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Cholesterol synthesis
hyper-
cholesterolemia

hyperproteinemia
plasma infusion
proteinuria

Hyperproteinemic Proteinuria Induced by Plasma Infusion

PETER N. MCLAINE, MELVIN I. MARKS, TADLA BALIAH, and KEITH N. DRUMMOND [39]

Renal Laboratory, McGill University-Montreal Children's Hospital Research Institute, Montreal, Quebec, Canada

Extract

Five of seven children receiving plasma for correction of coagulation disorders developed transient proteinuria during 10 of 21 infusions. Frozen plasma with a mean protein and cholesterol concentration of 6.0 g/100 ml and 174 mg/100 ml, respectively, was used. In patients developing proteinuria, the mean volume of plasma infused per kilogram of body weight was 203.5 ml as compared with 93.4 ml in patients without proteinuria ($p < 0.001$). The mean concentration of serum protein at onset of proteinuria was 9.6 g/100 ml. The quantity of proteinuria ranged from 0.05 to 3.7 g/12 h exceeding 0.5 g/12 h in 7 of 10 study periods and 1.8 g/12 h in four of five patients. Excretion of protein in the urine returned to normal values 2–7 days following termination of the plasma infusion in three of five patients; in two patients who were discharged before proteinuria disappeared no evidence of proteinuria appeared upon subsequent follow-up. Differential protein clearance studies revealed highly selective proteinuria. A significant relation was observed between the serum cholesterol concentration and the corresponding serum protein level. With serum protein levels of 6.5–8.0 g/100 ml the mean cholesterol level was 209 mg/100 ml; with levels from 8.1 to 10.4 g/100 ml the mean cholesterol levels was 300 mg/100 ml ($p < 0.001$). Prolonged plasma infusion may result in significant transient proteinuria.

Speculation

Elevation of serum protein concentration following plasma infusion renders the glomerular capillary basement membrane more permeable to proteins, particularly those proteins of low molecular weight, and proteinuria results. Changes in blood volume, glomerular filtration rate, or renal hemodynamics may be important in the development of proteinuria; however, hormonal, allergic or other metabolic responses to the nonautologous protein may also be operative. Induction of hyperproteinemia may lead to increased cholesterol synthesis or mobilization with resultant hypercholesterolemia; conversely, the hypercholesterolemia may be a reflection of an elevated lipoprotein concentration following plasma infusion.

Introduction

Proteinuria has been observed [11, 26] in patients with hyperproteinemia resulting from multiple myeloma and Waldenstrom's macroglobulinemia whose renal function was otherwise normal. Proteinuria has also been produced in experimental animals following infusions of albumin and plasma [9, 29, 30]. We observed that children with normal renal function hospitalized for the correction of coagulation disorders developed proteinuria during infusions of plasma. This paper describes the frequency with which proteinuria developed during intravenous infusion of plasma, describes selectivity and relation to the plasma protein level, and discusses the possible mechanisms involved.

Materials and Methods

Seven children with coagulation disorders requiring infusions of plasma were studied on 21 separate admissions (table I). Frozen plasma [31] with a mean protein and mean cholesterol concentration of 6.0 g/100 ml and 174 mg/100 ml, respectively, was used. Renal disease was excluded by evidence that a physical examination, urinalysis, blood urea nitrogen, and serum creatinine were normal.

Prior to infusion of plasma, the serum and urine protein concentrations of the patients were determined. After infusion began, each urine was tested for proteinuria by a dipstick method [32]. If the concentration of protein in the urine was greater than 30 mg/100 ml, all subsequent urine was collected in 12-h periods and the protein level was determined by a quantitative sulfosalicylic acid method [8, 17]. Proteinuria was defined as protein excreted in the urine in excess of 50 mg/12 h. If this level was reached measurements were made every 24 h of total serum protein, cholesterol, and the selectivity of the urine protein. If proteinuria did not occur, the serum protein concentration was measured at the end of the plasma infusion. In eight of the study periods plasma had been infused before the usual base-line studies could be obtained. Urine was concentrated in dialysis tubing [33] 10–20 times against a sucrose medium for selectivity studies [20]. The volume of plasma infused during each 12-h interval was recorded. Serum protein was measured by the biuret method [10]; cholesterol was measured by an autoanalyser technique [16].

Selectivity studies were performed with a modification of the methods of Cameron and White [6] and MacLean and Robson [18]. Immunodiffusion plates [34] containing antibodies to human transferrin (mol wt 88,000), immunoglobulin G (IgG mol wt 150,000), and α_2-macroglobulin (mol wt 840,000) were used to determine the urine-serum (U/S) ratios for each of these proteins. To calculate the relative clearances of these proteins the U/S ratios of both IgG and α_2-macroglobulin were expressed as a percentage of the U/S ratio of transferrin (100%) and plotted on a logarithmic scale against the respective molecular weights of these proteins. From the slope of the line obtained the angle *theta* (Θ) was measured. This angle reflects the degree of selectivity of the proteinuria; values in excess of 67° indicate high selectivity; those less than 54° represent poor selectivity [13].

Results

Proteinuria developed in 10 of the 21 study periods (table I). Two patients failed to develop proteinuria. The total volume of plasma infused ranged from 1,000 to 13,000 ml and was administered over 1–16 days. In patients developing proteinuria, the mean volume of plasma infused per kilogram of body weight (fig. 1)

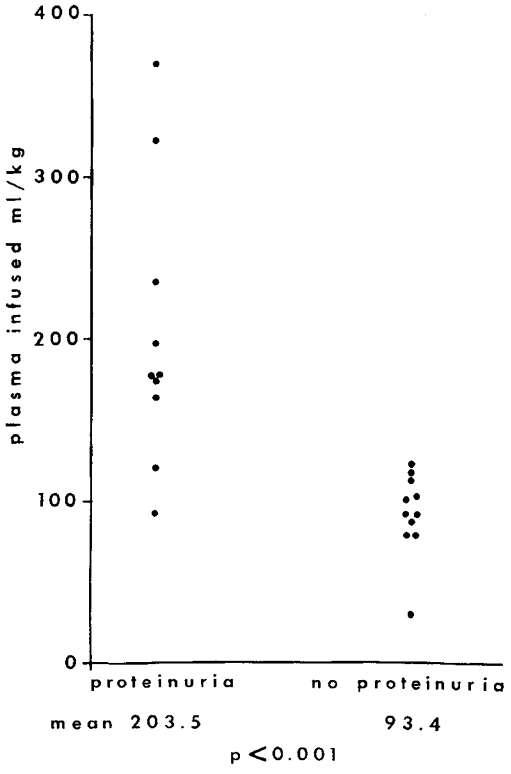

Fig. 1. The volume of plasma infused (ml/kg body wt) is compared in those study periods with proteinuria to those without proteinuria. The difference between these two groups is significant.

Table I. Clinical and laboratory data

Patient no.	Diagnosis	Sex	Age years,	Study period	Incidence of proteinuria	Total amt plasma infused, ml	Duration of infusion period, days	Serum protein at onset of proteinuria, g/100 ml	Maximum serum protein, g/100 ml
1	von Willebrand's disease	F	4.5	1	yes	5,500	11	nt[1]	10.1
2	Factor IX deficiency	M	7.0	1	no	2,000	4		8.8
				2	no	1,750	2		8.6
				3	yes	3,375	5	9.9	9.9
				4	yes	3,000	2	9.5	9.5
				5	yes	4,000	4	10.4	10.4
3	von Willebrand's disease	F	8.5	1	no	1,500	2		8.4
4	Factor IX deficiency	M	8.5	1	yes	6,125	7	9.2	10.1
				2	no	2,750	4		9.5
				3	no	4,250	7		9.5
5	Congenital afibrinogenemia	M	12.0	1	no	2,875	2		9.1
				2	no	3,375	4		9.3
				3	no	2,625	2		8.1
6	Factor IX deficiency	M	13.0	1	yes	13,000	16	nt[1]	9.9
				2	yes	6,125	5	nt[1]	10.2
				3	yes	5,750	9	9.5	9.6
				4	no	4,000	4		8.9
				5	no	1,000	1		8.4
7	Factor IX deficiency	M	13.5	1	yes	4,500	10	nt[1]	9.1
				2	yes	3,500	4	8.9	9.4
				3	no	3,750	6		9.9

[1] = not tested

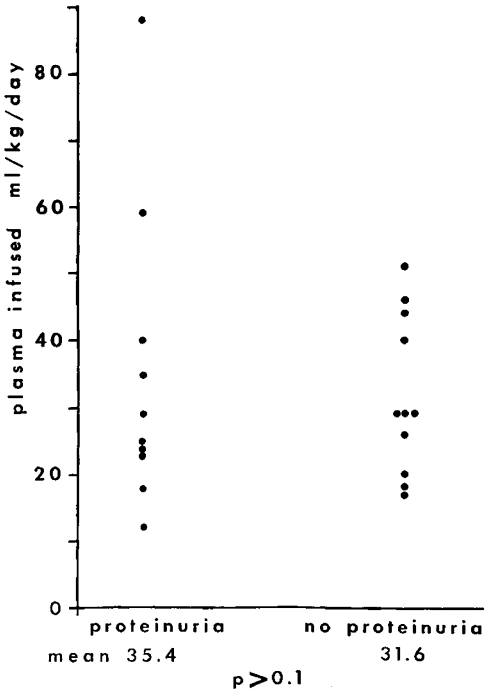

Fig. 2. The volume of plasma infused (ml/kg body wt/24 h) is compared in those study periods with proteinuria to those without proteinuria. The difference between these two groups is not significant.

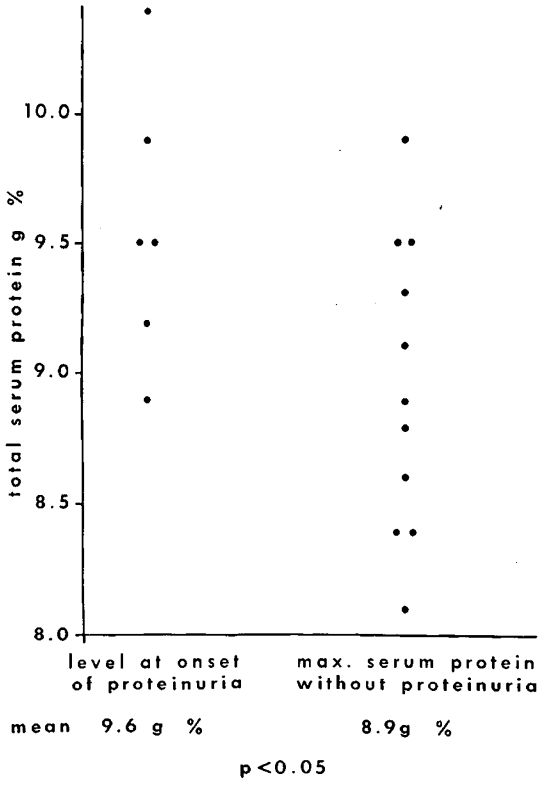

Fig. 3. Level of serum protein at the onset of proteinuria is compared to the maximum serum protein levels reached in those study periods without proteinuria. The difference between these two groups is significant.

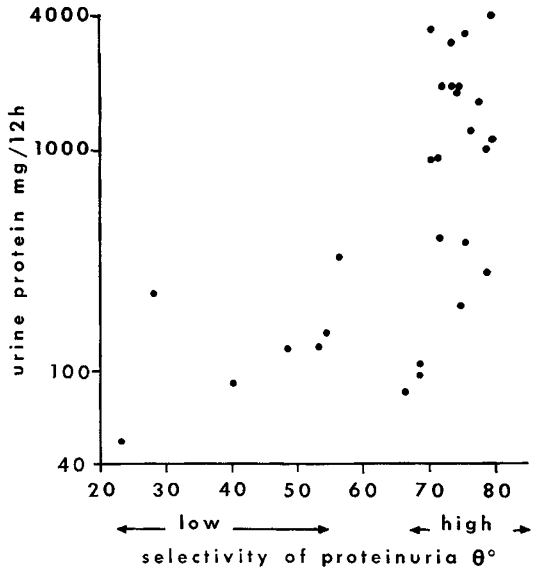

Fig. 4. The direct relation between the degree of selectivity of proteinuria and the quantity of protein excreted in the urine.

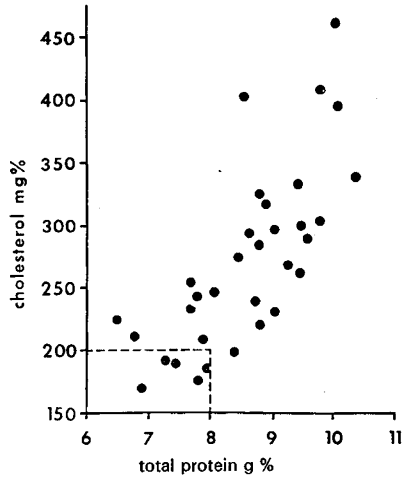

Fig. 5. Total serum protein concentration is compared to corresponding serum cholesterol level. A direct relation was observed; the mean cholesterol concentration in the infused plasma was 174 mg/100 ml.

was 203.5 ml (93.3–371.4 ml) as compared with 93.4 ml (28.6–123.2 ml) in patients without proteinuria ($p < 0.001$). In patients with proteinuria, the mean volume of plasma infused per kilogram per day (fig. 2) was 35.4 ml (12.0–88.2 ml) compared with 31.6 ml (16.7–51.5 ml) in those without proteinuria ($p > 0.1$).

The concentration of serum protein at the onset of proteinuria was determined in 6 of the 10 periods (table I). Values ranged from 8.9 to 10.4 g/100 ml (mean 9.6 g/100 ml) at this time as compared with the 11 periods in which proteinuria did not occur and in which the levels of serum protein ranged from 8.1 to 9.9 g/100 ml (mean 8.9 g/100 ml) ($p < 0.05$) (fig. 3). The level of serum protein in a given patient at the onset of proteinuria varied. In three of the study periods, in patients nos. 4 and 7, proteinuria failed to appear despite elevation of serum protein levels to a value above that at which proteinuria had previously developed. This suggests that no clearcut threshold for the onset of proteinuria exists. The quantity of proteinuria ranged from 0.05 to 3.7 g/12 h. Proteinuria exceeded 0.5 g/12 h in 7 of 10 study periods and 1.8 g/12 h in four of five patients. In three of the five patients, normal levels of protein excretion returned 2–7 days following termination of the plasma infusion. In the two patients who were discharged before proteinuria cleared, no evidence of protein in the urine was found upon subsequent follow-up.

Figure 4 shows a direct relation between the quantity of protein excreted in the urine and the degree of selectivity of proteinuria. Figure 5 illustrates the relation between the total serum protein concentration and the corresponding serum cholesterol levels. With serum protein levels of 6.5–8.0 g/100 ml the mean cholesterol level was 209 mg/100 ml; with protein levels of 8.1–10.4 g/100 ml the corresponding mean cholesterol level was 300 mg/100 ml ($p < 0.001$).

Discussion

In children with normal renal function but with coagulation disorders, transient proteinuria was induced by infusions of plasma. This reaction had been observed with experimental animals following infusions of a few hours or of several days duration [15, 22, 29, 30]. Light and electron-microscopic studies of renal parenchyma had demonstrated swelling, vacuolization and foot process fusion of glomerular epithelial cells [9, 30], but these changes were considered secondary to the proteinuria and reversible. In dogs, proteinuria developed when the serum protein was raised to levels between 9.6 and 10.4 g/100 ml [29]. In our patients, the levels ranged from 8.9 to 10.4 g/100 ml at the onset of proteinuria.

Proteinuria of different etiology may be characterized by differential protein clearances. Postural proteinuria and excretion of protein by the normal kidney are poorly selective [24, 25]; most patients with a minimal lesion nephrotic syndrome have highly selective proteinuria [6, 28]. Proteinuria was highly selective in the majority of patients in our study periods, which may be interpreted as a relative increase in glomerular basement membrane permeability to proteins of low molecular weight.

The mechanism of proteinuria following infusion of plasma is not known. Bliss and co-workers studied the effect of autologous and nonautologous plasma infusion in animals and man and described a number of hypersensitivity reactions in the nonautologous group [1–4]. These reactions were characterized by histamine release and increased capillary permeability with extravascation of plasma into the interstitial tissues. Increased capillary permeability has also been attributed to a vasoactive substance in the infused plasma [5]. Such factors may play a role in altering permeability of glomerular capillary basement membranes as well, and thus, may be involved in the development of the proteinuria we observed.

Studies in humans and animals receiving albumin or plasma infusions [7, 21, 22] have revealed increases in plasma volume, but findings in relation to changes in glomerular filtration rate or renal plasma flow have not been consistent. These variables were not measured but might be of value in elucidating the mechanism of proteinuria in these patients.

A relation was observed between the serum cholesterol level and the degree of hyperproteinemia. Many explanations for hyperlipemia in proteinuric states have been proposed and include the role of hypoalbuminemia [23], increased lipid and low density β-lipoprotein synthesis [19], and mobilization of hepatic cholesterol into the intravascular compartment [27]. The patients were not hypoalbuminemic; no attempt was made to study lipid or lipoprotein metabolism. Both hyper- and hypocholesterolemia have been reported in analogous experimental work in rats in whom hyperproteinemic proteinuria had been induced by parenteral protein administration [12, 14].

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37. Dr. K. N. DRUMMOND, Associate Professor, Department of Pediatrics, McGill University and Director, Renal Laboratory, Montreal Children's Hospital; Dr. M. I. MARKS, present address: Department of Pediatric Infectious Disease, University of Colorado Medical Center, Denver Colorado; Dr. T. BALIAH, present address: Hospital for Sick Children, Toronto, Canada.

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39. Requests for reprints should be addressed to KEITH N. DRUMMOND, M.D., Director, Renal Laboratory, Montreal Children's Hospital, 2300 Tupper Street, Montreal 25, Quebec (Canada).