Is it this simple? Could it be that simply defining blood pressure responses to variations in dietary salt will identify those patients genetically, or possibly environmentally, predisposed to developing kidney disease? Is salt-sensitive blood pressure an intermediate phenotype linked to the genesis of diabetic kidney disease?

The Strojek study

The interesting study of Strojek et al. [1] does not answer the question. What this study does suggest is that in a highly selected, small population of offspring of diabetics with chronic kidney disease (CKD), there are intriguing relationships of salt-induced changes in blood pressure and a higher mean urinary (THF + 5xTHF)/THE ratio. Thus, there is biological plausibility to explain the blood pressure change in response to change in dietary salt. However, does this explain a proclivity for developing diabetic kidney disease?

Give the authors credit for a creative pilot study to test the hypothesis that maybe the offspring of diabetic parents may have a kidney sodium-handling problem which could explain salt-induced changes in blood pressure. However, they did exclude offspring with hypertension, fasting hyperglycaemia, smokers and oral contraceptive users. This induces informative censoring bias, as these measures may impact salt-induced changes in blood pressure, the primary outcome measure of the study! Also important were the definitions employed to define ‘nephropathy’ in the diabetic patients. End-stage renal disease (ESRD), or 24 h urine protein of 500 mg/day or more seems quite narrow. No estimate of glomerular filtration rate (GFR) or measurements of microalbuminuria were performed which may have captured more diabetic patients with CKD.

Perhaps the biggest flawed assumption of the authors is that salt-induced higher blood pressure or ‘hypertension’ before the development of glucose intolerance predisposes to nephropathy. There still remains great debate as to whether elevated blood pressure, or ‘hypertension’, depending on the terminology, initiates kidney disease or instead propagates it, once an insult has occurred.

What are the risk factors for diabetic nephropathy? Is there a relationship between salt ingestion and kidney disease?

Rather than criticize this study, what may be more important to consider are the potential factors that could increase the risk for the development of kidney and cardiovascular disease in the offspring of diabetic parents. The critical need for identifying genes which code for this risk is essential. Multiple genetic projects are underway to evaluate heredity and phenotype interactions which could assist in the identification of patients at risk who may derive advantage from earlier risk reduction measures. Some of these studies do include salt sensitivity profiling, cold pressor testing, vascular reactivity, etc. However, the salt relationship may be one of the most interesting!

The fascination with blood pressure salt sensitivity was born out of numerous epidemiological and clinical trials which demonstrated that higher levels of blood pressure are associated with increased risk for progression of kidney disease [2–4], and that populations who are more commonly salt sensitive such as diabetics and African Americans more commonly have kidney disease [5]. Moreover, increased salt consumption in patients with salt sensitivity has been shown to result in increased glomerular filtration fraction and intraglomerular capillary pressure as well as increased proteinuria [6,7]. These are subclinical measures which have been associated with adverse renal outcomes [8].
Yet, which comes first? Is there a genetic or environmental interaction which sets the kidney up for future injury? Some have theorized that a vascular toxin, perhaps uric acid [9] or even salt [10], in susceptible patients, could lead to afferent glomerular arteriolar injury which could limit autoregulatory responses to increases in blood pressure. The kidney could become more vulnerable to the effects of even subtle elevations of systemic blood pressure. Subsequent glomerular capillary hypertension over time could lead to peritubular capillary rarefaction and injury which could limit kidney sodium excretory capability with the subsequent development of salt-sensitive hypertension [11]. Other theories have linked diminished nephron mass, and an overall reduction in glomerular filtration or altered filtration capacity with increased sodium reabsorption [12], with subsequent changes in the blood pressure–natriuresis response. However, these are all theoretical possibilities which have not been tested in clinical trials. Thus, the link between salt, blood pressure salt sensitivity and proclivity for kidney disease progression remains a hypothesis which needs to be tested.

Is a salt-induced change in microalbuminuria a better target for study?

Perhaps microalbuminuria is a more important biomeasure to predict risk for nephropathy and response to therapy in type 2 diabetes. In patients with type 1 diabetes, the onset of the disease process is known with relative certainty, screening for microalbuminuria is a valuable asset in heralding the onset of kidney disease. On the other hand, in the patient with type 2 diabetes, where the onset of the disease is insidious and variably progressive, the diagnosis may be delayed for years. Consequently, there is no consistency in the literature on the relationship of albuminuria and clinical outcome. Moreover, in the microalbuminuria type 2 diabetic population, there is the competing hazard of cardiovascular events which limits the numbers of patients who are likely to progress to develop CKD. There is important and consistent clinical evidence from numerous post hoc analyses of clinical trials in patients with hypertension, with or without diabetes or kidney disease, indicating that time-varying albuminuria during follow-up correlates with both cardiovascular and kidney outcomes [8,13–15]. Perhaps one needs to see a salt-induced change in both blood pressure and albuminuria in order to predict nephropathy. Or maybe albuminuria alone, independent of blood pressure, is good enough to predict adverse outcomes.

In the Strojek paper, albuminuria was not different between controls and the offspring of patients with or without diabetic nephropathy. Given the strong relationship between albuminuria and cardiovascular and kidney outcomes, I was surprised at this lack of difference, given their hypothesis. Without a salt-induced change in albuminuria, risk for kidney injury may be less likely. If so, then the blood pressure changes with salt, albeit provocative and of limited validity for the previously mentioned reasons, may be nothing more than a play of chance.

Conclusions

More studies like the Strojek trial [1] need to be conducted to explore possible biomarkers of microalbuminuria susceptibility carefully in the offspring of diabetics. I think using salt-induced changes in microalbuminuria might prove to be a better tool. It may miss people at risk in the ‘pre-microalbuminuria’ range but, given our inexact ability to identify patients at risk with specific candidate genes, it may be the best we can do to narrow the field.

Conflict of interest statement. None declared.

[See related Original Article by Strojek et al., p. 2113]

References

hypertension after exposure to catecholamines. Hypertension 1999; 34: 151–159

doi:10.1093/ndt/gfh983
Advance Access publication 19 July 2005

Indexing glomerular filtration rate for body surface area in obese patients is misleading: concept and example

Pierre Delanaye1, Régis P. Radermecker2, Marcelle Rorive2, Gisèle Depas3 and Jean Marie Krzesinski1

1Department of Nephrology, 2Department of Diabetes, Nutrition and Metabolic Disorders, and 3Department of Nuclear Medicine CHU Sart Tilman, University of Liège, Belgium

Keywords: glomerular filtration rate; body surface area; obesity

Introduction

Indexing physiological data such as the glomerular filtration rate (GFR) for body surface area (BSA) has two major goals: allowing direct comparison of these data in patients with different body size and also defining values that will be considered as normal [1,2]. The use of BSA for indexing GFR is old and it has become so conventional that one can talk about indexing for BSA as ‘an icon’ in nephrology [3]. Nevertheless, the practice is not immune from criticisms, especially in a population with unusual anthropometric data such as the obese population.

History: more than a century ago…

In the late 19th century, physiologists thought that the metabolic rate was proportional to the BSA [4]. Now we know that this assertion is not exact [5–7] but, at that time, it was considered as a law. Measurement of metabolic rate with direct calorimetry is complex.

Since 1879, authors have studied different methods to simplify the measurement of BSA which is thought to reflect metabolic rate [8]. The first important study was published in 1915 by the Du Bois brothers [9]. This reference method to measure BSA is ingenious and merits recall. Patients’ bodies were covered with moulds of gummed manila paper. The moulds were cut open, placed flat on photographic paper which was then exposed to sunlight. The unexposed paper was cut and weighed. Knowing the density of the photographic area, the BSA was deduced. The Du Bois brothers first studied five patients and derived a geometric formula estimating BSA with measurements of seven parts of the body (19 measurements in all) (Table 1). Correlation with direct measurement was excellent and this geometric formula is now considered as a reference method by most authors. In the discussion of the original article, it is interesting to note that the authors thought it was unreasonable to expect any formula based on height and weight to be able to overcome the variability of body shape in determining BSA. However, 1 year later, the same authors published, in the same journal, such a formula [10]. To their five initial patients, they added four others. Among the nine patients, there was a 2-year-old child suffering from rickets, one obese patient, one 36-year-old subject with the mental and physical development of a boy of 8, and an 18-year-old with type 1 diabetes and very low body mass index (BMI). Du Bois and Du Bois then developed a formula based on weight and height for BSA estimation with this limited and