Glomerular hemodynamics in severe obesity

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Chagnac, Avry, Talia Weinstein, Asher Korzets, Edward Ramadan, Judith Hirsch, and Uzi Gafter. Glomerular hemodynamics in severe obesity. Am J Physiol Renal Physiol 278: F817–F822, 2000.—Differential solute clearances were used to characterize glomerular function in 12 nondiabetic subjects with severe obesity (body mass index >38). Nine healthy subjects served as the control group. In the obese group, glomerular filtration rate (GFR) and renal plasma flow (RPF) exceeded the control values by 51 and 31%, respectively. Consequently, filtration fraction increased. The augmented RPF suggested a state of renal vasodilatation involving, mainly or solely, the afferent arteriole. Albumin excretion rate and fractional albumin clearance increased by 89 and 78%, respectively. Oral glucose tolerance tests were suggestive of insulin resistance. Insulin resistance was positively correlated with GFR (r = 0.88, P < 0.001) and RPF (r = 0.72, P < 0.001). Mean arterial pressure was higher than in the control group. Fractional clearances of dextrans of broad size distribution tended to be lowered. The determinants of the GFR were estimated qualitatively by using a theoretical model of dextran transport through a heteroporous membrane. This analysis suggests that the high GFR in very obese subjects may be the result of an increase in transcapillary hydraulic pressure difference (ΔP). An abnormal transmission of increased arterial pressure to the glomerular capillaries through a dilated afferent arteriole could account for the augmentation in ΔP.

dextran; glomerular barrier; hyperfiltration; insulin resistance; transcapillary hydraulic pressure difference

EXCESS BODY WEIGHT IS ASSOCIATED with functional and structural renal changes, such as increased glomerular filtration rate (GFR), renal plasma flow (RPF) (3, 15, 24, 26), and urinary albumin excretion (19, 26, 30). Experimental studies suggest that the kidney could be involved in the pathogenesis of the increase in blood pressure frequently affecting obese individuals (14, 27). Structural abnormalities have been reported in obese animals (23) and obese humans (1, 18, 22).

The kidney in nondiabetic obese patients exhibits glomerular hyperfiltration that is not associated with glomerular disease or nephrectomy. It thus provides an opportunity to study glomerular hyperfiltration and its determinants. Two of these determinants, the transcapillary hydraulic pressure difference (ΔP) and the ultrafiltration coefficient (Kf), cannot be directly measured in humans. Recently, single-nephron Kf has been estimated by using a method that combines morphometric measurements and a mathematical ultrastructural model (11, 12). However, this approach requires the performance of kidney biopsies, which is ethically questionable in patients without kidney disease. In the absence of ultrastructural information, we have determined sieving coefficients of dextrans of broad size distribution in an effort to indirectly determine whether obesity leads to hyperfiltration by elevating either ΔP or Kf. Our findings are the basis of this report.

METHODS

Study population. Twenty-one volunteers, 15 women and 6 men, aged 23–46 yr, participated in the study. Twelve were patients with severe obesity [body mass index (BMI) >38], and nine were nonobese, healthy people, who served as a control group. All denied a history of renal disease; none had diabetes as defined by the criteria of the 1997 expert committee on the diagnosis of diabetes mellitus (25). None was treated for hypertension. All were found to have a normal serum creatinine level and a negative dipstick test for urinary protein. Table 1 shows the characteristics of the two groups. Age and gender distribution were similar in the two groups. The body weight and BMI of the obese group were almost twice those of the control group. Their BMI varied between 38.1 and 49.7, with 11 of the 12 patients having morbid obesity, as defined by a BMI above 40. Although within the normal range, the mean fasting blood glucose in the obese group was higher than in the control group. Fasting insulin was elevated more than twofold in the obese group.

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

Study protocol. Patients underwent an oral glucose tolerance test (OGTT). The OGTT was performed at 8 AM after a 10-h fast. The subjects ingested 75 g of glucose dissolved in water. Blood samples were withdrawn through an indwelling intravenous catheter 10 and 1 min before and 60 and 120 min after the ingestion for measurement of plasma glucose and insulin. In one patient of the control group, fasting plasma glucose was measured but OGTT was not performed. Four to 5 days later all subjects underwent renal function tests. Each subject was studied at 8 AM after a light breakfast low in protein content. The subjects were kept recumbent in a hospital bed, and intravenous catheters were placed in each upper limb for infusion of clearance markers and blood sampling. A priming dose of inulin (50 mg/kg), p-aminomhippuric acid (PAH; 8 mg/kg), and dextran 40 (130 mg/kg) was administered. Thereafter, inulin, PAH, and dextran 40 were infused continuously. A water load (15 ml/kg) was given...
Table 1. General characteristics of the population

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<th>Control Group</th>
<th>Obese Group</th>
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<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Gender, F/M</td>
<td>6/3</td>
<td>9/3</td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>30.9 ± 2.4</td>
<td>35.2 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>BW, kg</td>
<td>64.7 ± 3.1</td>
<td>127.7 ± 6.6</td>
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<tr>
<td>BMI, kg/m²</td>
<td>22.2 ± 1.7</td>
<td>43.8 ± 1.0</td>
<td>*</td>
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<tr>
<td>BSA, m²</td>
<td>1.75 ± 0.06</td>
<td>2.23 ± 0.08</td>
<td>*</td>
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<tr>
<td>Fasting plasma</td>
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<tr>
<td>Glucose, mg/dl</td>
<td>90 ± 3</td>
<td>102 ± 2</td>
<td>&lt;0.005</td>
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<tr>
<td>Insulin, μU/ml</td>
<td>14 ± 1</td>
<td>35 ± 6</td>
<td>&lt;0.005</td>
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Values are means ± SE. n. No. of subjects; F, female; M, male; BW, body wt; BMI, body mass index; BSA, body surface area; NS, not significant. *Different by definition.

during the first 60-min prime, so as to promote a high rate of urine flow. Four accurately timed urine collections were then obtained by spontaneous voiding. Peripheral venous blood was drawn to bracket each urine collection. Blood pressure was measured during each urine collection.

GFR was determined from the average inulin clearance. RPF was calculated by dividing the average PAH clearance by the assumed renal PAH extraction ratio of 0.9. Oncotic pressure (I) was calculated by using the equation

\[ P = \frac{(U/P)_{In} - (U/P)_{D}}{(U/P)_{D}} \]

where (U/P) In is the urine-to-plasma concentration ratio of inulin, and (U/P) D is the urine-to-plasma concentration ratio of dextran. The integrated area of each slice was equated with the dextran concentration at the corresponding retention time, and molecular radius (MW; 9.9, 25.6, 53.5, and 72.6, respectively). Dextran 40 was analyzed by high-performance liquid chromatography using two columns in series (UltraHydrogel 250 and 500; Waters Division, Millipore, Milford, MA) (21). The columns were calibrated with three narrowly dispersed dextran fractions of known molecular weight (MW; 9.9, 25.6, 53.5, and 72.6, respectively). Dextran concentration was measured by using a refractive index detector (no. RID-6A, Instrumentation Shimadzu). An integrator (no. 4270, Spectraphysics, San Jose, CA) was used to divide the chromatogram into four slices per minute during the 40-min run. The integrated area of each slice was equated with the dextran concentration at the corresponding retention time. MW was calculated from its linear relationship with retention time, and molecular radius (r) was calculated by using the equation

\[ r = 0.33 \times (MW)^{0.483} \]

The urine-to-plasma concentration ratio was calculated for each dextran fraction, at 2-A intervals over a molecular radius range of 34–58 Å (20).

Analysis of glomerular membrane-pore structure. To characterize the size-selective properties of the glomerular barrier in each group of subjects, we employed two theoretical models, each of which represents the glomerular capillary wall as a heteroporous membrane characterized by two pore parameters (8). According to the first of these models (isoporous model with shunt), the major portion of the capillary wall is assumed to be perforated by restrictive, cylindrical pores of identical radius (r0). The model assumes that there exists in addition a parallel "shunt pathway" that does not discriminate among the infused dextrans on the basis of size, and through which passes a small fraction of the filtrate volume. The shunt pathway is characterized by a parameter, \( \omega_0 \), that governs the fraction of filtrate volume passing through the nonrestrictive portion of the membrane. The second model represents the glomerular capillary wall as being perforated by cylindrical pores with a continuous log-normal distribution of pore radii (log-normal model). The two parameters, which characterize this latter representation, are the mean pore radius (U) and the standard deviation about the mean (S) of the log-normal distribution of pore sizes. Each model also estimates volume flows and fluxes and protein concentration along the length of glomerular capillaries, thereby permitting computation of the ultrafiltration coefficient \( K_t \), which is the product of effective hydraulic permeability and total glomerular capillary surface area in the two human kidneys. These models take into account the effect of GFR determinants on convective and diffusivetransmembrane transport, requiring knowledge of GFR, RPF, afferent arteriole oncotonic pressure, and \( \Delta P \) (6, 9). Because \( \Delta P \) cannot be measured directly in humans, a sensitivity analysis was performed by using the mean group data. \( \Delta P \) values of 35, 40, and 45 mmHg were assigned. Individual data were then analyzed in 5 control and 11 obese subjects by using the \( \Delta P \) value, providing the least chi-squared sensitivity analysis.

Statistical analysis. Normally distributed data are expressed as means ± SE. Variables with skewed distribution, such as albumin urinary excretion rate and fractional albumin clearance, are expressed as median (range). The significance of differences between the obese and control groups was evaluated by a two-tailed Student's t-test. Student's t-test was applied to nonnormally distributed data after log transformation. Pearson correlation coefficients were used to evaluate correlations between variables.

RESULTS

Oral glucose tolerance test. Table 2 summarizes the results of the oral glucose tolerance test. The area under the glucose and insulin curves after oral glucose load was increased in the obese group by 67 and 230%, respectively. The ratio of the insulin-to-glucose area under the curves of the obese group was twice as high as that of the control group (0.79 ± 0.08 vs 0.40 ± 0.04, respectively, P < 0.005). These data are consistent with marked insulin resistance.

Table 2. Oral glucose tolerance test in control and obese subjects

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<th>Control Group</th>
<th>Obese Group</th>
<th>P Value</th>
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<tr>
<td>n</td>
<td>8</td>
<td>11</td>
<td></td>
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<tr>
<td>Plasma glucose</td>
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<tr>
<td>Baseline, mg/dl</td>
<td>90 ± 3</td>
<td>103 ± 2</td>
<td>&lt;0.005</td>
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<tr>
<td>60 min, mg/dl</td>
<td>101 ± 9</td>
<td>194 ± 14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>120 min, mg/dl</td>
<td>87 ± 4</td>
<td>149 ± 11</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>AUC, mg/min·1·ml⁻¹</td>
<td>192 ± 12</td>
<td>320 ± 20</td>
<td>&lt;0.0001</td>
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<tr>
<td>Plasma insulin</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, μU/ml</td>
<td>14 ± 1</td>
<td>36 ± 7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>60 min, μU/ml</td>
<td>50 ± 5</td>
<td>158 ± 14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>120 min, μU/ml</td>
<td>34 ± 4</td>
<td>137 ± 19</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>AUC, μU·min⁻¹·ml⁻¹</td>
<td>74 ± 6</td>
<td>245 ± 24</td>
<td>&lt;0.0001</td>
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Values are means ± SE. n. No. of subjects; AUC, area under the curve.
Filtration dynamics. Filtration dynamics data are shown in Table 3. GFR was 51% higher in the obese than in the control group. It was elevated in 8 of the 12 patients. The distribution of GFR in the two groups is depicted as a histogram in Fig. 1. An increase in RPF was proportionally smaller, averaging 31%. The increase in GFR was thus associated with an increase in filtration fraction. Mean arterial pressure, although normal in both groups, was higher in the obese group. Plasma oncotic pressure, the force opposing the formation of filtrate, was identical in the two groups.

A positive correlation was found between GFR and RPF in the combined obese and normal groups \( (r = 0.86, P < 0.001) \), suggesting that the change in RPF accounted for 74% of the variation in GFR. The area under the insulin curve was correlated with both RPF \( (r = 0.72, P < 0.001) \) and GFR \( (r = 0.88, P < 0.001) \).

Renal macromolecule handling. Albumin excretion rate was increased in the obese group: 8.5 (4.4–152) and 4.5 (2.5–7.0) µg/min in the obese and normal groups \( (P < 0.005) \). The fractional clearance of albumin was 0.16 (0.1–2.3) \( \times 10^{-5} \) and 0.09 (0.07–0.18) \( \times 10^{-5} \) in the obese and control groups, respectively \( (P < 0.05) \).

The mean dextran-sieving profiles in the obese and control groups are compared in Fig. 2. Fractional dextran-sieving clearances were nonsignificantly decreased in the obese group.

Analysis of membrane parameters. Heteroporous membrane models were used to estimate membrane parameters for the control and obese groups from the mean dextran-sieving curves profiles illustrated in Fig. 2. These models take into account the effect of GFR determinants on convective and diffusive transmembrane transport, requiring knowledge of GFR, RPF, afferent arteriole oncotic pressure, and \( \Delta P \) (7, 8). Because \( \Delta P \) cannot be directly measured in humans, we performed a sensitivity analysis, assigning \( \Delta P \) values of 35, 40, and 45 mmHg. We then subjected the data to two theoretical models, the isoporous+shunt model and the log-normal model. The sieving profiles predicted by each model are illustrated in Fig. 3A for the control group and in Fig. 3B for the obese group. Inspection of each panel of Fig. 3 suggests that the log-normal model replicates the observed findings better than the isoporous+shunt model. This is confirmed by a lower sum of at least \( \chi^2 \) in the former, indicating that, for any level of \( \Delta P \), the log-normal model predicts the observed sieving curve better than does the isoporous+shunt model. Thus the former model was used to estimate \( \Delta P \). Findings are summarized in Table 4. Whereas the best fit \( \Delta P \) value for the control sieving curve is 35 mmHg, the corresponding best fit in the obese group is 40 mmHg. We next analyzed the intrinsic membrane properties of the individuals by using the aforementioned best fit \( \Delta P \) values, i.e., 35 and 40 mmHg for the control and obese subjects, respectively (Table 5). This analysis indicates that the control and obese groups have essentially similar values for \( K_f \).

Table 3. Filtration dynamics in control and obese subjects

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Obese Group</th>
<th>( P ) Value</th>
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<tbody>
<tr>
<td>( n )</td>
<td>9</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>GFR, ml/min</td>
<td>90 ± 5</td>
<td>136 ± 8</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>RPF, ml/min</td>
<td>610 ± 41</td>
<td>801 ± 34</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>FF</td>
<td>0.15 ± 0.01</td>
<td>0.17 ± 0.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>86 ± 2</td>
<td>98 ± 3</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>IIa, mmHg</td>
<td>26.0 ± 0.8</td>
<td>26.4 ± 0.7</td>
<td>NS</td>
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Values are means ± SE. \( n \), No. of subjects; GFR, glomerular filtration rate; RPF, renal plasma flow; FF, filtration fraction; MAP, mean arterial pressure; IIa, oncotic pressure.

Fig. 1. Distribution of glomerular filtration rate (GFR) in control group (dark gray bars) and obese group (filled bars). \( n \), No. of subjects.

Fig. 2. Dextran-sieving coefficients in control group (○, dotted line) and obese group (●, solid line). Bars, 1 SE for each sieving coefficient. Sieving coefficients of 2 groups are not significantly different. \( n \), No. of subjects.
This study shows that both GFR and RPF of extremely obese patients are increased, the GFR being relatively more elevated than the RPF, resulting in an increased filtration fraction. The augmented RPF suggests a state of renal vasodilatation involving, mainly or solely, the afferent arteriole. RPF is a determinant of GFR independently of the capillary hydrostatic pressure: its increase is predicted to lower the intraluminal concentration of macromolecules as blood flows axially along the glomerular capillaries (9). This results in a decrease in glomerular intracapillary oncotic pressure, thus enhancing the net ultrafiltration pressure and contributing to the elevated GFR. However, because the increase in filtration fraction offsets the effect of the increase in RPF on the glomerular oncotic pressure, factors other than oncotic pressure must have contributed to the elevation of GFR. Although within the normal range, the MAP was higher in the obese group than in the control group. The combination of increased arterial pressure abnormally transmitted to the glomerular capillaries through a dilated afferent arteriole is expected to cause an elevated glomerular capillary pressure, resulting in an increased transcapillary pressure gradient $\Delta P$ and an elevated GFR. In the consideration of this, the third factor determining GFR, $K_f$, could be, on theoretical grounds, either normal, decreased, or increased. Because neither $\Delta P$ nor $K_f$ is directly measurable in humans, we have attempted to detect changes in the direction of each quantity by analyzing the sieving data with heteroporous models of glomerular size selectivity (8).

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The low-radius end of the sieving curve tended to be depressed. However, this difference did not reach significance. Theoretical and experimental studies on the effects of glomerular hemodynamics on sieving coefficients of macromolecules (6) have shown that increased $\Delta P$ and RPF and depressed $K_f$ are predicted to depress the small dextran-sieving coefficients. Thus the nonsignificant change in the sieving coefficients could be the end result of the effects of opposing forces, elevated $\Delta P$ and RPF, tending to depress the sieving coefficients, and an increased $K_f$ partially offsetting this effect. Yet the sieving curve findings should be interpreted cautiously.
tiously. Edwards and Deen (13) have analyzed the limitations of the method by using sieving data to estimate glomerular pressure. They have defined two kinds of errors responsible for the inconsistent results obtained by this method: random experimental errors and systematic errors due to imperfections in the theoretical models used to analyze the data. The authors have shown that these errors make a reliable quantitative estimation of $\Delta P$ from the sieving data unlikely. Furthermore, the shape of dextran molecules alters during transglomerular permeation. As a result, their transport is enhanced and the analysis of the sieving data of these molecules leads to an overestimation of the glomerular pore size. This overestimation affects the evaluation of the fraction of filtrate volume passing through the nonrestrictive portion of the membrane, but not that of $K_f$ (2). Thus this drawback of dextran is of limited consequence in the present study.

In the consideration of the limitations of this method, the estimate of $\Delta P$ obtained by using a model of transport through a heteroporous membrane should be regarded as qualitative. The group mean data were analyzed by using two models of glomerular filtration, the log-normal and the isoporous shunt models. From the least square analysis, the best fit was obtained by the log-normal model. It predicted a higher $\Delta P$ and a similar $K_f$ in the obese, compared with the control group. The present findings are at variance with another model of hyperfiltration, the diabetic kidney at an early stage, studied in Pima Indians with non-insulin-dependent diabetes mellitus of $<$3-yr duration (21). Differential solute clearance tests revealed a significant elevation of the sieving coefficients. The hyperfiltration of this obese population with early diabetes was associated with a significantly elevated RPF, in contrast to the nondiabetic obese population studied in the present report. Because an increase in RPF is expected to depress the small dextran-sieving coefficients, RPF did not constitute a force depressing the sieving curve, leaving unbalanced the eventual influence of an increased $K_f$ toward elevation of the sieving coefficients. In fact, by modeling at different $\Delta P$ values, Myers et al. (21) showed that at any given $\Delta P$ value, $K_f$ was increased. Thus the two models of hyperfiltration, the obese nondiabetic subjects and the obese patients with early NIDDM, appear to differ as far as glomerular hemodynamics is concerned.

The filtration fraction value of the control group in the present study is relatively low compared with that reported in previous studies, raising the concern of a possible bias in the interpretation of the abnormalities found in the obese. However, this difference is in large part artificial and reflects mostly the method used to estimate RPF. Most studies equate RPF with PAH clearance, not taking into consideration the incomplete extraction of PAH by tubules. In the present study, an assumed extraction ratio of 0.9 was used, giving a relatively high RPF and a relatively low filtration fraction. Because this correcting factor has been applied to both control and obese groups, it does not influence the results of the comparison between the groups. In taking into consideration this mode of calculation, the results for the control group of the present study fall well into the normal range (data not shown).

We wish to emphasize that the GFR in the present study has not been corrected for body surface area. Because the number of nephrons does not increase with increasing body fat, increasing obesity must result in an increase in the single-nephron GFR. Absolute GFR reflects this phenomenon whereas correcting GFR for body surface area obscures it. We have accordingly analyzed the data by using the uncorrected, absolute GFR. Finally, it should be noted that despite the marked hyperfiltration disclosed by the obese group, one-third of the subjects in this group had a GFR in the normal range. A possible explanation is that the GFR of these subjects was in the low-normal range before they gained weight and that this normal GFR represents hyperfiltration. Another possibility is that unknown factors may avert the hemodynamic changes in some obese subjects.

Obesity is associated with marked insulin resistance. The group of obese patients studied here exhibited features suggestive of marked insulin resistance, which was correlated with RPF, GFR, and filtration fraction. Dengel et al. (10), studying a population of obese nondiabetic patients with mild renal insufficiency, have shown a negative correlation between glucose disposal rate during hyperinsulinemic euglycemic clamp and filtration fraction, i.e., a positive correlation between insulin resistance and filtration fraction. This link could be an epiphenomenon indicative of an undetermined process occurring in the kidney of obese insulin-resistant patients and not directly caused by insulin resistance. However, experimental studies have suggested a direct effect of insulin on the glomerular microcirculation. Junco and Ito (17) have studied in vitro isolated segments of rabbit glomerular arterioles and shown that insulin reduces norepinephrine-induced efferent arteriolar constriction, an effect that is predicted to lower $\Delta P$. Insulin resistance involving glomerular vessels would thus result in an increased $\Delta P$. Tucker et al. (29) and Hayashi et al. (16) have confirmed the vasodilatory action of insulin on rat renal microvessels. However, their studies failed to show a preferential effect on the efferent arteriole, thus not supporting the concept of insulin resistance as a cause of increased $\Delta P$. Thus although the glomerular hemodynamic alterations we have shown in the obese population could be the consequence of resistance of the glomerular microcirculation to insulin action, this issue is still unresolved.

In summary, the elevated GFR of very obese non diabetic patients is associated with an increased RPF. The analysis of dextran-sieving data suggests, but does not prove that the pathogenesis of hyperfiltration differs from that of the diabetic kidney, in that it is mainly or solely due to an increased $\Delta P$. The role of insulin resistance as a factor contributing to these glomerular hemodynamics changes remains to be clarified.

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Plasma and urine dextran concentrations were measured during a
sabbatical leave at Stanford University.

We also thank Blouch, Div. of Nephrology, Stanford University Medical Center, for
advise in the measurement of dextran concentrations. We also thank

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