

Factors influencing pathological ankle-brachial index values along the chronic kidney disease spectrum: the NEFRONA study

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ABSTRACT

Background: The ankle-brachial index (ABI) is widely used to diagnose subclinical peripheral artery disease (PAD) in the general population, but data assessing its prevalence and related factors in different chronic kidney disease (CKD) stages are scarce. The aim of this study is to evaluate the prevalence and associated factors of pathological ABI values in CKD patients.

Methods: NEFRONA is a multicentre prospective project that included 2445 CKD patients from 81 centres and 559 non-CKD subjects from 9 primary care centres across Spain. A trained team collected clinical and laboratory data, performed vascular ultrasounds and measured the ABI.

Results: PAD prevalence was higher in CKD than in controls (28.0 versus 12.3%, $P < 0.001$). Prevalence increased in more advanced CKD stages, due to more patients with an $ABI \geq 1.4$, rather than ≤ 0.9 . Diabetes was the only factor predicting both pathological values in all CKD stages. Age, female sex, carotid plaques, higher carotid intima-media thickness, higher high-sensitivity C-reactive protein (hsCRP) and triglycerides, and lower 25-hydroxy-vitamin D were independently associated with an $ABI \leq 0.9$. Higher phosphate and hsCRP, lower low-density lipoprotein (LDL)-cholesterol and dialysis were associated with an $ABI \geq 1.4$. A stratified analysis showed different associated factors in each CKD stage, with phosphate being especially important in earlier CKD, and LDL-cholesterol being an independent predictor only in Stage 5D CKD.

Conclusions: Asymptomatic PAD is very prevalent in all CKD stages, but factors related to a low or high pathological ABI differ, revealing different pathogenic pathways. Diabetes, dyslipidaemia, inflammation and mineral-bone disorders play a role in the appearance of PAD in CKD.

Keywords: ankle-brachial index, atheromatosis, cardiovascular risk, chronic kidney disease, peripheral artery disease

INTRODUCTION

Cardiovascular events (CVE) remain the main cause of mortality and morbidity in chronic kidney disease (CKD) [1]. This increase in cardiovascular complications is evident from the earliest CKD stages, even before a fall in glomerular filtration rate can be detected [2]. Recent guidelines and position statements have therefore defined CKD as a high cardiovascular risk condition [3].

In this sense, risk score charts fail to adequately recognize CKD patients at a higher cardiovascular risk, and the study of novel molecules to identify specific biomarkers is still undergoing [4–7]. These gaps may be due to a different pathogenesis of the atheromatous process in CKD, which has been described as an accelerated vascular ageing. For this reason, novel approaches for a suitable and reliable vascular assessment are urgently required in CKD patients. Those that detect atheromatosis in subclinical stages, such as vascular ultrasound, have shown promising results [8, 9].

Peripheral artery disease (PAD) is a frequent manifestation of atheromatosis, which can lead to intermittent claudication and surgical requirements. However, both in the general and the renal populations, it tends to be asymptomatic in earlier stages. One of the most widespread tests to diagnose subclinical PAD is the ankle-brachial index (ABI), which is the ratio between the highest humeral systolic blood pressure and the systolic blood pressure of the lower limbs. A normal ABI is around 1 or slightly higher, due to the effect of gravity on the vascular system in a standing position. An ABI value ≤ 0.9

reflects a decrease in distal blood flow, and several studies have proved it to be a good predictor for CVE [10–12]. Therefore, the test is nowadays widely used in many clinical environments, including primary care (especially for high-risk subjects).

Nevertheless, there are some controversies yet to be resolved. On one hand, the most appropriate method to measure the ABI is as yet uncertain. Vascular surgeons tend to use the ‘classical’ method (highest value of systolic blood pressure of lower limbs), but a modified method was proposed by Schröder *et al.* using the most pathological value of all four obtained indexes. This is far more sensitive for CVE prediction [13, 14], and it is currently recommended for cardiovascular risk assessment [15]. Secondly, a high ABI value (≥ 1.3 – 1.4) has been considered not interpretable and disregarded in most studies because it does not allow assessment of the underlying blood flow. These values are due to vascular stiffness probably because of vessel wall calcification in the context of degenerative vascular ageing. However, some studies have shown that an ABI value ≥ 1.4 is also associated with a worse cardiovascular prognosis, particularly when ischaemia is superimposed [16–19].

On the other hand, data interpreting in depth the characteristics of pathological ABI values in CKD are scarce, specifically comparing different CKD stages. Also, no studies have described subclinical PAD according to high or low pathological ABI values in this population, despite the apparent important differences in pathogenesis and prognostic impact. The impact of mineral and bone metabolism disturbances (such as hyperparathyroidism and hyperphosphataemia) on cardiovascular disease and mortality is well known [20], but few studies have evaluated its relationship with the ABI in CKD [21, 22]. To the best of our knowledge, no study has analysed this connection along the CKD spectrum.

The NEFRONA project is an observational multicentre prospective project designed to evaluate the prevalence and evolution of subclinical atheromatosis in CKD patients with no history of CVE, and the contribution of early diagnosis for a more precise risk assessment [23, 24]. The aim of the present study is to analyse the factors related to subclinical PAD in different CKD stages, and to distinguish those associated with a low or a high pathological ABI.

MATERIALS AND METHODS

Study design

NEFRONA is a prospective multicentre cohort project that enrolled 2445 CKD subjects in 81 Spanish hospitals and dialysis clinics, from October 2010 to June 2012. Patients were eligible if they fulfilled the following conditions: age between 18 and 74 years; and CKD Stage 3 or higher as defined by current guidelines [glomerular filtration rate <60 mL/min/1.73 m² estimated using the 4-variable Modification of Diet in Renal Disease (MDRD) equation] [25]. Besides, 559 controls with an MDRD ≥ 60 mL/min/1.73 m² were recruited from nine primary care centres from different regions of the country. Exclusion criteria for both groups were active infections, pregnancy, life expectancy <12 months and history of CVE, carotid artery surgery or any organ transplantation.

All patients signed an informed consent, and the study was approved by the Ethics Committee of the Arnau de Vilanova University Hospital.

Study variables

Information regarding the protocol for collecting clinical and laboratory data is specified in the baseline descriptive article [26]. Detailed information about methods used to evaluate subclinical atherosclerosis has also been published [24]. All vascular studies were performed with a standardized protocol by three experienced itinerant teams including a nurse and a radiology technician, who also recorded anthropometric parameters and collected blood samples.

All participants underwent a vascular ultrasound to measure carotid intima-media thickness and to evaluate the presence and characteristics of atheromatous plaques, following the recommendations of the American Society of Echocardiography [27]. Common carotid intima-media thickness (CCIMT) was calculated as the mean value in right and left common carotid arteries. Plaque presence was evaluated in 10 vascular territories of left and right sides (internal and common carotid arteries and carotid bulbs, and common and superficial femoral arteries). The ABI was defined as the ratio between systolic blood pressure in posterior tibial or dorsalis pedis arteries, divided by the highest systolic blood pressure value of both brachial arteries, all of them detected with a continuous Doppler probe. The modified method was chosen for a higher sensitivity, selecting in each patient the most pathological of the four values [13]. A pathological ABI was defined as a value ≤ 0.9 (diagnostic of limb ischaemia) or ≥ 1.4 (related to arterial incompressibility and stiffness, usually ascribed to vascular ageing degeneration).

Statistical analysis

Mean \pm standard deviation was used to describe quantitative variables, while absolute and relative frequencies were used to describe qualitative data. When appropriate, continuous variables were categorized, either into dichotomous variables or into tertiles, searching for the optimal cut-off point using a Gini criterion. Fisher and Mann–Whitney tests were performed to evaluate the association of clinical, anthropometric, treatment-related and laboratory variables. Multiple logistic regression models were used to predict pathological ABI, using a stepwise algorithm with the Akaike’s criterion to determine the best combination of variables. Interactions were also considered in the multivariate models, and predicted probabilities were computed to graphically illustrate the effect of interactions. All statistical analyses were performed using the R package [28], and the threshold for significance was set at 0.05.

RESULTS

The mean age of the CKD population was 57.9 ± 12.8 years, and 61.7% were male patients. Prevalence of hypertension, dyslipidaemia and diabetes were 89.3, 64.9 and 25.7%, respectively. Mean CCIMT was 0.725 mm. The percentage of patients with atheromatous plaque was 70.1% (18.8% only in carotid arteries, 12.6% only in femoral arteries and 38.7% in both sites). Detailed

information on baseline characteristics of the patients has been previously published, and it has been summarized in [Supplementary data, Table S1](#) [26].

CKD patients had a higher prevalence of subclinical PAD than non-CKD controls, both for pathological low (28.0 versus 12.3%, $P < 0.001$) and high values (11.0 versus 1.4%, $P < 0.001$). More advanced CKD was associated with a lower prevalence of $ABI \leq 0.9$ (19.8% in Stage 3, 16.9% in Stages 4 and 5, and 13.4% in Stage 5D, $P = 0.03$), but to a clearly higher rate of $ABI \geq 1.4$ (5.6% in Stage 3, 10.2% in Stages 4 and 5, and 19.5% in Stage 5D, $P < 0.001$) as shown in Figure 1.

Clinical, anthropometric, treatment-related and laboratory variables were analysed to evaluate their relationship to subclinical PAD. Table 1 shows the results of the multivariate logistic regression models to predict subclinical PAD in CKD patients, showing differences in factors related to pathological low and high values. Main predictors of a low ABI were older age, female sex, diabetes, lower 25-hydroxy-vitamin D levels, higher high-sensitivity C-reactive protein (hsCRP) and triglyceride levels, higher CCIMT and carotid plaque presence. An interaction between age and vascular plaques was found, showing that age only had a significant effect on ABI in subjects with carotid plaques (Figure 2A). On the other side, diabetes, higher hsCRP and phosphate levels, lower low-density lipoprotein (LDL)-cholesterol levels and dialysis treatment predicted an $ABI \geq 1.4$. A very interesting interaction between serum phosphate and CKD stage was also found. Remarkably, serum phosphate exerts its maximum influence on vascular stiffness in earlier stages of renal impairment (Figure 2B).

Given the significant association of CKD Stage 5D with an $ABI \geq 1.4$, a stratified multivariate analysis was performed (Table 2), uncovering that the influence of risk factors varies throughout the spectrum of CKD. Diabetes was the only factor that maintained its independent association through all CKD

stages. In CKD Stage 3, serum phosphate and lower LDL-cholesterol levels were independently associated with vascular stiffness. However, an interaction between LDL-cholesterol and serum albumin was found. In Stages 4 and 5, diabetes and high hsCRP were the only significantly associated factors. Finally, in patients with Stage 5D CKD, high hsCRP and low LDL-cholesterol levels predicted an $ABI \geq 1.4$, with no interaction with albumin or other nutritional parameters. The effect of treatments for dyslipidaemia was tested and disregarded.

DISCUSSION

This study evaluates in depth the epidemiology of subclinical PAD and its related factors in a large CKD cohort. To the best of our knowledge, this is the first report assessing the prevalence of pathological ABI along the continuum of CKD, making the specific distinction between values suggestive of ischaemia and those related to vascular stiffness.

As with many other cardiovascular conditions, PAD is more prevalent in CKD patients than in non-CKD subjects, even in the earliest stages [29–31]. However, it is initially asymptomatic, and it can only be diagnosed through screening tests, the ABI being the one used most frequently. An abnormal ABI is defined as ≤ 0.9 or ≥ 1.4 in current guidelines [15], although a borderline ABI between 0.9 and 1.0 has also been associated with a higher CVE rate [32]. In CKD and haemodialysis patients both low and high pathological values have been linked to higher mortality rates [33, 34]. However, a low ABI value, associated with distal ischaemia in the context of vessel atheromatosis, was related to calcification of main arteries, while a high ABI, due to non-compressibility of the artery, was related to calcification of peripheral distal arteries [34].

Given the differences in the pathogenesis and prognostic implications of the two possible different pathological ABI values (≤ 0.9 or ≥ 1.4), a separate analysis was performed, revealing that factors associated with ischaemia differ from those related to vascular stiffness. The analysis of factors related to the presence of an $ABI \leq 0.9$ in CKD showed that most classical cardiovascular risk factors (diabetes, dyslipidaemia, inflammation) are also related to subclinical vascular disease. These findings are in line with previously published evidence of subclinical PAD in CKD [35, 36], but we did not find a significant correlation with glomerular filtration rate as in other studies [37, 38]. Vitamin D deficiency has been linked to enhanced atherosclerosis in experimental models [39]. In our sample, lower vitamin D levels were independently associated with the presence of an $ABI \leq 0.9$, a fact that has already been shown in the general population [40, 41]. CCIMT thickening, which is believed to be an earlier stage of atheromatosis, was also independently related to the presence of an $ABI \leq 0.9$, as a proof of the systemic condition of the atheromatous disease. Furthermore, a significant interaction between age and the presence of carotid atheromatous plaques was found regarding PAD prevalence prediction. Age has been shown to be the most powerful predictor for atheromatosis. However, there seems to be a subpopulation of patients who are protected from atheromatosis, whose probability of developing PAD is low regardless of their age, or even their renal function.

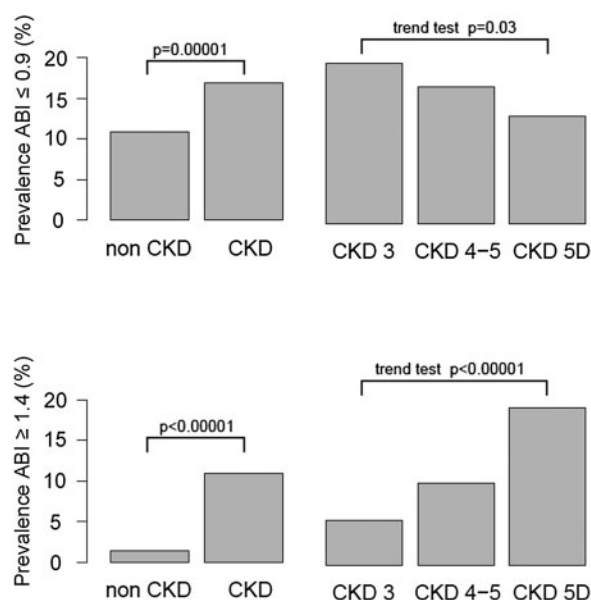


FIGURE 1: Prevalence of pathological ABI values (≤ 0.9 or ≥ 1.4) in CKD versus non-CKD patients, and in different CKD stages. For CKD stages, a trend test was performed considering the stages as an ordinal variable. ABI, ankle-brachial index; CKD, chronic kidney disease.

Table 1. Multivariate logistic regression to model subclinical PAD in CKD patients

	β (SE)	OR	95% CI	P-value
ABI ≤ 0.9 versus $0.9 < \text{ABI} < 1.4$				
Intercept	-3.10 (0.56)	0.04	0.01–0.13	
Mean CCIMT	2.08 (0.54)	7.99	2.79–23.07	0.0001
Diabetes	0.64 (0.16)	1.91	1.40–2.59	0.00004
Sex (female)	0.64 (0.15)	1.90	1.42–2.55	0.00002
Triglycerides 102–155 versus <102 mg/dL	0.30 (0.19)	1.36	0.93–1.98	0.11
Triglycerides >155 versus <102 mg/dL	0.56 (0.19)	1.74	1.21–2.53	0.003
hsCRP >6.9 mg/L	0.41 (0.17)	1.51	1.09–2.09	0.01
25-Hydroxy-vitamin D ≤ 18.9 ng/L	0.66 (0.19)	1.93	1.34–2.83	0.0005
Age (per year)	-0.03 (0.01)	0.97	0.95–0.99	0.002
Carotid plaque presence	-3.58 (0.89)	0.03	0.00–0.16	0.00005
Interaction age \times carotid plaque presence	0.07 (0.01)	1.07	1.04–1.10	<0.00001
ABI ≥ 1.4 versus $0.9 < \text{ABI} < 1.4$				
Intercept	-6.16 (1.31)	0.00	0.00–0.03	
Diabetes	0.94 (0.19)	2.55	1.74–3.73	<0.00001
LDL-cholesterol >86 mg/dL	-0.61 (0.18)	0.55	0.38–0.78	0.0008
hsCRP >6.9 mg/L	0.51 (0.19)	1.66	1.13–2.43	0.009
Serum phosphate (per mg/dL)	1.03 (0.36)	2.80	1.41–5.74	0.004
CKD Stage 4–5 versus CKD Stage 3	2.49 (1.52)	12.02	0.65–257.14	0.1
CKD Stage 5D versus CKD Stage 3	4.47 (1.39)	87.65	6.27–1479.06	0.001
Interaction serum phosphate \times CKD Stages 4–5	-0.65 (0.40)	0.52	0.23–1.13	0.1
Interaction serum phosphate \times CKD Stage 5D	-0.94 (0.37)	0.39	0.19–0.79	0.01

PAD, peripheral artery disease; CKD, chronic kidney disease; SE, standard error; OR, odds ratio; CI, confidence interval; ABI, ankle-brachial index; CCIMT, common carotid intima-media thickness; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

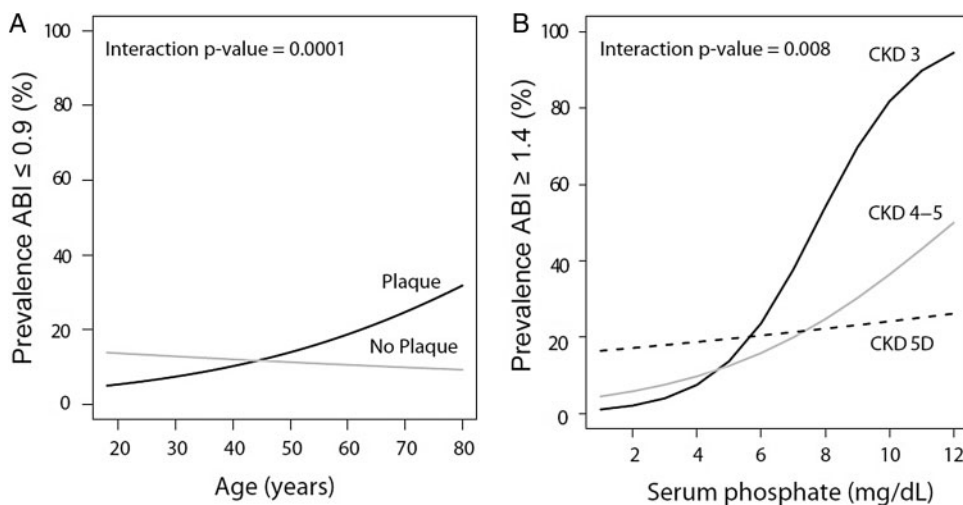


FIGURE 2: Effect of the interaction between age and carotid atheromatosis for ABI ≤ 0.9 prediction (A) and between serum phosphate and CKD stage for ABI ≥ 1.4 prediction (B). The lines represent prevalence (%), estimated from the corresponding logistic regression models including both the main effects and the interaction. The P-value assessing the statistical significance of the interaction is shown. ABI, ankle-brachial index; CKD, chronic kidney disease.

Thus, age is not associated with a higher prevalence of ABI values ≤ 0.9 in patients free of plaque. Our group has found this age-dependent variation in other markers of atheromatosis, such as greater intima-media thickness or the presence of atheromatous plaques [42]. This finding reflects the importance of detecting atheromatous plaques for an adequate vascular risk assessment, since plaque-free patients also have a lower risk of PAD.

Lower ABI values reflect a decrease in distal blood supply, while higher values result from vascular stiffness, which may or may not concur with distal ischaemia. Although more tests

would be necessary to ascertain blood flow, many studies have demonstrated that an ABI over the normal range is associated with poorer prognosis, both in general and in renal populations [16, 43, 44]. More specific studies have also demonstrated that the coexistence of vascular stiffness with intravessel ischaemia bears the worst prognosis [45]. Interestingly, the higher rate of PAD in more advanced CKD stages in this study is attributable to an increase in prevalence of ABI ≥ 1.4 at the expense of lower rates of ABI ≤ 0.9 . This fact is consistent with the known increase in vascular calcification in renal disease, and its prognostic implications will require a more detailed evaluation. In

Table 2. Multivariate logistic regression to model an ABI ≥ 1.4 stratified by CKD stage

CKD stage	Stage 3				Stages 4–5				Stage 5D			
	β (SE)	OR	95% CI	P-value	β (SE)	OR	95% CI	P-value	β (SE)	OR	95% CI	P-value
Intercept	–5.58 (1.01)	0.00	0.00–0.03		–2.72 (0.24)	0.07	0.04–0.10		–1.24 (0.21)	0.29	0.19–0.43	
Diabetes	1.07 (0.33)	2.93	1.54–5.57	0.001	1.45 (0.30)	4.24	2.37–7.72	<0.0001	0.64 (0.31)	1.90	1.02–3.47	0.04
Serum phosphate (per mg/dL)	0.87 (0.27)	2.40	1.42–4.14	0.001	0.76 (0.33)	2.13	1.10–4.03	0.02	0.70 (0.27)	2.02	1.19–3.41	0.009
hsCRP >6.9 mg/L									–0.62 (0.26)	0.54	0.33–0.89	0.02
LDL-cholesterol >86 mg/dL	–0.67 (0.34)	0.51	0.27–1.00	0.046								
Albumin (per g/dL)	1.03 (0.74)	2.81	0.65–12.39	0.17								
Interaction LDL-cholesterol \times albumin	–1.89 (0.88)	0.15	0.03–0.86	0.03								

ABI, ankle-brachial index; CKD, chronic kidney disease; SE, standard error; OR, odds ratio; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

our study, factors related to higher ABI values included higher hsCRP and, curiously, lower LDL-cholesterol levels, in a reverse epidemiological association already described and as a reflection of the nutritional status [46]. This anomalous effect of LDL-cholesterol on vascular prognosis has also been related to a potential confounding effect of inflammation [47]. However, this is not the case, as low cholesterol levels are associated with a higher ABI independently of hsCRP. Another possible explanation could be an altered proportion of lipidic subfractions or the presence of more pathogenic LDL-cholesterol forms [48]. Serum phosphate levels and CKD stage also predicted a high ABI, but with an interaction that revealed that the relationship is more evident in earlier CKD stages.

It is interesting to overview the differences in factors associated with vascular stiffness according to CKD stage. On one side, diabetes was the only factor that remained related, regardless of CKD stage. It appears that factors related to subclinical PAD in Stage 5D are similar to those associated with an ABI ≥ 1.4 , advanced CKD being an intermediate situation. On the other side, as shown by the interaction, serum phosphate was only related to non-compressibility in earlier CKD. The impact of end-stage renal disease on vascular calcification has been studied in detail. The contribution of higher serum phosphate levels both to the atheromatous and the vascular calcification processes is well known, both in the general and the renal population, although more strongly in the latter [22]. Phosphate levels have been formerly related not only to subclinical PAD [49, 50], but also to other markers of vascular damage [51, 52]. Other studies have previously described a distinct effect of hyperparathyroidism on an ABI suggestive of arterial stiffness [21]. Here, phosphate levels also seem to reveal a more advanced vascular damage, given its association to a higher ABI, which was more prevalent in Stage 5D patients. However, this relationship was only significant in earlier stages, reinforcing the great importance of an early control of serum phosphate, maybe even within the high-normal range. The complexity of the effect of serum phosphate in different subpopulations has been evaluated in depth in the NEFRONA study, revealing different thresholds for men and women [53]. Finally, the impact of lower LDL-cholesterol was significant both in early and advanced CKD, regardless of hypolipidaemic treatments. However, in Stage 3 CKD it seems to be linked to other nutritional parameters, such as serum albumin (maybe associated with low-protein diets), while in Stage 5D it remained as a single independent predictor.

This study has some limitations. The first one is its cross-sectional nature. The analysis of long-term follow-up outcomes will reveal more information about the evolution of subclinical PAD in CKD patients, as well as the predictive value of the baseline ABI. The second one is the lack of a test to evaluate blood flow in patients with an ABI value ≥ 1.4 , such as the toe-brachial index.

In conclusion, subclinical PAD, diagnosed as a pathological ABI, is more frequent in renal patients than in subjects with normal kidney function. Prevalence grows in more advanced CKD stages, at the expense of more patients with ABI ≥ 1.4 , revealing more vascular stiffness. It is important to remark that there are differences in factors related to ischaemic or to

stiffness-related subclinical PAD, and between different CKD stages. The effects of some classic factors differ when evaluated altogether, presenting interesting variations, such as a subgroup of atheromatosis-protected patients regardless of their age. Finally, there is a differential effect of serum phosphate and LDL-cholesterol in different CKD stages, probably related to nutritional parameters.

SUPPLEMENTARY DATA

Supplementary data are available online at <http://ndt.oxfordjournals.org>.

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CONFLICT OF INTEREST STATEMENT

None declared.

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