Diabetes Mellitus and Hypertension
State of the Art Lecture
OSWALDO LUIZ RAMOS

SUMMARY In rats with streptozotocin-induced diabetes an increase in arterial blood pressure was observed as early as the first week after the drug was injected. Blood pressure reached maximal values around the fourth week and remained stable for a long period of follow-up. The responsiveness of these rats to the three major vasopressor hormones, angiotensin II, norepinephrine, and vasopressin, was decreased in the early phase of diabetes and returned to normal in the late phase. Acute treatment at the third, sixth, and twelfth weeks with blockers of these vasopressor hormones resulted in a significant fall in blood pressure at the third week with captopril and at the twelfth week with propranolol plus phentolamine. No significant fall was observed when a specific vasopressin inhibitor was administered. Good control of the blood pressure was obtained when these rats were treated chronically with captopril or prazosin, and partial control was achieved when they were fed a low salt diet. An attenuation in arterial blood pressure levels was observed in rats with two-kidney, one clip hypertension when diabetes was induced by streptozotocin. Plasma creatinine levels in diabetic rats were significantly higher than those in control rats only in the sixth and twelfth weeks. Electron microscopy revealed some minor glomerular lesions only at the twelfth week.

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KEY WORDS • nervous system • streptozotocin • vasopressin • experimental diabetes • angiotensin II • sympathetic nervous system • vasopressin antagonist • converting enzyme inhibitor

HYPERTENSION is common in diabetic patients, and it interferes with the rate of development and progression of the specific diabetic complication, such as nephropathy, that in itself, might be a contributory factor causing and aggravating the hypertensive disease.1,2

Epidemiological Data
The real prevalence of hypertension in the diabetic population is not known. The difficulty in gathering accurate data is mainly due to the fact that there are two types of diabetes mellitus (DM), the insulin-dependent disease (IDD) and the non-insulin-dependent disease (NIDD), which appear to be distinct diseases.

In a multicenter survey in the United Kingdom,3 the prevalence of hypertension was 40% in male and 53% in female subjects with newly diagnosed NIDD. These rates were higher than those in sex- and age-matched control subjects. Krolewski et al.4 showed that in patients with diabetes of short, long, and very long duration, the prevalence of hypertension was 1.7, 1.9, and 2.1 times greater, respectively, than that observed in the white American population regardless of gender.

The prevalence of hypertension in IDD is also not certain. When an appropriate control population was used, no increase in the prevalence of hypertension was observed in young diabetic patients5; however, other surveys have reported higher prevalence in this group of patients.6-8 These conflicting results are understandable, given the frequent development of progressive degrees of renal insufficiency in these patients. Some reports showed that in patients with IDD, increases in blood pressure may precede macroproteinuria as well as major depressions of glomerular filtration rate.9,10 It is well known that in these patients the prevalence of hypertension increases gradually at the same time that renal damage progresses. It is fair to state that practically all patients with IDD will be hypertensive during the final stage of renal disease.

Functional Renal Abnormalities in Diabetes
It is well documented in the literature that hyperglycemia causes microvascular vasodilatation and hyperfiltration in patients in early phases of IDD11,12 as well as in rats with experimental diabetes.13 The mechanism underlying these hemodynamic alterations is a matter of debate. Zatz et al.14 showed that rats with streptozotocin-induced diabetes, either treated with enalapril or not, exhibited an increase in average kidney weight, in whole kidney and single-nephron glomerular...
filtration rate (GFR), and in glomerular plasma flow rate compared to age- and weight-matched controls. These authors also demonstrated that only the rats that were not treated with enalapril exhibited significant elevation in mean glomerular capillary hydraulic pressure and in transcapillary hydraulic pressure gradient. Rats with these hemodynamic alterations would eventually develop marked and progressive albuminuria. These findings emphasize the important role that the intrarenal renin-angiotensin system may play in these alterations.14

Recently, Ortola et al.13 showed that in rats with streptozotocin-induced diabetes that were moderately hyperglycemic, the GFR was elevated well above control values, whereas in diabetic rats with strict blood glucose control, GFR did not differ significantly from that in normal controls. In addition, the level of circulating atrial natriuretic factor (ANF) was elevated only in the moderately hyperglycemic rats. Thus it is possible that hyperglycemia induces chronic volume expansion that elicits ANF release, which could contribute to the hyperfiltration.

The renal hyperfusion inducing hyperfiltration accompanied by increased transcapillary hydraulic pressure gradient is said to be the main factor leading to progressive glomerular damage.14,16 "The hyperperfusion caused by microvascular dilatation would lead to elevation of capillary pressure and hyperflow, which, acting continuously, could damage the capillary walls and enhance their permeability to macromolecules. It would also augment capillary wall proliferation, with consequent thickening of basement membrane and narrowing of the lumina." Therefore it is not surprising that microalbuminuria is an early sign of diabetic nephropathy, being a good predictor of renal damage even before any other alterations of renal function have been noticed.17-20 In diabetic patients the presence of microalbuminuria is due initially to the disturbance of glomerular hemodynamics and eventually to the impairment of membrane selectivity.17

Another factor causing renal damage in diabetes is hypertension. It has been shown that when hypertension coexists with renal hyperfusion, the two act synergistically to induce progressive glomerular damage.17,21

**Hypertension and Diabetes**

To analyze some pathogenetic aspects of hypertension in diabetes mellitus, our group decided to study the development of high blood pressure in rats with streptozotocin-induced diabetes. In this experimental model, mild hypertension had been noticed by some investigators22 and denied by others.23 Kohlmann et al.24 administered a single intravenous dose of 50 mg/kg of streptozotocin to Wistar rats that did not receive any insulin supplementation. They noticed that the arterial blood pressure increased as early as the first week, reaching maximal values around the fourth week and remaining stable thereafter for a long period of follow-up. As can be seen in Figure 1, in control rats the baseline tail blood pressure of 117 ± 1 rose to 121 ± 1, 129 ± 1, 138 ± 1, and 139 ± 1 mm Hg respectively, in the first, second, third, and fourth weeks. This increase was somewhat larger when a higher streptozotocin dose (65 mg/kg) was used.24

The pathogenesis of this hypertension is not well known. In fact, the role of the major vasopressor hormones angiotensin II, norepinephrine, and vasopressin in maintaining elevated blood pressure in this animal model is controversial.23-28 To clarify the role of these hormones in the genesis of hypertension in diabetic rats, two sets of experiments were carried out by Kohlmann et al.24 The first tested vascular responsiveness to the three major vasopressor hormones during different phases of the hypertension. As shown in Figure 2, the vascular responsiveness to angiotensin II was significantly diminished in diabetic rats when compared to controls at the third and sixth weeks, but returned to control values at the twelfth week. The response to increasing doses of norepinephrine and vasopressin was similar. It seems clear, therefore, that hypertension in rats with streptozotocin-induced diabetes occurs only in the early phase of diabetes. This hypertension is accompanied by hyporesponsiveness to the three major vasopressor hormones, which returns to normal during the later phase.

The role of the vasopressor hormones in the genesis of hypertension in rats with streptozotocin-induced diabetes was evaluated also by treating them acutely with drugs to block their hypertensive action. As shown in Figure 3, blood pressure fell significantly in the third week when captopril (20 mg/kg) was administered. It
is worth while to note that the reduction in arterial blood pressure observed at the sixth and twelfth weeks was similar to that in control rats. Figure 3 also shows that, when the sympathetic nervous system was blocked by acute administration of propranolol plus phentolamine, a significant decrease in blood pressure occurred in the twelfth week. The reductions in arterial blood pressure observed at the third and sixth weeks were not significantly different from those in control animals. In addition, these rats demonstrated no significant changes in blood pressure at the third, sixth, and twelfth weeks after administration of a specific V, vasopressin inhibitor. Thus it was postulated that the hypertension observed in rats with streptozotocin-induced diabetes was caused mainly by an exacerbation of the renin-angiotensin system up to the third week. At the twelfth week the main factor in the maintenance of hypertension was the overactivity of the sympathetic nervous system. Vasopressin seemed to have an irrelevant role in the genesis of hypertension in these diabetic rats.

Another way to elucidate the pathogenetic factors involved in this type of hypertension is to treat the rats over the long term with blockers of these vasopressors. To accomplish this, Kohlmann et al. (unpublished data) measured arterial blood pressure for 6 weeks in streptozotocin-treated rats receiving either captopril (40 mg/kg/day) or prazosin (4 mg/kg/day). To evaluate the role of vasopressin on arterial blood pressure, diabetes was induced in Brattleboro rats. The results of these three experiments are summarized in Table 1. The arterial blood pressure in diabetic rats chronically treated with captopril was significantly lower than that in diabetic rats receiving no treatment, but not significantly different from the level in untreated control animals. In control animals in which captopril was administered, the arterial blood pressure was even lower than that observed both in untreated controls and in diabetic rats treated with captopril. In contrast to what was observed with captopril, the arterial blood pressure of diabetic rats receiving prazosin was lower than that of untreated controls and was similar to levels in controls that also received the drug. On the other hand, when diabetes was induced by streptozotocin in Brattleboro rats, the arterial blood pressure was significantly higher than levels in control Brattleboro rats, and slightly higher but not significantly different than levels in Wistar rats in which diabetes was induced (see Table 1).

It seems clear that, at least in the early phase of the hypertension observed in rats with streptozotocin-
induced diabetes, the renin-angiotensin system plays a decisive role. It is important to emphasize that continuous treatment with converting enzyme inhibitor prevents the appearance of hypertension in these animals. Furthermore, when captopril is administered to diabetic rats with sustained hypertension for 6 weeks (tail arterial pressure at the sixth week: 155 ± 2 mm Hg), blood pressure decreases progressively toward normal sodium content. Thus a low salt diet only partially prevents the appearance of high blood pressure in diabetic rats.

In conclusion, it is possible to state that chronic blockade of either the renin-angiotensin or sympathetic nervous system controls hypertension in rats with streptozotocin-induced diabetes. Moreover, the amount of sodium in the diet plays a role in the genesis of this hypertension.

It is also important to study the function and anatomy of the kidneys of these diabetic rats. In the control period, the mean plasma creatinine level was 0.8 ± 0.04 and rose to 0.94 ± 0.21, 1.1 ± 0.05, and 1.5 ± 0.09, respectively, in the third, sixth, and twelfth weeks after diabetes was induced. The plasma creatinine levels in the sixth and twelfth weeks were significantly higher than those in control rats. These results seem to indicate that diabetes causes progressive functional renal damage. On the other hand, it is important to consider that in the third week, when the plasma creatinine levels were not significantly different from those in controls, the diabetic rats were as hypertensive as those patients in the sixth and twelfth weeks.

### Table 1. Tail Arterial Pressure in Diabetic and Control Rats, Untreated or Chronically Treated with Captopril or Prazosin or Low Sodium Diet, and in Brattleboro Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Week</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<td>Diabetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Untreated</td>
<td>120 ± 2*</td>
<td>117 ± 1*</td>
<td>120 ± 2*</td>
<td>138 ± 1*</td>
<td>139 ± 1*</td>
<td>137 ± 1*</td>
<td>138 ± 1*</td>
<td></td>
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<tr>
<td>Captopril</td>
<td>124 ± 1</td>
<td>118 ± 1*</td>
<td>123 ± 1†</td>
<td>123 ± 1†</td>
<td>117 ± 2†</td>
<td>115 ± 2†</td>
<td>115 ± 2†</td>
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</tr>
<tr>
<td>Prazosin</td>
<td>118 ± 1</td>
<td>110 ± 2†</td>
<td>110 ± 2†</td>
<td>113 ± 1†</td>
<td>111 ± 1†</td>
<td>113 ± 2†</td>
<td>107 ± 1†</td>
<td></td>
</tr>
<tr>
<td>Brattleboro</td>
<td>138 ± 2*†</td>
<td>162 ± 6*†</td>
<td>155 ± 4*†</td>
<td>155 ± 4*†</td>
<td>158 ± 2*†</td>
<td>160 ± 4*†</td>
<td>154 ± 6*†</td>
<td></td>
</tr>
<tr>
<td>Low sodium</td>
<td>118 ± 1†</td>
<td>125 ± 1</td>
<td>124 ± 1*†</td>
<td>123 ± 1*†</td>
<td>124 ± 1*†</td>
<td>119 ± 1*†</td>
<td>123 ± 1*†</td>
<td></td>
</tr>
<tr>
<td>Control</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>118 ± 1</td>
<td>115 ± 1</td>
<td>117 ± 1</td>
<td>117 ± 1</td>
<td>118 ± 1</td>
<td>118 ± 1</td>
<td>117 ± 1</td>
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<tr>
<td>Captopril</td>
<td>124 ± 1</td>
<td>120 ± 1</td>
<td>116 ± 1</td>
<td>114 ± 2</td>
<td>113 ± 1*</td>
<td>106 ± 1*</td>
<td>104 ± 1*</td>
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<tr>
<td>Prazosin</td>
<td>123 ± 1</td>
<td>113 ± 2</td>
<td>112 ± 1*</td>
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<td>108 ± 1</td>
<td>109 ± 1*</td>
<td>110 ± 2*</td>
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<tr>
<td>Low sodium</td>
<td>119 ± 1</td>
<td>115 ± 1</td>
<td>114 ± 1</td>
<td>119 ± 1</td>
<td>117 ± 1</td>
<td>111 ± 1*</td>
<td>112 ± 2*</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SEM. *p < 0.05 vs control group; †p < 0.05 vs diabetic group.

### Table 2. Tail Arterial Pressure and Plasma Aldosterone Levels in Control, Goldblatt 2K1C Rats With and Without Diabetes Mellitus

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>Plasma aldosterone (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2K1C</td>
<td>115 ± 1</td>
<td>142 ± 5</td>
<td>153 ± 8</td>
<td>160 ± 5</td>
<td>164 ± 4</td>
<td>170 ± 6</td>
<td>169 ± 3</td>
<td>169 ± 2</td>
<td>166 ± 3</td>
<td>34.0 ± 5.9</td>
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<tr>
<td>2K1C + DM</td>
<td>116 ± 1</td>
<td>128 ± 3*</td>
<td>140 ± 5</td>
<td>141 ± 6*</td>
<td>144 ± 10*</td>
<td>139 ± 7*</td>
<td>139 ± 6*</td>
<td>135 ± 6*</td>
<td>132 ± 7*</td>
<td>15.3 ± 1.4*</td>
</tr>
<tr>
<td>2K1C +DM + P2K1C</td>
<td>115</td>
<td>140 ± 7</td>
<td>150 ± 6</td>
<td>158 ± 9</td>
<td>159 ± 9</td>
<td>143 ± 6*</td>
<td>145 ± 10*</td>
<td>144 ± 8*</td>
<td>139 ± 8</td>
<td>—</td>
</tr>
<tr>
<td>DM + 2K1C</td>
<td>116 ± 1</td>
<td>126 ± 2*</td>
<td>126 ± 2*</td>
<td>127 ± 2*</td>
<td>127 ± 2*</td>
<td>138 ± 8*</td>
<td>147 ± 6*</td>
<td>144 ± 6*</td>
<td>151 ± 7*</td>
<td>—</td>
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<tr>
<td>Control</td>
<td>118 ± 1</td>
<td>115 ± 1</td>
<td>117 ± 1</td>
<td>117 ± 1</td>
<td>118 ± 1</td>
<td>118 ± 1</td>
<td>117 ± 1</td>
<td>115 ± 1</td>
<td>117 ± 1</td>
<td>14.4 ± 2.6</td>
</tr>
</tbody>
</table>

Values are means ± SEM. Diabetes mellitus (DM) was induced concomitantly (2K1C DM), 4 weeks after (2K1C + DM), and 4 weeks before (DM + 2K1C) clipping the left kidney.

* *p < 0.05 vs 2K1C group.
In an attempt to determine the extent of renal damage in these rats, their kidneys were studied histologically by light and electron microscopy. On light microscopy the only lesions observed were the so-called Armani-Ebstein changes located in the straight portion of the proximal tubule and at the distal tubule, as described almost 30 years ago in diabetic patients with poor or no metabolic control. Electron microscopy revealed similar lesions at the tubular level. At the glomerular level, in spite of alterations in plasma creatinine levels, no changes were noted up to the sixth week after diabetes was induced. At the twelfth week, however, diffuse increases in the mesangial matrix and some degree of hypercellularity were observed. The tubules surrounding these glomeruli were somewhat degenerated and atrophic.

Thus, these results suggest that hypertension may precede deterioration of kidney function in diabetic rats. Additional studies are necessary to confirm these observations.

References

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