High Density Lipoprotein Turnover in Patients With Hypertension


Although hyperinsulinemia and decreased high density lipoprotein cholesterol concentration can occur in patients with hypertension, there is no information available concerning the dynamic state of high density lipoprotein metabolism. To address this issue, we quantified high density lipoprotein turnover in 12 patients with mild hypertension and 11 matched subjects with normal blood pressure. Patients with high blood pressure had lower high density lipoprotein cholesterol concentrations. Fractional catabolic rates of $^{125}$I-apolipoprotein AI (apoAI)/high density lipoprotein were faster in patients with hypertension ($0.36\pm0.02$ versus $0.26\pm0.02$ l/day, $p<0.001$). Total synthetic rates of apoAI were also significantly greater in patients with high blood pressure ($17.4\pm1.1$ versus $13.2\pm0.6$ mg/kg/day, $p<0.001$). Although significant correlation was observed between blood pressure and fractional catabolic rate of $^{125}$I-apoAI/high density lipoprotein in the experimental population ($r=0.52$, $p<0.01$), no relation was found when patients with normal blood pressure or hypertension were considered separately. However, a highly significant positive correlation was found between $^{125}$I-apoAI/high density lipoprotein fractional catabolic rate and insulin concentration in the entire population ($r=0.72$, $p<0.001$). In conclusion, the patients with mild hypertension studied were hyperinsulinemic, had a faster fractional catabolic rate of $^{125}$I-apoAI/high density lipoprotein, and a lower high density lipoprotein–cholesterol concentration. It is suggested that the changes seen in high density lipoprotein–cholesterol concentration and $^{125}$I-apoAI/high density lipoprotein fractional catabolic rates were secondary to the hyperinsulinemia and not due to the high blood pressure per se. (Hypertension 1991;17:386–393)

Although high blood pressure is considered to be a risk factor for the development of coronary artery disease (CAD), treatment of hypertension has not been shown to decrease this risk.$^{4-5}$ At the present time it is not clear why morbidity and mortality from CAD is not reduced when blood pressure is lowered, and it has recently been suggested that the insulin resistance$^{6,7}$ and hyperinsulinemia$^{8,9}$ seen in patients with high blood pressure may help explain this apparent clinical paradox. Hyperinsulinemia per se has been identified as a risk factor for CAD.$^{10-12}$ Since increases in plasma insulin concentration appear to be associated with decreases in plasma high density lipoprotein (HDL)–cholesterol concentration,$^{13-15}$ it is possible that abnormalities of HDL metabolism exist in hyperinsulinemic patients with hypertension and may contribute to the risk of CAD. More specifically, we have recently shown$^{16}$ that both the absolute turnover and fractional catabolic rates of apolipoprotein AI (apoAI)–labeled HDL were elevated in patients with non-insulin-dependent diabetes mellitus (NIDDM) and that the magnitude of the increase was directly related to the degree of hyperinsulinemia. To see if a similar phenomenon existed in patients with high blood pressure, we initiated the current study to determine if the turnover rate of apoAI-labeled HDL was greater than normal in patients with untreated hypertension and to see if this change was related to blood pressure or plasma insulin concentration.

Methods

Patients

The present study consisted of 12 patients with mild hypertension and 11 individuals with normal blood pressure. All subjects were in good general health, aside from having hypertension. Serum creatinine levels were within normal limits and similar in
TABLE 1.  Clinical Characteristics of Normal Subjects and Patients With Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49±4</td>
<td>49±3</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>8 M:3 F</td>
<td>10 M:2 F</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.8±1.6</td>
<td>31.1±1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>112±4</td>
<td>143±1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>75±3</td>
<td>96±1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>91±3</td>
<td>95±4</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting insulin (microunits/ml)</td>
<td>11±2</td>
<td>21±4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.08±0.07</td>
<td>1.07±0.03</td>
<td>NS</td>
</tr>
</tbody>
</table>

Plasma Measurements

Three fasting samples were collected from each subject for determination of insulin, glucose, HDL-cholesterol, and apoAI concentrations. Insulin was measured by radioimmunoassay17 using a guinea pig anti-pork insulin antibody obtained from Miles Pentex Laboratory, Kankakee, Ill. A rabbit anti-guinea pig second antibody and polyethylene glycol (4.5%) were then added to precipitate the insulin-antibody complex. The sensitivity of assay is ~5 microunits/ml, and the intra-assay and interassay coefficients of variance are 2.1% and 3.5%, respectively. Glucose was determined with an enzymatic assay using glucose oxidase.18 The intra-assay and interassay coefficients of variance are 1.2% and 2.6%, respectively.

HDL was separated from other lipoproteins in plasma by sequential ultracentrifugation at 170,000g for 24 hours at d=1.063 g/ml using a 50.2 rotor in a <855M Beckman ultracentrifuge (Beckman Instruments, Inc., Palo Alto, Calif.). Density was adjusted by the addition of solid KBr. HDL cholesterol was determined as the cholesterol content in the infranatant of d=1.063 g/ml, corrected for dilution factors and expressed as milligrams per deciliter of plasma equivalent.19 The interassay coefficient of variance is 4%.

ApoAI was quantified by radial immunodiffusion assay.20 The agar plates containing antihuman apoAI were obtained from Tago Immunodiagnostics, Inc., Burlingame, Calif. The intra-assay and interassay coefficients of variance are 3.2% and 6.9%, respectively. ApoAI concentration was also determined on multiple occasions during 125I-apoAI/HDL turnover studies to see if a steady state of plasma apoAI was maintained throughout the duration of the study.

High Density Lipoprotein Turnover

When planning these studies it was apparent that it would take approximately 18 months to complete them. Based on previous experience, we knew that the quality of the purified apoAI preparations and our ability to maintain a good iodinated "tracer" preparation declined with time. Therefore, it would not be possible to use one pool of purified apoAI for all studies. Consequently, we prepared pools of purified apoAI as described previously16 from either normal subjects or patients with hypertension in a sequential fashion. A new pool of purified apoAI was prepared every 4 months and was used for all patients studied during that period. Care was taken to make sure that turnover measurements made with one pool of apoAI always included approximately equal numbers of normal individuals and patients with hypertension, and between four and six individuals were studied with each pool of apoAI. HDL apolipoprotein pool was prepared by ether-ethanol delipidation21 of dialyzed HDL fraction (d=1.063–1.215) at a concentration no higher than 5 mg/ml. The extracted protein suspension was dissolved in saturated guanidine chloride, and apoAI was separated from other apoproteins (AIV, E, AII, and Cs).
by column chromatography via sepharyl 200 using a running buffer containing 50 mM Tris-Cl (pH 8.0), 3 mM EDTA, and 4 M guanidine chloride.\textsuperscript{16,22} Two each of left and right shoulder fractions containing low concentrations of apoAI were discarded, and the peak fractions were pooled and dialyzed against phosphate-buffered (20 mM, pH 7.4) saline exhaustively. Aliquots of approximately 1 mg/ml of apoAI were stored in a freezer at -70 °C and iodinated by modified McFarlane Method\textsuperscript{23,24} when needed. The purity of apoAI (molecular weight, 27,000 Da) was assessed by loading a 7% sodium dodecyl sulfate–polyacrylamide gel and electrophoresing against standards of various molecular weights. Preparations of apoAI were usually more than 99% pure. The iodinated apoAI was dialyzed against phosphate-buffered (5 mM, pH 7.4) saline containing 0.01% EDTA, 80 ng/ml gentamicin, and 80 \mu g/ml chloramphenicol. Autologous HDL was isolated from each patient by sequential ultracentrifugation\textsuperscript{25} using aseptic techniques and then was dialyzed against sterile saline. \textsuperscript{125}I-apoAI/HDL was then prepared by combining the iodinated apoAI with 2-4 ml autologous HDL at a concentration of 2-5 mg protein/ml and centrifuging it at \( d = 1.215 \) g/ml for 24 hours. More than 80% of \textsuperscript{125}I-apoAI bound with HDL surfaced to the top of the centrifuge tube. This freshly prepared \textsuperscript{125}I-apoAI/HDL was collected carefully with a sharp pipette, dialyzed, sterilized by passing through a 0.22 \mu m millipore filter precoated with \(-2 \) mg unlabeled HDL protein, and tested for pyrogenicity in rabbits.\textsuperscript{26} All patients were given 100 mg of a saturated solution of potassium iodide for 30 days, beginning 2 days before the ligand injection. Blood was drawn 10, 20, 30, 40, and 60 minutes and 3, 6, 12, 24, and 36 hours after injection of tracer. In addition, blood samples were obtained daily for the next 15 days. \textsuperscript{125}I-apoAI/HDL kinetics were quantified as described previously.\textsuperscript{16} Briefly, the disappearance curve of \textsuperscript{125}I-apoAI/HDL was plotted as the logarithm of percent of initial plasma \textsuperscript{125}I-apoAI/HDL radioactivity remaining against time, and a three-component model was used to determine the kinetic constants. This decision was based on our previous experience in measuring HDL disappearance in humans using apoAI-labeled HDL as the tracer\textsuperscript{16} when a three-component model was noted to be statistically superior to a two-component model (i.e., it had the lowest residual sum of squares) in fitting the disappearance curve of \textsuperscript{125}I-apoAI/HDL. This analysis was performed by resolving the nonlinear \textsuperscript{125}I-apoAI/HDL disappearance curve into three linear components using the Marquardt iterative method\textsuperscript{27} with the following equation:

\[
\begin{align*}
\% \text{ plasma radioactivity remaining} &= p(4)e^{-p(1)t} + p(5)e^{-p(2)t} + p(6)e^{-p(3)t} \\
\end{align*}
\]

in which \( p(1) \), \( p(2) \), and \( p(3) \) represent the slopes and \( p(4) \), \( p(5) \), and \( p(6) \) the intercepts of each of the linear components. With this analysis, the values of \( p(1) \), \( p(2) \), and \( p(3) \) were equal to the fractional clearance constant of each decay component, respectively, and \( p(4) \), \( p(5) \), and \( p(6) \) the percent of total \textsuperscript{125}I-apoAI/HDL removed via each decay component. The sum of \( p(4) \), \( p(5) \), and \( p(6) \) was equal to 100% of \textsuperscript{125}I-apoAI/HDL injected. The estimated parameters were then used to calculate total residence time (RT), which is equal to \[
\left( \frac{p(4)}{p(1)} + \frac{p(5)}{p(2)} + \frac{p(6)}{p(3)} \right) / 100
\]

fractional catabolic rate (FCR), which is equal to 1/RT, and total turnover rate or absolute synthetic rate, which is equal to plasma apoAI concentration × plasma volume × FCR.\textsuperscript{16} Plasma volume was estimated as the ratio of the amount of radioactivity injected (\( \mu Ci \)) to the plasma radioactivity (\( \mu Ci/ml \)) at time zero. The plasma radioactivity at zero time was extrapolated from the radioactivity in plasma at time 10, 20, 30, 40, and 60 minutes.

### Statistical Analysis

All results were expressed as mean±SEM, and statistical analysis was performed using the Statistical Analysis System. To compare data from normal individuals and hypertensive patients, one-way (group) and two-way (group and time) analysis of variance (ANOVA) were applied as appropriate.\textsuperscript{28} Correlation coefficients (\( r \)) were calculated\textsuperscript{29} as described by Pearson, with partial correlation coefficients calculated when deemed appropriate.

### Results

Plasma concentrations of HDL-cholesterol and apoAI of the two groups are compared in Table 2. These data demonstrate that plasma HDL-cholesterol concentration was lower (\( p<0.01 \)) in hypertensive patients (37±2 mg/dl) as compared with that seen in normal subjects (49±4 mg/dl). However, plasma apoAI concentration was not different between the two groups (126±6 versus 125±5 mg/dl). Consequently, the ratio of HDL cholesterol to apoAI was lower (\( p<0.01 \)) in patients with hypertension (0.30±0.01 versus 0.39±0.02).

Plasma apoAI concentrations were measured on day 1, 4, 7, 10, and 15 of the turnover study, and these results are seen in Figure 1. Concentrations of apoAI remained within 10% of initial value in all patients. No statistically significant variation in apoAI concent-

### Table 2. Plasma Concentrations of High Density Lipoprotein-Cholesterol, Apolipoprotein AI, and the Ratio of High Density Lipoprotein-Cholesterol to Apolipoprotein AI in Normal Subjects and Patients With Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>49±4</td>
<td>37±2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>apoAI (mg/dl)</td>
<td>126±6</td>
<td>125±5</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-cholesterol/apoAI</td>
<td>0.39±0.02</td>
<td>0.30±0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are mean±SEM. HDL, high density lipoprotein; apoAI, apolipoprotein AI.
Figure 1. Line graph showing plasma apolipoprotein Al (apoAI) concentrations during $^{125}$I-apoAI/high density lipoprotein (HDL) turnover studies in normal subjects (■) and patients with hypertension (○).

The disappearance with time was observed in either normal individuals or patients with hypertension.

The disappearance curves of $^{125}$I-apoAI/HDL from plasma in control subjects and patients with hypertension are shown in Figure 2. It can be seen that $^{125}$I-apoAI/HDL was removed at a faster rate in patients with high blood pressure ($p<0.001$). These curves were analyzed according to the three-component model as described in Methods; the kinetic constants are summarized in Table 3. The rate constants of each of the three components are designated $p(1)$, $p(2)$, and $p(3)$, and it can be seen that there was a significant increase in the removal rate of $^{125}$I-apoAI/HDL from the second (0.96±0.12 versus 0.67±0.11 I/day) and third (0.17±0.01 versus 0.12±0.01 I/day) phases in patients with high blood pressure ($p<0.05$). The proportion of the total removal of radioabeled HDL from each of the three components is also shown in Table 3, designated $p(4)$, $p(5)$, and $p(6)$. It can be seen that approximately half of the total removal of $^{125}$I-apoAI/HDL was from $p(5)$ (48.1±3.8% and 46.0±2.5%) in both groups. It is also apparent from Table 3 that there were no differences in the degree to which radioactive HDL was removed by first phase $p(4)$ (14.2±3.9% versus 16.1±3.7%), second phase $p(5)$ or third phase $p(6)$ (37.6±6.0 versus 37.1±5.0%) in the two groups.

The data shown in Table 3 can be used to determine the RT and FCR of $^{125}$I-apoAI/HDL, and the results of these calculations appear in Table 4. It is apparent from these data that RT was significantly ($p<0.001$) shorter (2.84±0.15 versus 4.02±0.27 l/day) and FCR, being the reciprocal of RT, significantly ($p<0.001$) faster (0.36±0.02 versus 0.26±0.02 I/day) in patients with high blood pressure. Total turnover rate of $^{125}$I-apoAI/HDL was also calculated (see Methods), and the results shown in Table 4 demonstrate that the synthetic rate was significantly ($p<0.005$) greater in patients with hypertension (17.4±1.1 versus 13.2±0.6 mg/kg/day).

The results to this point have not differentiated between men and women, given the preponderance of men in both groups. However, to make sure that the data have not been confounded by this decision, the results of the men in the two groups are compared in Table 5. It can be seen that the differences between the control population and the patients with hypertension persist when only men are considered.

The relation between systolic blood pressure and the FCR of $^{125}$I-apoAI/HDL is shown in the left panel of Figure 3. Although there was a statistically significant correlation ($r=0.52$, $p<0.01$) in the entire experimental population, there was no relation between these two variables when either normal individuals ($r=-0.16$, $p=NS$) or patients with hypertension ($r=-0.04$, $p=NS$) were considered separately. The results were essentially identical when diastolic blood pressure was substituted for systolic blood pressure. The relation between FCR of $^{125}$I-apoAI/HDL and fasting plasma insulin concentration is shown in the right panel of Figure 3, and there was a highly significant correlation between these variables when all subjects were considered together ($r=0.72$, $p<0.001$). Furthermore, this correlation persisted when either control subjects ($r=0.78$, $p<0.005$) or patients with hypertension were considered separately ($r=0.61$, $p<0.05$). Finally, the relations between insulin and FCR in the entire group ($p<0.01$) and in both subgroups ($p<0.05$) persisted when partial correlation coefficients were deter-
Discussion

The results presented show that the group of patients with relatively mild hypertension and hyperinsulinemia that we studied had significant changes in apoAI/HDL kinetics. Specifically, the FCR of apoAI/HDL was faster than normal in patients with high blood pressure. Because the plasma apoAI pool size was similar in control subjects and patients with hypertension, the total synthetic rate of apoAI was also significantly greater than normal in patients with high blood pressure. In addition, plasma HDL-cholesterol concentration was significantly lower in patients with hypertension than in the control population. Thus, multiple changes in HDL metabolism have been shown to be present in this group of patients with high blood pressure. Furthermore, the differences in HDL metabolism observed between normal subjects and hypertensive patients remained valid when women were excluded from the data analysis. Similarly, the differences in FCR, RT, and turnover rate of apoAI/HDL between normal subjects and hypertensive patients remained highly significant when the analysis of covariance was performed adjusting for the degree of obesity (body mass index).

Given all of these changes, it was somewhat surprising to find that plasma apoAI concentrations were similar in the two groups of subjects and that no correlation existed between the FCR of apoAI/HDL and plasma apoAI concentration. Although there was a modest ($r=0.35$) relation between plasma apoAI concentration and total apoAI/HDL synthetic rate, it was of marginal statistical significance ($p<0.09$). However, the FCR of apoAI/HDL was significantly correlated with plasma HDL-cholesterol concentration ($r=-0.45$, $p<0.05$). Consequently, it seems that plasma HDL-cholesterol concentration is more dependent on the metabolism of apoAI/HDL than is plasma apoAI concentration.

The changes in the kinetics of apoAI/HDL noted in patients with high blood pressure are in the same direction as those we have recently described in patients with NIDDM. Furthermore, it has been reported that the fractional catabolic rate of HDL was increased in patients with hypertriglyceridemia. The fact that apoAI/HDL fractional catabolism is increased in three clinical syndromes—hypertension, NIDDM, and hypertriglyceridemia—can be viewed in two general ways. On the one hand, it could be argued that this change is intrinsic to each of the three conditions. Alternatively, the change in apoAI/HDL kinetics could be relatively independent of the specific disease per se but secondary to a change common to all three. Unfortunately, at the present time it is not possible to choose between these two general possibilities. However, we believe that a strong argument can be made in favor of the

Table 3. Decay Constants of Iodine-125 Apolipoprotein AI/High Density Lipoprotein Turnover in Normal Subjects and Patients With Hypertension

<table>
<thead>
<tr>
<th>Group</th>
<th>p(1)(l/day)</th>
<th>p(2)(l/day)</th>
<th>p(3)(l/day)</th>
<th>p(4)(%)</th>
<th>p(5)(%)</th>
<th>p(6)(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>21.6±11.0</td>
<td>0.67±0.11</td>
<td>0.12±0.01</td>
<td>14.2±3.9</td>
<td>48.1±3.8</td>
<td>37.6±6.0</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>28.3±13.3</td>
<td>0.96±0.12</td>
<td>0.17±0.01</td>
<td>16.1±3.7</td>
<td>46.0±2.5</td>
<td>37.9±5.0</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>&lt;0.06</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
latter alternative. More specifically, there is evidence suggesting that an increase in plasma insulin concentration plays a central role in regulation of both plasma HDL-cholesterol concentration and the FCR of $^{125}$I-apoAI/HDL. Patients with hypertension, NIDDM, and hypertriglyceridemia have been shown to be inversely related. The suggestion that plasma insulin concentration, rather than disease, is most responsible for the increase in fractional apoAI/HDL catabolism is supported by the present results showing that there was a highly statistically significant correlation between FCR of apoAI/HDL and plasma insulin concentration in both the control population ($r=0.78, p<0.005$) and in patients with high blood pressure ($r=0.61, p<0.05$). In contrast, there was no correlation between systolic or diastolic blood pressure and FCR of apoAI/HDL in either population.

The suggestion that hyperinsulinemia may be responsible for the increase in apoAI/HDL fractional catabolic rate seen in patients with high blood pressure, NIDDM, and hypertriglyceridemia is not only consistent with the observation that patients with these syndromes often have high plasma insulin levels, it also provides a possible mechanism for the change in HDL turnover. Thus, there is evidence that the higher the ambient plasma insulin concentration, the higher the VLDL turnover rate, the greater the HDL flux. Consequently, it could be hypothesized that the hyperinsulinemia seen in patients with hypertension, NIDDM, or hypertriglyceridemia leads to an increase in VLDL turnover, resulting in both an increase in HDL flux and a decrease in plasma HDL-cholesterol concentration. This formulation has the advantage of being consistent with available experimental data, as well as being amenable to experimental validation. However, there are certainly other possible explanations for the changes in plasma HDL-cholesterol concentration and apoAI/HDL fractional catabolic rate seen in patients with high blood pressure, NIDDM, and hypertriglyceridemia. For example, changes in postheparin lipoprotein lipase, adipose tissue lipoprotein lipase, and hepatic lipase activity have been demonstrated to correlate positively (lipoprotein lipase) and negatively (hepatic lipase) with plasma HDL-cholesterol concentration. In addition, there is evidence that FCR of $^{125}$I-HDL correlates with both hepatic and adipose tissue lipoprotein lipase activity. Thus, it is also possible that variations in the activity of one or both of these enzymes contribute to the increase in apoAI/HDL FCR and decrease in plasma HDL-cholesterol concentration seen in patients with all three clinical syndromes. These suggested mechanisms are not mutually exclusive, and there is evidence that changes in plasma insulin concentration can modulate lipoprotein and hepatic lipase activity. Perhaps the most important point to make at

### Table 4. Plasma Volume, Apolipoprotein AI Concentration, Total Fractional Catabolic Rate and Turnover Rate of $^{125}$I-Apolipoprotein AI/HDL in Normal Subjects and Patients With Hypertension

<table>
<thead>
<tr>
<th>Group</th>
<th>ApoAI concentration (mg/ml)</th>
<th>Plasma volume (ml/kg)</th>
<th>FCR (l/day)</th>
<th>Turnover rate (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>1.26±0.06</td>
<td>40.4±2.4</td>
<td>0.26±0.02</td>
<td>13.2±0.6</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>1.25±0.05</td>
<td>38.8±2.0</td>
<td>0.36±0.02</td>
<td>17.4±1.1</td>
</tr>
</tbody>
</table>

Values are mean±SEM. ApoAI, apolipoprotein AI; RT, residence time; FCR, fractional catabolic rate.

### Table 5. Values for All Measured Variables in Normal and Hypertensive Men

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive (n=8)</th>
<th>Hypertensive (n=10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (hr)</td>
<td>46±4</td>
<td>47±3</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27±2</td>
<td>30±2</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>110±5</td>
<td>142±2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76±4</td>
<td>95±1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>93±3</td>
<td>93±2</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting insulin (microunits/ml)</td>
<td>11±2</td>
<td>21±5</td>
<td>&lt;0.07</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>45±4</td>
<td>37±2</td>
<td>&lt;0.07</td>
</tr>
<tr>
<td>apoAI (mg/dl)</td>
<td>127±7</td>
<td>125±5</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-cholesterol/apoAI</td>
<td>0.35±0.02</td>
<td>0.30±0.01</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Fractional catabolic rate (l/day)</td>
<td>0.25±0.02</td>
<td>0.37±0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Residence time (day)</td>
<td>4.20±0.35</td>
<td>2.80±0.16</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Turnover (mg/kg/day)</td>
<td>13±0.7</td>
<td>18±1.3</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Values are mean±SEM. HDL, high density lipoprotein; apoAI, apolipoprotein AI.
this juncture is that it seems most likely that some phenomenon, common to patients with high blood pressure, NIDDM, and hypertriglyceridemia, is responsible for the decrease in plasma HDL-cholesterol concentration and increase in apoAI/HDL fractional catabolic rate associated with these syndromes.

It should also be pointed out that it does not necessarily follow that all individuals with a low plasma HDL-cholesterol concentration have an increased FCR of apoAI/HDL. Indeed, we have presented evidence that low plasma HDL-cholesterol concentrations in patients with chronic renal failure were associated with a decrease, not an increase, in the catabolic rate of apoAI/HDL. Since patients with chronic renal failure are also insulin resistant and hyperinsulinemic, it could be argued that these data question the importance of plasma insulin concentration in regulation of HDL metabolism. On the other hand, it is interesting to note that both very low density lipoprotein (VLDL) and HDL turnover rates are decreased in patients with chronic renal failure, whereas VLDL and HDL turnover rates are increased in patients with endogenous hypertriglyceridemia and NIDDM. Thus, what appears to be constant is the nature of the relation between VLDL and HDL kinetics. Obviously, there is a factor, or factors, present in patients with chronic renal failure that play a more important role than hyperinsulinemia in regulation of VLDL and HDL kinetics. For example, lipoprotein lipase activity is decreased in patients with chronic renal failure. In addition, there is also evidence that patients with chronic renal failure have a factor in their plasma that inhibits lipoprotein lipase activity. Thus, several possible mechanisms could result in abnormal VLDL-triglyceride hydrolysis and HDL metabolism, consistent with the close link observed between VLDL and HDL metabolism seen in other groups of patients. It is not entirely clear why hyperinsulinemia and insulin resistance seen in these patients did not cause hypersecretion of VLDL or accelerated FCR of apoAI/HDL. However, since VLDL is secreted by liver, and apoAI/HDL is catabolized largely by kidney and liver, it is certainly possible that the impaired kidney and liver functions seen in these patients can contribute significantly to the abnormal metabolism of VLDL and HDL directly, thus rendering the effect of hyperinsulinemia in this particular case less overwhelming. Thus, this specific situation should not detract from the possible usefulness of our hypothesis in patients in whom insulin resistance and hyperinsulinemia may be the most obvious metabolic abnormalities.

In summary, the patients with mild hypertension that we studied were hyperinsulinemic, synthesized more apoAI/HDL, had a faster FCR of apoAI/HDL, and a lower plasma HDL-cholesterol concentration as compared with individuals with normal blood pressure. It is suggested that the changes in HDL-cholesterol concentration and apoAI/HDL FCR are secondary to the hyperinsulinemia, rather than to the increase in blood pressure. Furthermore, it appears likely that similar changes in plasma HDL concentration and turnover rate previously noted in patients with NIDDM and hypertriglyceridemia are also secondary to increases in plasma insulin concentration.

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High density lipoprotein turnover in patients with hypertension.
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