Acute sodium loading in patients with uncomplicated diabetes mellitus: renal and hormonal effects

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1. Diabetes mellitus is associated with high body sodium, but the pathogenetic mechanism is still unknown. The possibility that an abnormal renal handling of sodium, an abnormal responsiveness of sodium-modulating factors or a shift in the set point for sodium metabolism may contribute to or be associated with sodium retention was tested with an acute saline infusion.

2. A consecutive sample of 33 patients with stable non-azotaemic diabetes mellitus (24 insulin-dependent patients) and 30 normal control subjects was studied. Two litres of a 0.9% NaCl infusion were infused over 4 h. The urinary sodium excretion during the infusion and the next 18 h was analysed in relation to blood pressure, creatinine and lithium clearances, Na⁺-K⁺ co-transport, Na⁺-Li⁺ countertransport, plasma levels of renin, angiotensin II, aldosterone, noradrenaline, adrenaline, atrial natriuretic factor and digoxin-like factor.

3. Diabetic patients and control subjects did not differ in blood pressure, body mass index, clearances of creatinine, sodium or lithium, intracellular sodium, Na⁺-K⁺ co-transport and Na⁺-Li⁺ countertransport, urinary and plasma levels of digoxin-like factor, plasma renin activity, angiotensin II, aldosterone, noradrenaline, adrenaline and atrial natriuretic factor. The intravenous saline infusion caused a similar natriuresis in diabetic patients and normal subjects; the renin-angiotension-aldosterone system was suppressed to a higher degree in diabetic patients than in normal subjects, whereas atrial natriuretic factor was stimulated to a similar extent; plasma digoxin-like activity was unchanged in both groups.

4. The natriuretic response to saline infusion was comparable between patients with insulin-dependent and non-insulin-dependent diabetes mellitus, those with lower or higher HbA1c levels and those with positive or negative family history of essential hypertension.

5. Using an acute saline infusion to study sodium-modulating factors, no abnormality can be detected which could represent a pathogenetic mechanism for sodium retention in diabetes mellitus. The normal natriuretic response to acute sodium loading in diabetic patients indicates that the set point for sodium homeostasis may be normal despite the presence of high exchangeable sodium.

INTRODUCTION

Diabetes mellitus is associated with an increase in body sodium [1]. The pathogenetic mechanism leading to sodium retention is poorly understood. High blood glucose concentration activates sodium-glucose co-transport in the proximal renal tubule, but sodium retention may develop in the absence of hyperglycaemia [2]. Acute hyperinsulinaemia reduces sodium excretion in normal subjects [3] and diabetic patients [4]. The effects of a long-term hyperinsulinaemia on sodium homeostasis are not known; in experimental models, after a 7 day insulin infusion, a positive sodium balance was observed in dogs [5], whereas no sodium retention occurred in rats [6]. Variations in the activity of sodium-retaining hormones such as angiotensin II, aldosterone or catecholamines cannot explain sodium retention [1]. Although a decrease in the glomerular filtration rates augments the degree of sodium retention [7], high body sodium occurs in diabetic patients with a normal renal functional state [1]. This does not exclude the possibility that the kidney could play at least a permissive role in the development or maintenance of high body sodium. Certain findings, such as a decreased natriuretic response to water immersion [8] or acute saline infusion [9], suggest that the diabetic kidney may retain sodium more avidly than the non-diabetic kidney. Na⁺-Li⁺ countertransport and the Na⁺-H⁺ exchange are frequently increased in hypertensive diabetic patients [10]; it has been suggested that a high Na⁺-Li⁺ countertransport may be associated with

Key words: aldosterone, atrial natriuretic factor, diabetes mellitus, ouabain-like factor, plasma renin activity, sodium, sodium-lithium countertransport, sodium-potassium co-transport.

Abbreviations: ANF, atrial natriuretic factor; +FH, positive family history of hypertension; —FH, negative family history of hypertension; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; PRA, plasma renin activity.

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an increased sodium reabsorption in the proximal renal tubule [11]. Finally, a lack of natriuretic factors should also be considered; a blunted natriuretic response to atrial natriuretic peptide has been reported in patients with insulin-dependent diabetes [12].

The natriuretic response to an acute sodium load has been frequently utilized to investigate the renal handling of sodium. Using this approach, subtle abnormalities have been demonstrated in certain clinical conditions, including patients with essential hypertension [13] and normotensive offspring of hypertensive parents [14]. The natriuretic response to a saline infusion was therefore investigated in patients with diabetes mellitus as compared with normal subjects. In order to obtain an integrated analysis of sodium-modulating factors, the natriuresis was analysed in relation to blood pressure, the renal functional state, \( \text{Na}^+ - \text{K}^+ \) co-transport, \( \text{Na}^+ - \text{Li}^+ \) countertransport, components of the renin–angiotensin–aldosterone system, humoral indicators of sympathetic nervous activity, atrial natriuretic factor (ANF) and digoxin-like activity.

**METHODS**

Thirty normal subjects and 33 patients with diabetes mellitus were studied in the Hypertension Unit of the Ospedale Italiano. Normal subjects included 18 males and 12 females, ranging in age from 17 to 58 years (mean ± SD, 35 ± 17 years); they had a normal fasting plasma glucose concentration and a blood pressure consistently below 140/90 mmHg. None of the subjects was taking oral contraceptives, aspirin or non-steroidal anti-inflammatory agents. The diabetic patients included 17 males and 16 females, ranging in age from 16 to 64 years (mean ± SD 44 ± 14 years). Six diabetic patients were following diet treatment, three were treated with diet and oral hypoglycaemic agents (non-insulin-dependent diabetes mellitus, NIDDM) and 24 with diet and insulin (insulin-dependent diabetes mellitus, IDDM). The metabolic state, as judged by serum glucose levels, was stable during the 3 months preceding the investigation. None of the patients suffered from cardiovascular complications including peripheral arteriopathy, congestive heart failure, angina, myocardial infarction, arrhythmia and ischaemic cerebral disease, or was taking antihypertensive agents, diuretics, digitalis, aspirin, non-steroidal anti-inflammatory agents or potassium supplements. All had a blood pressure consistently below 140/90 mmHg and a urinary microalbumin excretion <30 μg/min; four of the diabetic patients had background retinopathy. A positive or negative family history of essential hypertension (+FH or −FH, respectively) was defined as reported previously [15]. All subjects and patients were informed about the investigative nature of the study and gave their informed consent. The protocol of the study was approved by the ethical committee of our institution.

To avoid very low or high sodium intakes, we instructed all subjects to adhere to their usual diet but not to add salt to their food. Compliance with the diet was monitored by determination of the 24 h urinary sodium excretion. Measurements were performed at least twice during the week preceding the study and required to be between 100 and 170 mmol; when the natriuresis was outside this range, dietary instructions were repeated and the study was postponed until the 24 h urinary excretion of sodium was within the desired range. The dose of insulin or hypoglycaemic agents and carbohydrate intake were not altered. The following investigations were performed.

1. A 24 h urine sample was collected for determination of sodium, potassium, creatinine, glucose, albumin (microalbuminuria) and digoxin-like factor. At 20.00 hours, the subjects took 14 mmol of lithium (500 mg of lithium carbonate). At the end of the collection period, at 08.00 hours, an intravenous cannula was inserted into a forearm vein and a 2 h urine collection was performed for determination of creatinine, sodium, potassium and lithium excretion rates; at the end of this period, after at least 60 min of rest in the supine position, blood pressure and heart rate were determined every 5 min using the automated recorder Dynamap 845 XT (Critikon, Tampa, FL, U.S.A.) to obtain basal values (mean of 12 determinations), and blood was collected for determination of serum creatinine, uric acid, sodium, potassium, lithium, glucose, C-peptide, fructosamine, cation transport in erythrocytes, plasma renin activity (PRA), aldosterone, angiotensin II, noradrenaline, adrenaline, ANF and digoxin-like factor; in diabetic patients, HbA1c levels were also measured. The study was performed in the fasting state for all normal subjects and diabetic patients not receiving insulin; insulin-treated diabetic patients injected the usual morning dose of insulin and ate a light low-sodium (<5 mmol) breakfast without coffee or tea.

2. A saline infusion was started and 2 litres of 0.9% NaCl were infused over 4 h in the supine position. During the last hour of the infusion, 12 readings of blood pressure were obtained, as described above. At the end of the infusion, blood was collected for determination of serum creatinine, uric acid, sodium, potassium, glucose, PRA, aldosterone, angiotensin II, noradrenaline, adrenaline, ANF and digoxin-like factor. Urine was collected in different portions, (a) during the 4 h infusion period (10.00–14.00 hours), (b) the following 8 h (14.00–22.00 hours) and (c) 10 h (22.00–08.00 hours) for determination of the sodium, potassium and creatinine excretion rates. After the infusion was ended, the subjects received a diet containing 100 mmol of NaCl and 60 mmol of KCl/day.

Plasma and urinary sodium and potassium were determined by flame photometry (IL 943, Instru-
Acute sodium loading in diabetic patients

**Table 1. Clinical and biochemical characteristics of normal subjects and diabetic patients.** Values are means ± SD. Statistical significance: \( P < 0.05, \) \( P < 0.01 \) versus normal subjects; \( P < 0.05, \) \( P < 0.01 \) versus NIDDM patients.

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>Diabetic patients</th>
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<tbody>
<tr>
<td></td>
<td>All</td>
<td>NIDDM</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35 ± 14</td>
<td>44 ± 14</td>
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<tr>
<td>Blood pressure (mmHg)</td>
<td>119/69 ± 12/10</td>
<td>116/71 ± 12/9</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>61 ± 9</td>
<td>71 ± 11</td>
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<tr>
<td>Fructosamine (μmol/l)</td>
<td>238 ± 40</td>
<td>408 ± 111</td>
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<tr>
<td>Plasma creatinine (μmol/l)</td>
<td>68 ± 13</td>
<td>57 ± 12</td>
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<tr>
<td>Plasma sodium (mmol/l)</td>
<td>140.1 ± 2.6</td>
<td>137.4 ± 2.5</td>
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<tr>
<td>Plasma potassium (mmol/l)</td>
<td>4.22 ± 0.34</td>
<td>4.39 ± 0.26</td>
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<tr>
<td>Serum glucose (mmol/l)</td>
<td>5.5 ± 1.2</td>
<td>12.6 ± 6.0</td>
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<tr>
<td>Serum C-peptide (μmol/l)</td>
<td>761 ± 293</td>
<td>417 ± 344</td>
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<tr>
<td>Na⁺-K⁺ co-transport (μmol of Na⁺ h⁻¹ l⁻¹ of erythrocytes)</td>
<td>343.7 ± 234.1</td>
<td>256.1 ± 161.8</td>
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<tr>
<td>Passive permeability of Na⁺</td>
<td>14.2 ± 8.1</td>
<td>13.1 ± 3.4</td>
</tr>
<tr>
<td>Na⁺-Li⁺ countertransport (μmol of Li⁺ h⁻¹ l⁻¹ of erythrocytes)</td>
<td>209 ± 125</td>
<td>250 ± 130</td>
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<tr>
<td>Intracellular sodium (mmol/l of erythrocytes)</td>
<td>7.03 ± 2.65</td>
<td>6.27 ± 3.14</td>
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<td>Creatinine clearance (ml/min)</td>
<td>145 ± 61</td>
<td>140 ± 36</td>
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<tr>
<td>Sodium clearance (ml/min)</td>
<td>0.82 ± 0.55</td>
<td>0.60 ± 0.46</td>
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<tr>
<td>Lithium clearance (ml/min)</td>
<td>23 ± 10</td>
<td>23 ± 11</td>
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<tr>
<td>Uric acid clearance (ml/min)</td>
<td>9 ± 4</td>
<td>12 ± 9</td>
</tr>
<tr>
<td>24h sodium excretion (mmol)</td>
<td>137 ± 38</td>
<td>113 ± 38</td>
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<tr>
<td>24h potassium excretion (mmol/l)</td>
<td>66 ± 21</td>
<td>66 ± 21</td>
</tr>
<tr>
<td>24h microalbuminuria (μg/min)</td>
<td>9.9 ± 12.7</td>
<td>9.9 ± 10.4</td>
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**RESULTS**

**Demographic features**

Normal subjects were on average younger than diabetic patients \((P=0.0058)\); this difference was due to the older age of NIDDM as compared with IDDM patients \((P=0.0505)\) (Table 1). Mean age did not differ between IDDM patients and normal subjects \((P=0.73)\). There was no significant difference between normal subjects and diabetic patients in mean body weight \((70.5±12.4 \text{ kg;} P=0.21)\), height \((171.9±8.6 \text{ cm;} P=0.12)\) and body mass index \((28)\) \((23.9±3.9 \text{ versus } 23.3±4.1 \text{ kg/m}²; P=0.54)\).

Thirteen of the normal subjects and 13 of the diabetic patients had +FH. Normal subjects with −FH or +FH did not differ in age \((33.3±12.5 \text{ versus } 35.9±15.9 \text{ years;} P=0.21)\) or BMI \((23.8±3.7 \text{ versus } 24.4±4.0 \text{ kg/m}²; P=0.37)\), diabetic patients with −FH or +FH also had similar age and BMI \((42.2±14.4 \text{ versus } 49±12.7 \text{ years;} P=0.07 \text{ and } 22.7±4.5 \text{ versus } 23.9±3.6 \text{ kg/m}²; P=0.22)\).

**Basal data**

Systolic and diastolic blood pressures did not differ between normal subjects and diabetic patients.
(P = 0.28 and 0.42), whereas heart rate averaged higher in the latter (P = 0.003), with no difference between NIDDM and IDDM patients (P = 0.46) (Table 1). Systolic and diastolic blood pressure tended to be higher (F = 3.9455-6.7317, P = 0.05) in normal subjects and diabetic patients with +FH (126/73 ± 14/11 and 122/76 ± 12/8 mmHg, respectively) than in those with −FH (115/66 ± 6/7 and 112/68 ± 10/10 mmHg).

As expected, serum glucose and fructosamine levels were higher and C-peptide levels were lower in the diabetic patients than in the normal subjects (P = 0.0001). The serum fructosamine was higher (P = 0.002) and C-peptide lower (P = 0.0001) in IDDM than in NIDDM patients (Table 1). Moreover, HbA1c averaged 8.0 ± 2.4% in non-insulin- and 9.7 ± 2.5% in insulin-treated patients (P = 0.067). These variables did not differ between normal subjects or diabetic patients with +FH and −FH.

Plasma creatinine and sodium levels were slightly lower (P = 0.007 and 0.025, respectively) in diabetic patients than in normal subjects (Table 1). The urinary excretion of sodium (P = 0.34) and potassium (P = 0.97) as well as the clearance of creatinine (P = 0.73), sodium (P = 0.10), lithium (P = 0.84) and uric acid (P = 0.13) did not differ between the two study groups. There was no difference between NIDDM and IDDM patients, except for the sodium clearance, which was lower in NIDDM than in IDDM patients and normal subjects (F = 11.712, P = 0.0025) (Table 1). All these variables did not differ between subgroups with +FH or −FH.

The 24 h urinary excretion rates of digoxin-like factor did not differ between normal subjects and diabetic patients (6.07 ± 2.3 versus 7.36 ± 6.63 ng/mmole of creatinine; P = 0.14).

The intracellular sodium content (P = 0.31), the Na⁺−K⁺ pump (P = 0.76), Na⁺−K⁺ co-transport (P = 0.10) and Na⁺−Li⁺ countertransport (P = 0.21) did not differ between normal subjects and diabetic patients (Table 1). In IDDM patients intracellular sodium and Na⁺−K⁺ co-transport tended to be, on average, lower than in NIDDM patients (P = 0.13 and 0.17, not significant) (Table 1). Ion fluxes did not differ between subgroups with +FH and −FH, except for the Na⁺−K⁺ co-transport, which tended to be higher in subjects with +FH than in those with −FH, both in control (552 ± 641 versus 314 ± 254 μmol of Na⁺/l of erythrocytes/h; P = 0.092) and diabetic patients (340 ± 110 versus 212 ± 175 μmol of Na⁺/l of erythrocytes/h; P = 0.037).

Saline infusion: clinical and biochemical findings

Blood pressure did not change significantly during saline infusion in both normal subjects (from 119/65 ± 12/10 to 122/69 ± 16/11 mmHg; P = 0.17 and 0.98) and diabetic patients (from 116/71 ± 12/9 to 118/68 ± 16/11 mmHg; P = 0.34 and 0.25); there was no difference between the two study groups (F = 2.268 and 3.3637). In contrast, the response of heart rate differed (F = 12.9182; P = 0.0007), being increased in control subjects (from 61 ± 9 to 64 ± 9 beats/min; P = 0.0009) and decreased in diabetic patients (from 71 ± 11 to 69 ± 10 beats/min; P = 0.032). The response of blood pressure or heart rate to saline infusion did not differ between subgroups with −FH or +FH (F = 0.009 to 0.9249) or between NIDDM and IDDM patients (Table 2).

The urinary excretion of sodium during the saline infusion and during the next 18 h did not differ between normal subjects and patients with diabetes (P = 0.097, 0.96 and 0.063) (Table 2). Although diabetic patients, on average, excreted 29 mmol of Na⁺ less than normal subjects during the 22 h observation period, this difference was also not significant (P = 0.20). The excretion of potassium and creatinine during and after the saline infusion was comparable between normal subjects and diabetic patients (P = 0.073–0.91) (Table 2).
urinary excretion of sodium, potassium and creatinine did not differ between subgroups with −FH or +FH (F=0.296–2.119) or between NIDDM and IDDM patients (Table 2).

When the patients were divided into those with a HbA1c concentration, >9% (‘poor’ metabolic control; n=15) and those with a HbA1c level <9% (‘good’ metabolic control), the natriuretic response to sodium was comparable during the saline infusion (54.8±34.9 versus 47.1±27.6 mmol; P=0.48) as well as during the following 8 h (120.1±77 versus 101.8±45 mmol; P=0.41) and 10 h (103.2±46.7 versus 81.8±62 mmol; P=0.30).

As compared with pre-infusion values, the saline infusion caused a significant increase in the plasma sodium level in normal subjects (from 140.1±2.6 to 141.3±2.5 mmol/l; P=0.018) and diabetic patients (from 137.4±4.4 to 138.9±3.4 mmol/l; P=0.032). In both groups there was a significant fall in serum uric acid level (from 319±73 to 293±69 μmol/l; P=0.0001 in normal control subjects and from 269±84 to 240±83 μmol/l, P=0.003 in diabetic patients) and in plasma potassium level (from 4.21±0.34 to 4.07±0.26 mmol/l, P=0.034 in normal subjects and from 4.39±0.26 to 4.19±0.27 mmol/l, P=0.0031 in diabetic patients). There was no difference in these sodium-mediated variations between the two study groups (F=0.1157–0.3951).

### Saline infusion: hormonal responses

The saline infusion caused a significant suppression of PRA, and plasma angiotensin II and aldosterone levels and stimulation of the plasma ANF level in both normal subjects and diabetic patients (Table 3). The plasma adrenaline level was unchanged during saline infusion, whereas the plasma noradrenaline level was slightly decreased (Table 3). The sodium-induced suppression of PRA and aldosterone tended to be more pronounced in diabetic patients than in normal subjects (F=5.8819, P=0.018 and F=8.0134, P=0.0063, respectively), while the response to saline infusion was comparable for plasma angiotensin II (F=1.898), noradrenaline (F=0.4913), adrenaline (F=0.2217) and ANF (F=0.1678). Furthermore, the response of the renin–angiotensin–aldosterone system, plasma catecholamines and plasma ANF was comparable between NIDDM and IDDM patients (Table 3); there was also no difference between subgroups with −FH and +FH (F=0.003–3.6539).

The hormonal response did not differ between diabetics with ‘poor’ or ‘good’ metabolic control (F=3.3509, P=0.077 for PRA, F=2.0643 for plasma aldosterone, F=4.0012; P=0.053 for plasma angiotensin II, F=1.7173 for plasma noradrenaline, F=0.3663 for plasma adrenaline and F=3.3461, P=0.078 for plasma ANF).

Plasma levels of digoxin-like factor tended to decrease after sodium infusion in both normal subjects (from 16.4±5.3 to 13.4±3.7 pg/ml; P=0.0025) and diabetic patients (from 13.7±3.4 to 10.13±4.0 pg/ml; P=0.013). However, when the plasma concentration was corrected for serum proteins, the digoxin-like factor did not change significantly during the saline infusion. There was no difference in the response to sodium between normal subjects and diabetic patients (F=0.4111), NIDDM...
or IDDM patients \((F=3.6779; \ P=0.074)\) or subgroups with \(-FH\) or \(+FH\) \((F=2.1497\) for normal subjects, \(F=2.5626\) for diabetic patients).

**DISCUSSION**

The findings of the present study indicate that the natriuretic response to a saline infusion is not abnormal in patients with uncomplicated diabetes mellitus. Moreover, the urinary sodium excretion during and after saline infusion is not affected by the quality of metabolic control, the type of diabetes or the presence of \(+FH\). Other variables, which could theoretically influence the renal handling of sodium, have been considered: these include the cation fluxes across cell membranes, the clearance of lithium as an index of proximal renal tubular reabsorption, the renin–angiotensin–aldosterone system, plasma catecholamines and the natriuretic substances ANF and digoxin-like factor. With the exception of a more pronounced suppression of PRA and plasma aldosterone during saline infusion in diabetic patients than in control subjects, all these factors were comparable between normal subjects and diabetic patients. Therefore, using the method of a rapid saline infusion, it is not possible to identify a disturbance of sodium-modulating variables, which could represent a pathogenetic mechanism leading to sodium retention in patients with non-azotaemic diabetes mellitus.

Certain factors can influence the ability of the kidney to excrete a sodium load, but their influence does not appear to differ in the two study groups. Older subjects have been shown to conserve sodium less efficiently than younger subjects \([29]\), and the fractional excretion of sodium during a saline infusion has been found to correlate positively with age in normal subjects \([9]\). In this study, there was no difference in age between normal subjects and IDDM patients. The prior dietary sodium intake \([30]\), blood pressure \([10]\) and the basal activity \([9]\) or the suppressibility of the renin–angiotensin–aldosterone system \([31]\) all affect the natriuretic response after a rapid saline infusion. The 24\(h\) urinary sodium excretion, as an index of dietary sodium intake, blood pressure, the basal activity of the renin–angiotensin–aldosterone system and the basal activity or the responsiveness to sodium of the natriuretic hormones ANF and ouabain-like factor were comparable between normal subjects and diabetic patients. \(\text{Na}^+-\text{Li}^+\), countertransport may be elevated in diabetic patients with hypertension or albuminuria \([6, 32–34]\); probably due to the absence of these complications, \(\text{Na}^+-\text{Li}^+\), countertransport was normal in our NIDDM and IDDM patients. \(+FH\) may be associated with a blunted natriuretic response to a saline infusion \([14]\); the sodium excretion during and after infusion did not differ between our normal subjects with \(+FH\) or \(-FH\) and the same observation was made recently in 11 subjects with \(+FH\) as compared with appropriate controls \([35]\). In the diabetic group the urinary sodium excretion was also comparable between \(-FH\) \((260\text{ mmol}/22\text{ h})\) and \(+FH\) \((256\text{ mmol}/22\text{ h})\) patients. Only the sodium-mediated suppression of PRA and plasma aldosterone tended to be more pronounced in diabetic patients than in normal subjects, but, considering the comparable level of these hormones at the end of the infusion, it appears unlikely that this difference may have been of major relevance in the modulation of sodium excretion.

A previous study of seven male IDDM patients \([5]\) described a diminished natriuretic response after a rapid saline infusion. In that study, two litres of saline were infused over 2\(h\), and the diabetic patients excreted 14\(\text{ mmol}\) of sodium and the normal subjects 34\(\text{ mmol}\) of sodium over 4\(h\). The value obtained in control subjects is much lower than that observed in our study or in normal subjects studied previously \([10]\) by a similar protocol. Moreover, only four of our 33 diabetic patients excreted less than 20\(\text{ mmol}\) of sodium (the upper limit of urinary sodium for diabetic patients in that study) during the saline infusion; this does not support the presence of a subpopulation with a low sodium excretion. The diabetic patients in the previous investigation were studied under conditions of normoglycaemia and of hyperinsulinaemia \([10]\). Our patients were hyperglycaemic during the infusion procedure; although plasma insulin was not measured, we can assume that they were also hyperinsulinaemic, since plasma C-peptide levels were high in NIDDM patients and exogenous insulin was injected before the study in IDDM patients. Considering that in the present study the degree of blood glucose elevation was more marked in IDDM than in NIDDM patients but the natriuretic response was similar, it is hard to admit that the difference in glycaemia may entirely explain the large difference in natriuretic response between this and the previous study. The level of body sodium, which is determined by the interaction of dietary sodium intake and sodium-retaining or natriuretic forces, should also be considered among the determinants of the natriuretic response to an acute sodium load \([36]\). It has been suggested that there is a basal level of body sodium, which is reached when the sodium intake is very low; if the body sodium falls below this level, any additional sodium will be retained; if the body sodium lies above it, any extra sodium will be excreted \([37]\). This basal level of body sodium has also been called the set point for sodium homoeostasis \([38]\). Under certain circumstances, the set point can be shifted. Patients with primary hyperaldosteronism have, on average, a 16\% increase in body sodium \([39]\), and, when placed on a very low sodium intake, reduce their sodium excretion very quickly, suggesting that they carry very little extra sodium \([40]\). Moreover, they excrete an acute sodium load very quickly \([9]\). This suggests that the set point has been reset. Patients with
diabetes mellitus resemble patients with primary hyperaldosteronism in that they have an increased exchangeable body sodium [41]. As recently reviewed, this abnormality has been uniformly demonstrated in all studies including diabetic patients [42]. Despite the high exchangeable sodium, diabetic patients do not show a natriuretic hyperresponsiveness to a saline infusion. This suggests that an elevated body sodium per se is not sufficient to alter the set point for sodium homoeostasis, but that a second factor, such as an abnormal adrenal secretion of aldosterone, may be required. On the other hand, an abnormal natriuretic response may occur in the presence of a normal exchangeable body sodium, as in patients with essential hypertension [43, 44]. In the latter it is still unknown whether the set point for sodium homoeostasis may be shifted. Certain observations suggest that it could be, since the biological half-life of sodium is prolonged in essential hypertension [45] and the time required to achieve sodium balance after dietary changes may be increased in salt-sensitive hypertensive patients [46].

Several abnormalities in the acute regulation of PRA and plasma aldosterone have been noted in diabetic patients [47], although basal values are frequently normal [48]. Plasma levels of ANF have been reported to be elevated in 23 euglycaemic IDDM patients [49] or normal in non-nephropathic hyperglycaemic IDDM patients [50, 51]. The responsiveness of ANF to isotonic volume expansion in IDDM patients was reported to be abnormal after infusion of 90 mmol of sodium/1.73 m² and normal after infusion of 121 mmol of sodium/1.73 m² [48]. In this study, on average, basal plasma levels of PRA, angiotensin II, aldosterone, catecholamines and ANF did not differ between normal subjects and diabetic patients; with infusion of a large amount of sodium (approximately 240 mmol/1.73 m²) there was a similar responsiveness of ANF, plasma catecholamines and angiotensin II in the two study groups, whereas PRA and plasma aldosterone tended to be more suppressed in diabetic patients. Plasma and urinary levels of digoxin-like factor have not been previously reported in patients with diabetes mellitus. The substance measured in our assay is a low-molecular-mass factor binding specifically to antidigoxin antibodies, which rapidly and reversibly inhibits Na⁺/K⁺-ATPase from mammalian tissues and competitively prevents digoxin binding to its cellular receptor [23]. Excretion of the substance in the urine is highly correlated with fractional excretion of sodium both in normal subjects and in rats, and is increased in response to salt loading [23]. When infused, it elicits a natriuretic response [23]. In the present study, the basal urinary excretion rates and the plasma levels of digoxin-like factor did not differ between normal subjects and diabetic patients. Although a reduction in activity of the ouabain-sensitive Na⁺/K⁺-ATPase pump in erythrocytes of diabetic patients has been postulated [52], the present results indicating a normal Na⁺ pump and normal plasma levels of digoxin-like factor are not compatible with the hypothesis that this abnormality may be related to a high concentration of a circulating Na⁺/K⁺-ATPase-inhibiting factor.

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