Obesity-induced glomerular hyperfiltration: its involvement in the pathogenesis of tubular sodium reabsorption

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Abstract

Background. Obesity is associated with hypertension and glomerular hyperfiltration. A major mechanism responsible for the obesity-associated hypertension is renal salt retention. An increased glomerular filtration fraction (FF) is expected to raise postglomerular oncotic pressure and to increase proximal tubular sodium reabsorption. The aim of the present study was to verify whether obesity-associated hyperfiltration leads to increased postglomerular oncotic pressure and increased proximal sodium reabsorption.

Methods. Twelve obese subjects (BMI > 36) and 19 lean subjects participated in the study. They underwent measurement of glomerular filtration rate (GFR), renal plasma flow (RPF) and fractional excretion of lithium (FE Li).

Results. GFR, RPF and FF were 61%, 28% and 29% higher, respectively, in the obese than in the control group (P < 0.00001 for GFR, P < 0.005 for RPF and P < 0.00005 for FF). Half of the obese group had increased FF with increased GFR, while the other half had normal FF with high-normal or increased GFR. Postglomerular oncotic pressure was 13% higher (P < 0.03) and FE Li was 33% lower (P < 0.005) in the obese group with high FF than in the lean group. Postglomerular oncotic pressure and FE Li were normal in the obese group with normal FF.

Conclusions. These results suggest that glomerular hyperfiltration may lead to increased proximal tubular sodium reabsorption in the obese.

Keywords: hyperinsulinaemia; insulin resistance; metabolic syndrome; peritubular oncotic pressure; tubular reabsorption

Introduction

Hypertension and obesity are major factors responsible for the occurrence of cardiovascular disease. The prevalence of both factors has increased during the last decades [1,2]. Studies in animal models and in humans support a causal relationship between weight gain and high blood pressure [3–4]. Multiple factors are involved in the pathogenesis of obesity-associated hypertension [5]. Many of these factors increase blood pressure by causing sodium retention, namely elevated renal sympathetic activity, activation of the renin–angiotensin–aldosterone system, abnormalities of the natriuretic peptide system [5,6] and hyperinsulinaemia/insulin resistance [4,7]. In addition, Hall [5] suggested that intrarenal factors might cause salt retention in obesity, leading to increased sodium reabsorption in the loop of Henle. Finally, Cappuccio et al. showed that the metabolic syndrome is associated with increased proximal tubular sodium reabsorption [8–10].

Obesity is associated with glomerular hyperfiltration in animal models [11]. Human studies also revealed abnormal renal haemodynamics in obese subjects, showing increased glomerular filtration rate (GFR) [12–15], increased renal blood flow [13–17] or both [13–15]. Filtration fraction was found to be elevated in overweight subjects [18] and in obese subjects [13,14]. A previous study from our lab [19] demonstrated that in subjects with severe obesity, weight loss results in a decrease in GFR, renal plasma flow (RPF), filtration fraction (FF) and arterial pressure. The expected consequence of this obesity-associated elevation in FF is haemoconcentration in the postglomerular circulation and an increase in the oncotic pressure of the plasma entering the peritubular capillaries. Since one of the major determinants of proximal tubular reabsorption is the pressure gradient determined by Starling forces, this augmented oncotic pressure is expected to promote proximal tubular sodium reabsorption [20–22], salt retention and an increase in systemic arterial pressure.

The aim of the present study was to verify the hypothesis that obesity-associated hyperfiltration leads to increased postglomerular oncotic pressure and proximal tubular sodium reabsorption.
Subjects and methods

Thirty-one male subjects, aged 21–55 years, participated in the study. Twelve were severely obese (BMI $\geq 36$ kg/m$^2$), and 19 were healthy lean (BMI $\leq 25$ kg/m$^2$) people who served as a control group. All denied a history of kidney disease. None was treated for diabetes mellitus or hypertension. All had a normal serum creatinine and a negative dipstick test for urinary protein. A 24-h urine collection was performed during the week prior to the renal function test studies for assessment of sodium intake. The accuracy of the 24-h urine collections was assessed by a careful questioning of the subjects about the timing of the collection and its completeness. Subjects received 300–600 mg of lithium carbonate at 22:00, the day before the tests. They were instructed to drink 250 mL of water at bedtime. Renal function tests were started at 08.00 a.m. after a 10-h fast, excepting a drink of 250 mL of water at 07.00 a.m. Intravenous catheters were placed in each arm for infusion of clearance markers and blood sampling. A priming dose of inulin (50 mg/kg) and p-aminohippuric acid (8 mg/kg) was administered. Thereafter, inulin and p-aminohippuric acid were continuously infused. A 200–300 mL water load was given during the first 60-min prime. Four accurately timed urine collections of 40–60 min were then obtained by spontaneous voiding. Peripheral venous blood was drawn to bracket each urine collection.

Blood pressure was measured by a trained observer, after 30 min of rest in the supine position, using an electronic oscillometric blood pressure-measuring device (Datascope, Accutorr). The cuff was appropriately sized to the diameter of the arm and the arm was positioned at the heart level. Measurements were performed at least four times during the study, each measurement being the mean of three readings.

The study was approved by the local Ethics committee. Informed consent was obtained from all participants.

Laboratory procedures

Plasma and urinary concentrations of inulin and p-aminohippuric acid were analysed by colorimetric methods [23,24]. Lithium in the serum and urine was measured using the ICP-OES (Inductively Coupled Plasma Optical Emission Spectrometer) method. Plasma insulin and urine albumin were measured using radioimmunoassays (DPC; Los Angeles, CA, USA). Hba1c, plasma glucose and urine creatinine, sodium and potassium were measured using standard laboratory methods. Plasma albumin and total protein were determined on a Roche/Hitachi 917 analyser using the bromcresol green dye binding and the biuret methods, respectively. High-sensitivity C-reactive protein (hs-CRP) levels were determined using an immunoturbidimetric method on an Olympus 2700 analyser.

Plasma insulin and hs-CRP were measured in all obese subjects and in 13 out of the 19 control subjects. Hba1c was measured in 11 out of the 12 obese subjects and in 14 of the control subjects. Albumin excretion rate was measured in all obese subjects and in 18 of the control subjects.

Calculations

The mean arterial pressure was calculated as the diastolic pressure plus one-third of the pulse pressure. BMI was calculated as BW/H$^2$, where BW is the body weight expressed in kg and $H$ is the height expressed in m. GFR was determined from the average value for the timed inulin clearances, and RPF from the average value for the timed p-aminohippurate clearances. FF was calculated as GFR divided by RPF. Plasma globulin was calculated as plasma protein minus plasma albumin. The afferent arteriole oncotic pressure (mmHg) was calculated as 0.0303 $\times$ Alb $\times$ Glob $−$ 0.0115 $\times$ globulin$^2$ [25], where Alb is the plasma albumin concentration and Glob is the plasma globulin concentration, both expressed in g/L. The postglomerular oncotic pressure, i.e. the oncotic pressure of plasma entering the peritubular capillaries, was calculated as afferent oncotic pressure/(1 $−$ FF). The fractional excretion of lithium (FE Li) was calculated as lithium clearance/GFR, using two timed urine collections. FE Li was determined as the average value for these two measurements. Since previous studies from our lab [14,19] had revealed that FF increases in some but not in all subjects with obesity-associated glomerular hyperfiltration, efferent oncotic pressure and fractional lithium excretion were calculated separately for obese subjects with increased FF and for those with FF within the normal range. The normal range for FF was defined as an FF value included in the range of mean $\pm$ SD of the control group.

Statistical analysis

Normally distributed data are expressed as mean $\pm$ SD. Variables with skewed distribution are expressed as median (range). The significance of differences between the groups was evaluated by a two-tailed Student’s $t$-test. The Student’s $t$-test was applied to non-normally distributed data (albumin excretion rate and fractional lithium excretion) after log transformation. Normality of distribution was evaluated using the Kolmogorov–Smirnov test. Pearson’s correlation coefficient was used to assess the relationship between variables. $P < 0.05$ was considered as significant.

Results

Population characteristics

Table 1 shows the characteristics of the two groups. Systolic arterial pressure was $<140$ mmHg in all lean subjects and in 9 out of the 12 obese. Three obese subjects had a systolic blood pressure of 149, 150 and 151 mmHg, respectively. Diastolic arterial pressure was $<90$ mmHg in all subjects. The mean systolic and diastolic arterial pressure, although normal in both groups, was higher in the obese than in the control group. Fasting blood glucose ranged between 3.96 and 5.50 mmol/L in all subjects, except in two obese subjects who had a fasting blood glucose of 5.89 and 6.38 mmol/L. Hba1c levels in these two subjects were 5.7 and 6.5%, respectively. The mean fasting blood glucose, although normal in both groups, was higher in the obese than in the control group. Fasting plasma insulin was five
times higher in the obese than in the control group. Plasma hs-CRP was 10-fold higher in the obese than in the lean groups. Albumin excretion rate was four times higher in the obese than in the control group. The daily urinary excretion of sodium was 68% higher in the obese than in the lean subjects. The 24-h urinary excretion of creatinine was 46% higher in the obese than in the lean subjects. Urinary creatinine excretion during renal function tests was higher in the obese than in the lean group, 13.6 ± 1.5 and 9.9 ± 1.4 µmol/min, respectively (P < 0.00001), confirming the adequacy of the 24-h urine collections.

Table 2 shows the characteristics of the normal and high FF subgroups. BMI, hs-CRP, urinary sodium, albumin and creatinine excretion rates were similar in the two subgroups. The obese subjects with normal filtration had higher plasma glucose, Hba1c and plasma insulin levels than those with increased FF. There was a trend towards a higher systolic arterial pressure in the obese subgroup with normal FF compared with the high FF subgroup.

### Glomerular dynamics

Data are shown in Table 3. GFR was 61% higher in the obese than in the control group. RPF was also increased, although less prominently, by 28%. This resulted in a 29% increase

### Table 1. Population characteristics: obese and control groups

<table>
<thead>
<tr>
<th></th>
<th>Obese group</th>
<th>Control group</th>
<th>P</th>
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<tbody>
<tr>
<td>N</td>
<td>12</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>37 ± 9</td>
<td>33 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>BW (kg)</td>
<td>137 ± 18</td>
<td>70 ± 5</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.79 ± 0.07</td>
<td>1.76 ± 0.06</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>42.7 ± 4.2</td>
<td>22.7 ± 1.7</td>
<td>*</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>128 ± 17</td>
<td>113 ± 6</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mmHg)</td>
<td>72 ± 12</td>
<td>62 ± 5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>90 ± 13</td>
<td>79 ± 4</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>5.11 ± 0.62</td>
<td>4.61 ± 0.41</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Fasting plasma insulin (pmol/L)</td>
<td>135 ± 74</td>
<td>26 ± 4</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>Hba1c (%)</td>
<td>5.6 ± 0.4</td>
<td>5.3 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma hs-CRP (mg/L)</td>
<td>6.26 ± 3.47</td>
<td>0.61 ± 0.40</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Urinary albumin excretion (mg/day)</td>
<td>23 (6–141)</td>
<td>5.7 (2–10)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Urinary sodium excretion (mmol/day)</td>
<td>278 ± 89</td>
<td>165 ± 58</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>Urinary potassium excretion (mmol/day)</td>
<td>80 ± 28</td>
<td>68 ± 29</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary creatinine excretion (mmol/day)</td>
<td>20.1 ± 3.2</td>
<td>13.7 ± 2.1</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

*Significant per definition.
NS, not significant; BW, body weight; BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein.

### Table 2. Population characteristics of the normal and high filtration fraction obese subgroups

<table>
<thead>
<tr>
<th></th>
<th>Obese with normal filtration fraction</th>
<th>Obese with high filtration fraction</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>39 ± 11</td>
<td>35 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>BW (kg)</td>
<td>145 ± 13</td>
<td>130 ± 20</td>
<td>NS</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.81 ± 0.06</td>
<td>1.77 ± 0.08</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>44.2 ± 4.4</td>
<td>41.1 ± 3.7</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>138 ± 11</td>
<td>119 ± 18</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mmHg)</td>
<td>77 ± 9</td>
<td>66 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>97 ± 9</td>
<td>84 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>5.50 ± 0.50</td>
<td>4.68 ± 0.37</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fasting plasma insulin (pmol/L)</td>
<td>186 ± 44</td>
<td>84 ± 62</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hba1c (%)</td>
<td>5.8 ± 0.4</td>
<td>5.3 ± 0.3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Plasma hs-CRP (mg/L)</td>
<td>5.80 ± 3.43</td>
<td>6.72 ± 2.67</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary albumin excretion (mg/day)</td>
<td>23 (6–141)</td>
<td>22 (8–109)</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary sodium excretion (mmol/day)</td>
<td>251 ± 77</td>
<td>305 ± 98</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary potassium excretion (mmol/day)</td>
<td>73 ± 23</td>
<td>87 ± 32</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary creatinine excretion (mmol/day)</td>
<td>19.4 ± 3.0</td>
<td>20.8 ± 3.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 3. Filtration dynamics, postglomerular capillary oncotic pressure and fractional excretion of lithium in obese and control subjects in obese and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Obese group</th>
<th>Control group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>GFR (mL/min)</td>
<td>178 ± 34</td>
<td>110 ± 13</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>RPF (mL/min)</td>
<td>797 ± 220</td>
<td>623 ± 94</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>0.230 ± 0.041</td>
<td>0.178 ± 0.015</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>Pi (mmHg)</td>
<td>26.8 ± 3.5</td>
<td>26.5 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Pi (mmHg)</td>
<td>34.9 ± 4.9</td>
<td>32.3 ± 2.9</td>
<td>&lt;0.07</td>
</tr>
<tr>
<td>FE Li</td>
<td>0.17 (0.11–0.29)</td>
<td>0.22 (0.14–0.31)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate; RPF, renal plasma flow; Pi, afferent arteriole oncotic pressure; Pi, postglomerular oncotic pressure; FE Li, fractional excretion of lithium.
Fig. 1. Glomerular filtration rate (GFR) (A), renal plasma flow (RPF) (B) and filtration fraction (C) in control and obese groups.

Postglomerular oncotic pressure and proximal tubular sodium reabsorption

Data are shown in Table 3. Postglomerular oncotic pressure was 8% higher in the obese group than in the control group. This increase was shy of statistical significance ($P < 0.07$).

FE Li was 23% lower in the obese group than in the control group ($P < 0.05$).

**Sub group analysis for subjects with increased FF and normal FF**

Results are shown in Table 4. GFR was similarly increased in both the high and the normal FF subgroups; therefore, the difference in FF was due to a variation in RPF: the normal FF subgroup had an increased RPF, while the increased FF subgroup had a normal RPF. Obese subjects with increased FF had a 13% increase in postglomerular oncotic pressure and a 33% decrease in FE Li. Obese subjects with FF within the normal range had no changes in postglomerular oncotic pressure and FE Li. Sodium intake, as assessed by the measurement of the 24-h urinary sodium excretion, was 305 ± 98 mmol/day in the obese subjects with high FF and 251 ± 77 mmol/day in those with normal fraction ($P = NS$).

Postglomerular oncotic pressure and FE Li were negatively correlated ($r = -0.38$, $P < 0.05$).

**Discussion**

This study shows that obesity-associated glomerular hyperfiltration leads to increased postglomerular oncotic pressure and enhanced proximal tubular sodium reabsorption, suggesting that glomerular hyperfiltration may play a role in the pathogenesis of hypertension in obesity.

Glomerular hyperfiltration is associated with overweight and obesity [12–15,18]. Previous studies in obese subjects [13,14,18] showed that RPF increases less than GFR; hence
FF increases. However, examination of raw data from previous studies from our lab [14,19] revealed that the extent of change in RPF is not only of lesser magnitude than the change in GFR, but that it is heterogeneous, varying from no change to a change similar to that of GFR. This results in a variable change in FF, ranging from nil when RPF increases in parallel to GFR to maximal when GFR increases while RPF does not.

Glomerular ultrafiltration is an important physiologic determinant of proximal tubular reabsorption. It induces an increase in protein concentration in the postglomerular circulation, resulting in a higher oncotic pressure in the plasma entering the peritubular capillaries than in the systemic circulation. Since hydraulic pressure drops along the efferent arterioles [26–28], the high peritubular capillary oncotic pressure in the normal kidney generates a transcapillary pressure gradient favoring net uptake of the reabsorbate from the intercellular space into the peritubular capillaries. This allows net reabsorption of the fluid transported from the tubular lumen to the intercellular space, preventing its back-leak into the lumen. In the kidney of obese subjects with increased FF, the physiological increase in postglomerular capillary oncotic pressure is more prominent than in lean subjects and is expected to raise proximal tubular water reabsorption above normal. The effect of glomerular ultrafiltration on postglomerular capillary oncotic pressure and proximal tubular sodium reabsorption was demonstrated in animal models [20–22].

Data presented in the current study are in accordance with these theoretical considerations and experimental findings. The subjects with severe obesity have, as expected, an elevated GFR, associated with a less constant increase in RPF, resulting in a variable increase in FF. Those with an FF above the normal range have an elevated oncotic pressure in the plasma entering the peritubular capillaries and a decreased FE Li reflecting increased proximal tubular sodium reabsorption. In the subgroup of obese subjects with normal range FF, neither postglomerular oncotic pressure nor proximal tubular sodium reabsorption increased above the control value. These findings suggest that a raised postglomerular oncotic pressure is responsible in part for the increased proximal tubular sodium reabsorption in the obese subject.

Mechanisms other than sodium chloride reabsorption secondary to water flux may account for the raised proximal reabsorption of sodium found in these obese subjects. Obesity is associated with activation of the renin–angiotensin–aldosterone system [29–31] induced by multiple factors, including secretion of renin and renin precursors by adipocytes [32]. This may result in increased angiotensin II leading to increased proximal sodium reabsorption [33], independent of the effect of this hormone on FF.

It has been suggested [34,35] that in the diabetic kidney, increased proximal sodium reabsorption due to an unknown factor may activate tubulo-glomerular feedback and thus elicit glomerular hyperfiltration. The consequent increase in GFR would result in enhanced filtered sodium load and a restored normal sodium balance. This same mechanism may be involved in obesity. Interestingly, in view of the findings shown in the present study, a vicious circle would be created, whereby an increase in sodium reabsorption proximal to the macula densa would increase GFR, resulting in increased FF, heightened postglomerular oncotic pressure, enhanced proximal sodium reabsorption and again increased GFR. This effect of hyperfiltration on salt reabsorption would moderate the hyperfiltration-induced increase in sodium excretion, thus perpetuating both phenomena—salt retention and hyperfiltration.

Another determinant of sodium excretion, which may affect the physical forces involved in sodium excretion, is the renal interstitial space. Hall [5] suggested that the increased interstitial pressure related to subcapsular fat infiltration and abdominal fat accumulation causes tubular compression, thus slowing urine flow and increasing sodium reabsorption in the loop of Henle. An increase in interstitial pressure may also result in increased net sodium reabsorption at a proximal site [36]: the increased hydrostatic pressure in the interstitial matrix separating tubules from postglomerular capillaries may concur with the elevated postglomerular capillary oncotic pressure to further raise the pressure gradient driving fluid into capillaries, thus increasing sodium reabsorption by proximal tubules.

Abnormal proximal tubular salt handling in obese subjects was previously reported in the Olivetti Heart Study [8–10], which revealed the link between increased proximal tubular sodium reabsorption and metabolic syndrome. The present study confirms these findings in severe obesity and suggests that glomerular hyperfiltration may underlie this phenomenon.

It is noteworthy that the sodium intake of the obese subjects was higher than that of the lean ones. An increase in sodium intake in healthy subjects is expected to decrease proximal sodium reabsorption [37–40]. In the present study, proximal sodium reabsorption was higher in the obese subjects than in the lean ones; therefore, the higher sodium intake of the obese subjects cannot account for their reduced proximal tubular reabsorption. Furthermore, obese subjects with high and normal FF did not differ in their sodium intake.

Recently, Krikken et al. [41] demonstrated that FF is higher in overweight subjects eating a high, as compared to a low, sodium diet, while sodium intake does not affect FF in lean subjects. The findings of that study suggest that the association between GFR and BMI may depend on the salt intake. Could the higher sodium intake in the obese group account, in part or totally, for the obesity-associated hyperfiltration? This cannot be excluded. However, it should be stressed that in that study [41], the difference between the high and low salt diet was large, 650%, while in the present study the difference between the obese and lean sodium intake was substantially smaller, 69%. Hence we cannot exclude that the relatively high salt intake in the obese group could at least partially explain the hyperfiltration associated with obesity. If indeed, this relatively modest increase in salt intake concurred with other factors to aggravate hyperfiltration in the obese subjects, the high salt diet would increase FF and thus reinforce the vicious circle linking hyperfiltration, salt retention and hypertension.

FE Li was used in this study to evaluate renal sodium handling. Lithium is freely filtrated by the glomeruli, undergoes proximal tubular reabsorption by the same transport system as sodium and thereafter is excreted without
further significant reabsorption or secretion at more distal segments of the nephron [42]. Thus, FE Li is a marker of proximal tubular sodium handling, and a decrease in FE Li reflects an increase in proximal sodium reabsorption. An exception to this rule is the case of subjects under sodium restriction, where this relationship loses its validity [43]. This is not the case in our study groups.

The increased sodium reabsorption at a proximal site of the nephron adds up to that occurring at distal nephron sites in obesity [5,6,29–31,44]. The concurrence of sodium-handling abnormalities at both proximal and distal nephron sites impedes the development of compensatory mechanisms aimed at restoring sodium balance. The consequent salt retention explains the plasma volume expansion, the increased blood pressure and the shift in pressure natriuresis relationship, which characterize obesity.

Until now the importance of the concept of obesity-associated hyperfiltration resided mainly in the fact that it may play a role in the pathogenesis of chronic kidney disease in the obese subject [45]. The importance of the present findings is in showing that glomerular hyperfiltration may play a role in the pathogenesis of obesity-associated hypertension. This results in a vicious circle: high systemic blood pressure is transmitted to glomerular capillaries through a dilated afferent arteriole [14]; this aggravates hyperfiltration, which further increases salt retention and systemic arterial pressure. Bosma et al. [46] recently showed that in renal transplant recipients, the overweight- and obesity-associated increase in FF is a risk factor for renal graft loss and patient death, independent of other prognostic factors. The results of the present study suggest that an increased FF may not only be a marker of increased cardiovascular risk and graft loss but may also play a role in the progression of kidney disease and in the pathogenesis of cardiovascular mortality through its effect on salt reabsorption.

In light of the increased obesity-associated risk for cardiovascular disease and mortality, it has been recommended that subjects with metabolic syndrome should be treated with blockers of the renin–angiotensin system [47]. This treatment is expected to ameliorate glomerular hyperfiltration with a decrease in GFR and FF. In light of the findings of the present study, the decrease in the latter is expected to lead to a reduction in proximal tubular sodium reabsorption and thus possibly provide an additional long-term advantage.

These mechanisms may also apply to two other conditions associated with glomerular hyperfiltration and increased FF: diabetes mellitus and chronic renal insufficiency. In diabetes mellitus, glomerular hyperfiltration may result in increased proximal tubular salt reabsorption in the same way as it does in obesity. In chronic renal insufficiency the functioning nephron number is decreased, resulting in hyperfiltration of the remaining glomeruli. This increased single-nephron GFR is expected to elevate postglomerular oncotic pressure of remnant nephrons, causing the same chain of events as in obesity: increased salt reabsorption, hypertension, aggravated hyperfiltration due to increased glomerular pressure and further nephron loss. The concept of hyperfiltration-induced increase in sodium reabsorption has also implications for the management of hypertension and kidney disease in obesity. Therapeutic interventions resulting in decreased FF, such as weight loss [19] and administration of glomerular pressure-reducing drugs, may alleviate hypertension partly by decreasing proximal salt reabsorption. This, in turn, is expected to lead to a further decrease in glomerular pressure and hyperfiltration, thus reducing both renal and systemic end organ damage.

In summary, this study shows that glomerular hyperfiltration associated with severe obesity is heterogeneous as far as FF is concerned. When associated with high FF, hyperfiltration increases postglomerular capillary oncotic pressure and proximal tubular sodium reabsorption. These results suggest that in addition to being a known mediator of glomerular damage, glomerular hyperfiltration may play a role in the pathogenesis of hypertension by enhancing salt reabsorption. It remains to be established whether therapeutic manoeuvres aimed at decreasing glomerular hyperfiltration normalize proximal tubular handling of sodium.

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Conflict of interest statement. None declared.

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