Absence of Glomerulosclerosis in Watanabe Heritable Hyperlipidemic Rabbits

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Dear Sir,

The role of lipids in the pathogenesis and progression of glomerulosclerosis has become a focus of recent investigation. Some studies suggest that the development of glomerulosclerosis is analogous to that of atherosclerosis [1]. This hypothesis is in part based upon studies in the spontaneously hyperlipidemic obese Zucker rat [2], in rats with an increased dietary intake of cholesterol [3] and on experimental models such as the aminonucleoside [4] and the remnant kidney model [5] in the rat. Pharmacological intervention in lipid metabolism is capable of preventing the development of glomerulosclerosis [2, 5]. Recently, another spontaneously hyperlipidemic rat strain developing glomerulosclerosis with age was reported [6]. Cholesterol-fed hyperlipidemic guinea pigs are also susceptible to the development of glomerulosclerosis [7]. In humans, however, primary hyperlipidemia does not seem to be a risk factor for the development of glomerulosclerosis.

The Watanabe heritable hyperlipidemic (WHHL) rabbit is an established model for atherosclerosis. We examined kidneys of WHHL rabbits available from a study analyzing the effect of pravastatin (Bristol Myers Squibb, Princeton, N.J., USA) a β -hydroxy- β -methylglutaryl-coenzyme A reductase inhibitor, on the development of atherosclerosis in this strain [8, 9]. The experimental group (group P, n = 7) was treated from the age of 3 months with pravastatin for a period of 9 months. Pravastatin was administered orally, in an increasing dosage by means of pravastatin-enriched chow. The dose administered was 20 mg/kg/day for the first 5 months and 40 mg/kg/day for the last 4 months of the study. A second group of rabbits, matched for age, sex and body weight, served as controls (group C, n = 10). The animals had free access to tap water and were fed 100 g/day of a commercially pelleted diet containing 15.5% digestible protein (LK-04, Hope Farms, Woerden, The Netherlands). Serum lipids were determined every 4 weeks, and the rabbits were sacrificed at 12 months of age. Coronary arteries and the complete aorta from the arch to the iliac bifurcation were examined for intimal atherosclerotic lesions by a point-counting method. The kidneys were processed for light microscopy and stained with either HE, periodic acid Schiff or methenamine silver.

Baseline plasma total cholesterol levels were comparable (C: 11.26 ± 1.67 , P: 12.73 ± 3.00 mmol/l). Pravastatin treatment caused a reduction in plasma total cholesterol of approximately

43% (C: 14.82 ± 3.15 , P: 6.72 ± 2.59 mmol/l). Serum creatinine did not differ (C: 87 ± 12 , P: 92 ± 16 μ mol/l). Body weight at the end of the study and the combined weight of the left and right kidneys were comparable between groups (body weight: C: $2,697 \pm 228$, P: $2,571 \pm 273$ g; combined kidney weight: C: 17.4 ± 2.5 , P: 17.7 ± 0.7 g). Urinary protein concentrations did not differ [C: 15.7 (10.5-65.5), P: 33.0 (13.2-186.3) g/ mmol creatinine].

Kidney sections of each animal were examined for evidence of any of the features of glomerulosclerosis including: adhesions to Bowman's capsule, deposition of hyaline material, capillary collapse, mesangial increase or foam cells. No evidence of glomerulosclerosis was observed in either group. Frozen sections stained with oil red O revealed no glomerular fat deposition. Kidneys from both groups revealed foci with a foamy aspect of

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Fig. 1. Photomicrograph of a control kidney showing a foamy aspect of tubular cells, interstitial foam cells, cholesterol clefts and some mononuclear cells. PAS. $\times 100$.

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Fig. 1. Photomicrograph of a control kidney showing a foamy aspect of tubular cells, interstitial foam cells, cholesterol clefts and some mononuclear cells. PAS. $\times 100$.

Fig. 2. Photomicrograph of a control kidney showing glomeruli with global sclerosis in a part of the cortex corresponding to the medullary lesion shown in figure 1. PAS. $\times 100$.

tubular cell cytoplasm. The corresponding interstitium contained foam cells, cholesterol clefts and occasionally mononuclear cells (fig. 1). Oil red O demonstrated fat deposition in these cells, shown to be cholesterol by the Okamoto method of staining. These lesions were primarily located at the corticomedullary junction. The glomeruli in the corresponding cortex showed global sclerosis (fig. 2). These glomeruli did not contain foam cells. Similar tubular lesions have been described in cholesterol-fed hypercholesterolemic rabbits [10]. There was no apparent effect of treatment with pravastatin (C: 5/10, P: 2/7 animals with the described tubular lesions). Neither vascular anomalies nor atheromatous emboli were observed in either group. In the aorta, pravastatin treatment significantly reduced the total area of intima covered with atherosclerotic plaques (C: 25.2 ± 8.1 , P: $12.0 \pm 11.3\%$) and reduced the incidence of coronary vascular lesions (C: 34.1, P: 25.0%).

In conclusion, results from this study indicate that although WHHL rabbits are susceptible to atherosclerosis, they are resistant to

the development of glomerulosclerosis as was also found by Raij et al. [11]. We speculate that a regional difference in the response of vascular beds, i.e., the aorta and the glomerulus, to the deleterious effects of hyperlipidemia may exist. This study supports previously reported findings of species-specific differences in the susceptibility to glomerulosclerosis [12].

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