. Evolution of urine osmolality in men and women of study S according to the different classes of CKD (I to V). Means ± SE for men (closed circles) and women (open circles). The dashed lines indicate iso-osmolality to plasma. The relatively large SEs in the first age and CKD classes are probably due to the small number of subjects of each sex in these classes. When SEs are not visible, they are smaller than the symbols. Comparison by two-way ANOVA (sex and CKD, or sex and age). The sex difference was significant in both cases.
TABLE TITLES AND LEGENDS

Table 1. Title. General information regarding the ten studies used to evaluate urine concentration.

Legend. (a) The references indicated here are those of the initial studies. In the present review, new analyses were performed in men and women separately (shown in Table 2), using the raw data provided by one of the authors.

Table 2. Title. Demographics and 24 h urine data in men (M) and women (W) of nine independent studies.

Legend. Values are means ± SE. Hth = healthy subjects, DM = subjects with diabetes mellitus, CKD = subjects with chronic kidney disease. The men to women ratio (M/W) for each variable in each study was calculated using the means observed in each sex. Student’s t test between men (M) and women (W): *, p < 0.05; **, p < 0.01; ***, p < 0.001.

Table 3. Title. Twenty four hour urine data in men and women of study D on the control diet with three different levels of sodium intake.

Legend. Low, medium and high = target sodium intakes of 50, 100, or 150 mmol/d, respectively) one month each in random order. Values are means ± SE. Comparison by two-way ANOVA (sex and sodium intake).
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<table>
<thead>
<tr>
<th>n</th>
<th>Age range</th>
<th>Subjects</th>
<th>Author who provided the data</th>
<th>Institution</th>
<th>Related references (a)</th>
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<td>Healthy subjects</td>
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<td></td>
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<tr>
<td>A</td>
<td>37</td>
<td>20 - 45 Volunteers undergoing clinical investigations + potential kidney donors</td>
<td>A Hadj-Aissa</td>
<td>Hôpital Edouard Herriot, Lyon, France</td>
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<td>C</td>
<td>117</td>
<td>50 - 69 Subset of subjects from the SU.VI.MAX. cohort</td>
<td>S Hercberg</td>
<td>Several centers in France</td>
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<td>D</td>
<td>378</td>
<td>≥ 22 Subjects of the DASH-Na study during the run-in period or after one month on different sodium intakes</td>
<td>PR Conlin</td>
<td>Brigham and Women's Hospital, Boston, USA, and several centers in the USA</td>
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<td>E</td>
<td>141</td>
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<td>38, 65</td>
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<td>F</td>
<td>37</td>
<td>≤ 50 Healthy subjects</td>
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<td>G Washington University Medical Center, Washington D.C., USA</td>
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<td>31 ± 4 Volunteers undergoing investigations of urine concentration</td>
<td>DG Bichet</td>
<td>Hôpital du Sacré-Cœur, Université de Montréal, Montréal, Canada</td>
<td>15, 7</td>
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<tr>
<td>R</td>
<td>65</td>
<td>21 - 79 Patients with DM (regular follow-up)</td>
<td>B Bauduceau</td>
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<tr>
<td>S</td>
<td>148</td>
<td>17 - 86 Patients with CKD (regular follow-up)</td>
<td>P Jungers</td>
<td>Hôpital Necker-Enfants Malades, Paris, France</td>
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</tr>
<tr>
<td>T</td>
<td>33</td>
<td>22 - 66 Patients with CKD from a variety of causes</td>
<td>SQ Lew</td>
<td>G Washington University Medical Center, Washington D.C., USA</td>
<td>36</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Condition</th>
<th>n</th>
<th>Age</th>
<th>BMI</th>
<th>U_{osm}, eU_{osm} or UCI</th>
<th>Urine volume</th>
<th>Osmolar excretion</th>
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<tbody>
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<td></td>
<td></td>
<td></td>
<td>y</td>
<td>kg / m²</td>
<td>mosm / kg H₂O</td>
<td>L / 24 h</td>
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<tr>
<td></td>
<td>M , W</td>
<td>M</td>
<td>W</td>
<td>M</td>
<td>W</td>
<td>M / W</td>
<td>M / W</td>
</tr>
</tbody>
</table>

**URINE OSMOLALITY**

A  | Hth  | 24 , 13 | 35 ± 2 | 33 ± 2 | 24 ± 1 | 22 ± 1 * | 644 ± 35 | 508 ± 56 | 1.27 * | 1.78 ± 0.11 | 2.07 ± 0.30 | 0.86 | 1.22
B  | Hth  | 15 , 12 | 33 ± 2 | 38 ± 3 | 23 ± 1 | 21 ± 1 | 689 ± 47 | 551 ± 71 | 1.25 | 1.34 ± 0.13 | 1.39 ± 0.18 | 0.96 | 1.28
C  | Hth  | 55 , 62 | 59 ± 1 | 59 ± 1 | 25 ± 1 | 24 ± 1 | 578 ± 21 | 416 ± 16 | 1.39 *** | 1.64 ± 0.07 | 1.86 ± 0.06 | 0.88 * | 1.22
D  | Hth  | 163 , 215 | 48 ± 1 | 49 ± 1 | 29 ± 1 | 30 ± 1 * | 597 ± 17 | 521 ± 15 | 1.15 *** | 1.73 ± 0.06 | 1.47 ± 0.05 | 1.18 *** | 1.39
R  | DM   | 35 , 30 | 58 ± 3 | 58 ± 2 | 29 ± 1 | 32 ± 1 | 507 ± 30 | 418 ± 26 | 1.21 * | 1.87 ± 0.13 | 1.86 ± 0.10 | 1.00 | 1.17
S  | CKD  | 87 , 61 | 62 ± 2 | 57 ± 2 | 25 ± 1 | 24 ± 1 | 435 ± 17 | 337 ± 16 | 1.29 *** | 1.92 ± 0.08 | 2.18 ± 0.10 | 0.88 * | 1.13

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E  | Hth  | 90 , 51 | 24 ± 1 | 27 ± * | 25 ± 1 | 25 ± 1 | 149 ± 6 | 125 ± 6 | 1.19 ** | 1.45 ± 0.08 | 1.51 ± 0.09 | 0.96 | 1.13
F  | Hth  | 18 , 19 | 30 ± 2 | 33 ± 2 | 24 ± 1 | 25 ± 1 | 145 ± 20 | 120 ± 14 | 1.21 | 1.33 ± 0.14 | 1.48 ± 0.18 | 0.90 | 1.15
T  | CKD  | 18 , 15 | 45 ± 3 | 44 ± 3 | 28 ± 1 | 27 ± 2 | 32 ± 4 | 25 ± 4 | 1.30 | 2.56 ± 0.17 | 2.43 ± 0.16 | 1.05 | 1.37

(a) In studies C, D, and R, U_{osm} was not measured. An estimation of U_{osm} (eU_{osm}) was calculated (see text).
Values are means ± SE. Hth = healthy subjects, DM = subjects with diabetes mellitus, CKD = subjects with chronic kidney disease. The men to women ratio (M/W) for each variable in each study was calculated using the means observed in each sex.
In all studies, subjects were on a free ad lib diet and fluid intake. For Study D, data reported here corresponds to the run-in period.
Student's t test between men (M) and women (W): *, p < 0.05; **, p < 0.01; ***, p < 0.001.
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<table>
<thead>
<tr>
<th>Sodium DIET</th>
<th>Na excretion (mmol / 24 h)</th>
<th>U_{osm} (mosm / kg H2O)</th>
<th>Urine volume (L / 24 h)</th>
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<tbody>
<tr>
<td></td>
<td>M</td>
<td>W</td>
<td>M / W</td>
</tr>
<tr>
<td>Low</td>
<td>67 ± 4</td>
<td>62 ± 4</td>
<td>1.08</td>
</tr>
<tr>
<td>Medium</td>
<td>118 ± 5</td>
<td>95 ± 4</td>
<td>1.24</td>
</tr>
<tr>
<td>High</td>
<td>159 ± 5</td>
<td>126 ± 5</td>
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