To the Editor: 

Escribano et al.\(^1\) recently described that a high-protein formula was associated with higher kidney volumes in infants. Whether this has an effect on long-term kidney and cardiovascular parameters (the programming effect) remains to be determined. However, I feel that such long-term effects may even turn out to be undesirable.

Low nephron numbers have been associated with a higher blood pressure in the long run,\(^2\) caused by glomerular hyperfiltration.\(^3\) Renal size is often used as a marker for nephron endowment, although many studies show no association between nephron number and renal size.\(^2\) In addition, nephron formation has ceased before term birth, which indicates that effects of postnatal interventions, such as a high-protein diet, will not lead to a higher nephron number: the size increase is merely due to hypertrophy.

Glomerular hyperfiltration has been shown to be more detrimental when starting early in life. For instance, a congenital solitary functioning kidney leads to signs of glomerular hyperfiltration and injury in 32% of children at the mean age of 8.4 years,\(^4\) exceeding the risks of donor nephrectomy. In addition, animal studies have shown that preventing hyperfiltration during a short period before adulthood leads to a long-lasting lower blood pressure.\(^5\) As the higher-protein formula did lead to a significant higher renal workload,\(^1\) this may start the vicious circle of glomerular hyperfiltration. It remains to be determined whether this hypertrophy persists and what the impact is on later blood pressure, but this may be unfavorable.

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The Authors Reply: In a recent study\(^1\) we demonstrated that a higher protein intake in healthy infants during the first months of life was associated with an increase in kidney size. Schreuder\(^2\) has questioned whether this renal overgrowth may be beneficial or harmful in the long term.

An increase in protein intake may lead to renal functional overload caused by nitrogenous products derived from protein metabolism, which can cause a compensatory kidney overgrowth. Because the intervention of this trial occurred after the nephrogenesis period, it is logical to think that overgrowth must have been caused by a hypertrophy of the nephron structures rather than an increase in the glomeruli number.

We have also tested how high intake of protein causes increased body mass for up to 2 years of life.\(^3\) This increase in body mass may lead to a secondary increase of renal workload. If this is not accompanied by an increase in the excretory capacity (not increasing the nephron number), it will create an imbalance that can promote the functional overload. This single nephron hyperfiltration would be at the risk of progressive renal disease.\(^4\)

If protein intake in the early stages of development is reduced, we would be able to benefit metabolic programming, reducing later obesity risk. This measure may lead to smaller kidneys, but with similar functional reserve, and not cause an overload that could be harmful to later health. In this case, smaller body mass and smaller kidneys could be better. The follow-up studies attempted in this cohort are important to explore the potential long-term effects.

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Appendix

FSGS lesions in IgA nephropathy

To the Editor: The interesting and detailed morphological assessments of injury in immunoglobulin A (IgA) nephropathy reported by El Karoui et al. describe the frequent presence of focal segmental glomerulosclerosis (FSGS) lesions in patients with IgA nephropathy. A remarkably high number of their adult patients, 101 of the total 128, had lesions termed ‘consistent with FSGS’, classified by this group as hyalinosis and collapsing glomerulopathy. The authors invoke the Columbia classification of FSGS in making these distinctions. The authors use the term ‘capillary collapse and obliteration’, but the illustrations provided (their Figure 1) show instead that the capillaries are solidified by excess matrix without the characteristic implosion or retracted appearance typical of idiopathic collapsing glomerulopathy as originally described and as seen in a similar morphological form in HIV-associated nephropathy. The interesting glomerular epithelial cell proliferation is not, by application of the criteria proposed in the Columbia classification, sufficient to classify these as typical collapsing lesions.

We propose that the authors emphasize the poor prognosis of this aggressive sclerosing lesion characterized by epithelial cell proliferation without implosion of the capillary tuft, and not confound the already complex terminology by attempting to fit this into the collapsing glomerulopathy category of the Columbia classification. To apply the collapsing terminology to these lesions also implies that they are likely to share similar pathogenetic mechanisms, which remains to be proven. The observation that these lesions are linked to a poor prognosis is important, and distinct recognition and terminology is their due. Perhaps ‘active proliferative sclerosis’ or ‘sclerosis with epithelial reactivity’ would come closest to capturing the essence of the lesions as described.


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The Authors Reply: We agree completely with the observation of Fogo et al. that the shrunken capillary loops in the collapsing glomerulopathy of immunoglobulin A nephropathy (IgAN) more frequently have the appearance of being obliterated by extracellular matrix than by adhesion of capillary walls, a difference perhaps related to adjacent mesangial deposits. In this respect, our lesion does not completely correspond to the appearance of collapsing glomerulopathy, as carefully defined in primary focal segmental glomerulosclerosis (FSGS).

In effect, the authors are waging a battle similar to that waged years ago by the makers of Xerox and Frigidaire to preserve the sanctity of a brand name. However, as then, this battle has already largely been lost. The term has now been employed with varying fidelity in 20 different conditions (including IgAN in an article cosigned by one of the authors of the above letter). Collapsing glomerulopathy has thus been degraded from a specifically defined entity to a more generic term, often of dubious validity.

We prefer to retain the term collapsing glomerulopathy in IgAN, emphasizing the similarities with the lesion as classically defined: (1) presence in a setting of clearcut FSGS; (2) shriveling of the glomerular tuft with near-total obliteration of capillary lumina; (3) marked halo-like proliferation of the overlying epithelium (identical immunohistochemically to that in primary FSGS and HIV-associated nephropathy); (4) rapid progression to end-stage renal disease. For us, it comes closer to the original description than many of the entities currently parading as ‘collapsing glomerulopathy’.

That being the case, we feel it would be counterproductive to substitute an entirely new designation of the sort that the authors suggest. However, it would be reasonable to add the modifier ‘IgA-associated’ to acknowledge the definite differences between the original and the copy.