SHORT COMMUNICATION

RELATIONSHIP OF PLASMA ZINC TO HUMAN HYPERTENSION

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SUMMARY

1. Plasma zinc (µg/100 ml) was determined by atomic absorption spectrophotometry in ninety renal venous, inferior vena caval or peripheral venous specimens obtained from fifteen normal control subjects and thirty hypertensive patients, none of whom had renal failure.

2. Peripheral or central venous plasma zinc levels in ten patients with essential hypertension were not significantly different from those of control subjects. There were, however, significantly lower venous plasma zinc levels found in sixteen patients with renal artery stenosis and four patients with renal parenchymal disease.

3. The only clinical variable found to have a significant inverse correlation with plasma zinc was the mean arterial blood pressure.

4. There were no significant differences in zinc concentrations between central venous and renal venous plasma specimens.

Key words: blood pressure, hypertension, zinc, trace metals.

There has been increasing interest in the possibility that abnormalities of trace-metal metabolism may be involved in some as yet undefined manner in the pathogenesis of arterial hypertension. The interrelationships of zinc ions and cadmium ions, and their age-related accumulation in the body, have been considered to be accessory or augmenting factors in experimental and human hypertension (Thind, 1972; Perry, 1972; Schroeder, 1967). The objectives of the present investigation were: (1) to compare the plasma zinc levels of normal control subjects with those of patients with essential or secondary forms of hypertension, (2) to look for any differences in zinc levels between the renal venous plasma and inferior vena caval plasma in hypertensive patients, and (3) to seek any possible relationships of plasma zinc to clinical findings in hypertension.

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METHODS

Thirty hypertensive patients were admitted for investigation and therapy of hypertension. All antihypertensive medications were withheld for 7–10 days. While retrograde renal vein catheterization was performed to determine renal venous plasma renin activity (Thind, Blakemore & Zinsser, 1970), additional heparinized plasma samples from each renal vein and inferior vena cava below the entrance of renal veins (equivalent of a peripheral venous specimen) were obtained for zinc analysis. Central venous plasma specimens were obtained in three normal control subjects who had their inferior vena cava catheterized for demonstration of testicular varicosities. The remaining twelve normal subjects were volunteers who readily gave their informed consent to have peripheral blood drawn for this project. All of the control subjects were known to be in good health with no past medical history of renal disease and it was felt that an extensive renal study was not warranted under these circumstances.

All specimens were frozen and stored until zinc determinations were performed by atomic absorption spectrophotometry by modifications of the direct dilution method (Sprague & Slavin, 1965). The original Sprague & Slavin (1965) procedure utilized 1:1 dilution of plasma and they reported approximately 100% recovery. We, however, utilized 1:2 dilution to minimize differences in physical properties between plasma and standards even further, and confirmed their recovery. We have confirmed the observation of Prasad, Oberleas & Halsted (1966) that sodium reduces absorbance readings for zinc. The standards were made in sodium chloride solution (50 mmol/l), which is the approximate final sodium concentration in the diluted plasma. Air–acetylene mixture was used as fuel and a Boling three-slot burner head was used on the Perkin–Elmer model 303 atomic absorption spectrophotometer.

RESULTS

Plasma zinc concentrations and some of the clinical data in patients with the three forms of hypertension diagnosed primarily by renal arteriography and other standard investigations for hypertension, and in normal control subjects, are summarized in Table 1. Mean peripheral venous plasma zinc concentration in patients with essential hypertension was not significantly different from that of normal subjects, but in patients with renal artery stenosis or renal parenchymal disease (chronic pyelonephritis) was significantly lower than that of normal subjects ($P < 0.005$ for renal artery stenosis and $P < 0.05$ for renal parenchymal disease). The renal venous plasma zinc concentrations did not differ significantly from the concentrations in inferior vena caval plasma ($P > 0.20$) in each category of hypertensive patients. A comparison of zinc in the venous effluent of the kidney with renal artery stenosis (involved kidney) was made with that of the opposite (uninvolved) kidney in seven patients with unilateral renal artery stenosis. It is noteworthy that in six of seven patients, the renal venous zinc concentration of the involved kidney was higher than that of the uninvolved kidney; this difference, however, was not significant by paired $t$ test (involved kidney, $99.5 ± 5.4$ (SEM); uninvolved kidney, $90.6 ± 4.1$ μg/100 ml). The possibility that plasma zinc may be a function of the mean arterial blood pressure was considered. There was a significant inverse correlation between the mean arterial blood pressure and circulating levels of plasma zinc ($P < 0.05$). A correlation between plasma zinc levels and other clinical variables such as blood urea nitrogen, serum
creatinine, plasma proteins and serum electrolytes was sought; however, no correlation was found. The mean age ± SEM of the healthy control subjects (33.1 ± 2.8 years) was not different from that of all patients with hypertension (40.5 ± 2.6 years). The duration of hypertension was not different in essential and renal forms of hypertension. Although the average mean arterial blood pressure in patients with renal artery stenosis was not different from that of patients with renal parenchymal disease, both were significantly higher (P < 0.005 and 0.025 respectively) than that in patients with essential hypertension.

TABLE 1. Relationship of circulating plasma zinc to arterial blood pressure and kidney function. Type of hypertension was classified on the basis of renal arteriography and standard investigations for hypertension. Mean blood pressure is the diastolic blood pressure plus one-third of the difference between the systolic and diastolic blood pressures; IVC, inferior vena cava below entrance of renal veins; PV, peripheral venous specimen; RRV, right renal vein; LRV, left renal vein; n, number of patients.

<table>
<thead>
<tr>
<th>Type of hypertension</th>
<th>Average BP mean ± SEM (mmHg)</th>
<th>Blood urea N mean ± SEM* (mg/100 ml)</th>
<th>Creatinine, mean ± SEM† (mg/100 ml)</th>
<th>Mean plasma zinc mean ± SEM (µg/100 ml)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IVC or PV</td>
</tr>
<tr>
<td>Normal (control)</td>
<td>96 ± 1.8</td>
<td>51 ± 4.1</td>
<td>113 ± 4.6</td>
<td>120 ± 5.5</td>
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<tr>
<td></td>
<td>(n = 15)</td>
<td>(n = 15)</td>
<td>(n = 15)</td>
<td>(n = 10)</td>
</tr>
<tr>
<td>Essential</td>
<td>129 ± 2.4</td>
<td>15.1 ± 4.1</td>
<td>120 ± 5.5</td>
<td>115 ± 13.2</td>
</tr>
<tr>
<td></td>
<td>(n = 10)</td>
<td>(n = 10)</td>
<td>(n = 10)</td>
<td>(n = 4)</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>151 ± 4.9</td>
<td>17.6 ± 5.4</td>
<td>92 ± 4.2</td>
<td>95 ± 3.8</td>
</tr>
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<td>(n = 16)</td>
<td>(n = 15)</td>
<td>(n = 16)</td>
<td>(n = 15)</td>
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<tr>
<td>Renal parenchymal</td>
<td>156 ± 15.4</td>
<td>15.3 ± 5.6</td>
<td>96 ± 4.9</td>
<td>107 ± 10.0</td>
</tr>
<tr>
<td>disease†</td>
<td>(n = 4)</td>
<td>(n = 4)</td>
<td>(n = 4)</td>
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</tr>
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</table>

* Normal blood urea N = 10.0–25.0 mg/100 ml.
† Normal serum creatinine = 0.5–1.3 mg/100 ml.
‡ Blood urea N and serum creatinine of the sixteenth subject were reported normal.
§ Plasma zinc was significantly lower than that of normal control subjects and essential hypertension.
¶ Chronic pyelonephritis diagnosed by history of upper urinary tract infection, positive urine culture for micro-organisms, intravenous pyelographic or arteriographic evidence of loss of cortex with or without renal contraction and, in one patient, renal biopsy.

DISCUSSION

We have demonstrated low venous plasma zinc levels in hypertensive patients with renal artery stenosis and renal parenchymal disease in the absence of chronic uraemia. Low plasma zinc levels have been reported in most patients with chronic renal failure (Mansouri, Halsted & Combos, 1970; Halsted & Smith, 1970; Condon & Freeman, 1970; Mahler, Walsh & Haynie, 1971). Condon & Freeman (1970), however, did not find excessive urinary excretion of zinc or abnormalities of plasma proteins or pH of blood or total-body zinc deficiency in chronically uraemic subjects. The only clinical variable found to have a significant inverse correlation with
plasma zinc in our hypertensive patients was the level of the mean arterial blood pressure. Essential hypertensive patients were mildly hypertensive and plasma zinc levels were not different from those of normal control subjects. This finding is consistent with the only report of serum zinc levels in essential hypertension, in which case there was no difference from normal (Sinha & Gabrieli, 1970). The significantly more severe hypertension in our patients with renal artery stenosis and renal parenchymal disease was associated with low plasma zinc concentrations. It is conceivable that abnormalities of plasma zinc may become apparent in severe essential hypertension.

Trace metals, such as zinc and cadmium, are higher in concentration in the normal human kidney cortex than in renal medulla (Yunice et al., 1968; Livingston, 1972). The only tissue found to have a zinc deficit in patients with chronic uraemia was the kidney with virtual loss of renal cortical tissue due to intrinsic renal disease (Condon & Freeman, 1970). Experimentally, in the rat, Schroeder, Nason, Prior, Reed & Haessler (1968) showed that reduction of renal mass by unilateral renal artery constriction was associated with loss of renal zinc and no loss of renal cadmium.

Although no clinically significant renal impairment was apparent in our patients, there was usually radiographic evidence of either reduced total renal mass or patchy loss of renal cortical substance in patients with secondary forms of hypertension. The mechanism or mechanisms for hypozincæmia in chronic renal failure have not been defined. It is possible that such mechanisms might also be operative in our hypertensive patients.

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REFERENCES

Zinc and hypertension


