II stimulation [3], hypertension, diabetes [4] and cardiac infarction [5]. Alpha Klotho expression is supposed to be decreased by renal dysfunction, circulatory disturbance and increase in oxidative stress in the kidney. On the other hand, HMG-CoA reductase inhibitors have been reported to up-regulate alpha Klotho expression [6], and angiotensin II receptor blockers are considered to prevent the down-regulation of alpha Klotho [3]. Further investigation is required to clarify the precise underlying mechanisms.

We consider that alpha Klotho induces HSP70 and thereby exerts anti-apoptotic and antioxidant effects mediated by HSP70 [1]. In addition, it has been reported that alpha Klotho is affected by insulin/IGF-1 [7], Wnt signaling [8] and peroxisome proliferator-activated receptor gamma [9]. However, whether any of these factors might also affect the expression of alpha Klotho remains to be elucidated.

In relation to the involvement of alpha Klotho in the activity of the parathyroid glands, (i) induction of alpha Klotho by low blood calcium is considered to trigger the signal for parathyroid hormone (PTH) secretion [10]. On the other hand, (ii) FGF23 is considered to bind to FGFR, for which alpha Klotho acts as a cofactor, to suppress PTH secretion [11]. In addition, (iii) as the data are somewhat different from those in this letter, it was reported that the expression of alpha Klotho is reduced in secondary hyperparathyroidism [12].

Blood levels of FGF23 are known to be elevated in chronic kidney disease, and it can be speculated that PTH secretion is reduced by this signal (aforementioned signal 2) alone. However, in actual chronic kidney disease, PTH levels are generally considered to be increased by low-calcium stimulation, and thus this signal (aforementioned signal 1) is also likely to be involved. If the PTH increase by chronic low-calcium stimulation is the cause of secondary hyperparathyroidism, it is possible that signal 1 also induces the formation of nodules that maintain the expression of alpha Klotho in the parathyroid glands, allowing maintenance of the functions of these glands.

In a study conducted by us, the expression of alpha Klotho in a kidney cell line was reduced by H2O2 stimulation [13]. In addition, as published in American Society of Nephrology’s Annual Meeting 2009 we also demonstrated that TGFβ stimulation reduced the mRNA expression of alpha Klotho. In addition, alpha Klotho expression has also been shown to be reduced in breast cancer [14].

These findings suggest that the expression level of alpha Klotho may fluctuate under the influence of growth factors and other factors during the process of acquisition by cells of the potential to autonomously proliferate and form tumours.

In actual renal failure patients with secondary hyperparathyroidism, the expression of alpha Klotho is possibly affected by various factors, including treatment with vitamin D, treatment with calcium preparations and phosphate binders, oxidative stress, circulatory disturbances and changes in the blood calcium concentration, and not only by relatively simple factors as is the case with primary hyperparathyroidism. Including the result of (iii), elucidation of the regulation of Klotho expression in renal failure patients with secondary hyperparathyroidism requires further investigation, such as in the cases accumulated by Ohkido et al.

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Membranous nephropathy remains the commonest primary cause of nephrotic syndrome in a northern European Caucasian population

Dear Sir,

We read with interest the paper from Hanko et al. [1] which demonstrates that, between 1976 and 2005, focal segmental glomerulosclerosis (FSGS) was not the com-
monest adult primary glomerulopathy diagnosed on native renal biopsy in the Northern Irish population, contrary to reports from other parts of the world. The authors allude to the fact that comparing incidence of histological diseases between centres is heavily influenced by ascertainment bias since the tendency to recommend renal biopsy for patients with mild proteinuria or isolated microscopic haematuria varies widely [2]. Most nephrologists recommend renal biopsy for adults with nephrotic syndrome unless the clinical features suggest diabetic nephropathy. Therefore, comparing the incidence of histological causes of nephrotic syndrome is likely to reflect true changes in disease incidence rather than ascertainment bias.

The Scottish Renal Biopsy Registry [3] has been recording histological diagnoses prospectively since 2003. The native renal biopsy rate in Scotland between 2003 and 2008 was 126.3 per million population (pmp)/year [2] compared with 70.8 pmp/year in the northern Irish population. In the 6 years between 2003 and 2008, three centres in Glasgow and Dundee, serving a population of 1 956 133 (40% of the Scottish population), performed 1069 native biopsies, of which 209 were performed for nephrotic syndrome (26.5 pmp/year). Of nephrotic patients, 57.9% were male, mean age 56.4 years (SD 18.3), median estimated glomerular filtration rate at time of biopsy 60.2 ml/min/1.73m² (SD 31.6), mean urinary protein: creatinine ratio 857 mg/mmol (SD 490) and mean serum albumin concentration 22.1 g/l (SD 7.7). One hundred thirty-seven (65.5%) were diagnosed with a primary glomerulopathy. Of these, 54 had idiopathic membranous nephropathy (MGN), 32 had FSGS, 24 had minimal change nephropathy (MCN), 13 IgA nephropathy (IGAN), 9 mesangiopilary GN (MCGN), 2 post-infectious GN and 1 fibrillary GN (illustrated as incidence pmp per year in Figure 1). The commonest secondary cause of nephrotic syndrome leading to renal biopsy was diabetic nephropathy. In patients <45 years of age of minimal change, nephropathy was the commonest diagnosis, and >45 years, membranous nephropathy was commonest.

Our results therefore support the findings of Hanko et al. that, in a predominantly Caucasian northern European population, we have not witnessed the increasing incidence of FSGS as a cause of nephrotic syndrome that has been seen in other populations from North America [4,5], Brazil, Pakistan and the Congo, with membranous nephropathy remaining the commonest primary glomerulopathy causing nephrotic syndrome.

Conflict of interest statement. None declared.

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Reply

Dear Editor,

We would like to thank McQuarrie and colleagues for providing data from the Scottish Renal Biopsy Registry which adds to the literature on the variation in patterns of primary glomerular disease in different countries and ethnic populations. We assume that the report was of adult patients. In common with other northern European Caucasian populations, membranous nephropathy was the most common cause of nephrotic syndrome with a lower proportion of FSGS.

We note with interest that the actual incidence of FSGS in this Scottish population was 50% higher than in Northern Ireland at 0.27 per hundred thousand population per year (php/year) compared to 0.18 php/year [1]. Although the biopsy rate in Scotland exceeded that in our population (126.3 vs 70.8 pmp/year), the practice of recommending renal biopsy for patients with nephrotic syndrome not attributable to diabetes is common to both countries; it is unlikely that variability in biopsy practice alone accounts for this difference in incidence.

Although numbers are small, there is an indication that, even within geographically close countries with populations of similar ethnic decent, there may be differences in the incidence of FSGS. This highlights again, as in our paper, the limitations in our knowledge of the aetiological factors, environmental or genetic, associated with this condition.

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