DIETARY REGIMENS POOR IN ANIMAL PROTEINS DECREASE CYANATES PRODUCTION THROUGH UREA REDUCTION IN CHRONIC KIDNEY DISEASE

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Introduction and Objectives

Chronic Kidney Disease (CKD) is associated with early atherosclerosis, micro-inflammation and cardiovascular disease (CVD)[1]. Protein carbamylation resulting in urea-derived cyanate compounds, implied in many pathophysiological events in nephrology, could represent a potential link between CKD and CVD[2].

The aim of the study was to verify the hypothesis that reducing serum urea by dietary treatments poor in animal proteins could result in reduced carbamylation products.

Methods

We enrolled 60 (46 males, mean age 66 years) CKD 3b-4 patients in a pilot cross-over randomized controlled trial.

The enrolled patients were divided into 2 arms of 30 patients each by a software randomization. Arm A alternatively underwent 3 dietary schemes as follows: 3 months free diet (FD – proteins (p.) 1 gram/body weight/day (g/bw/d), animal proteins (a.p.) 78%), 6 months Very Low Protein Diet supplemented with ketoacids (VLPD – p. 0.3-0.5 g/bw/d + 0.05 g/bw/d supplementation, a.p. 0%), 3 months FD, 6 months Mediterranean Diet (MD – p. 0.7-0.8 g/bw/d, a.p. 44%); Arm B: 3 months FD, 6 months MD, 3 months FD, 6 months VLPD.

We measured blood pressure, serum and urine routine markers.

Homocitrulline (Hcit) and Hcit/Lysin (Lys) ratio, used as markers of protein carbamylation, were measured by LC-MS/MS. Differences between variables were tested with parametric (t-Student) or non-parametric (Wilcoxon) tests, as opportune, while Spearman test was used to correlate serum urea with Hcit, Lys and Hcit/Lys. All analyses were conducted as *intention-to-treat*. P-values ≤ 0.05 were considered statistically significant.

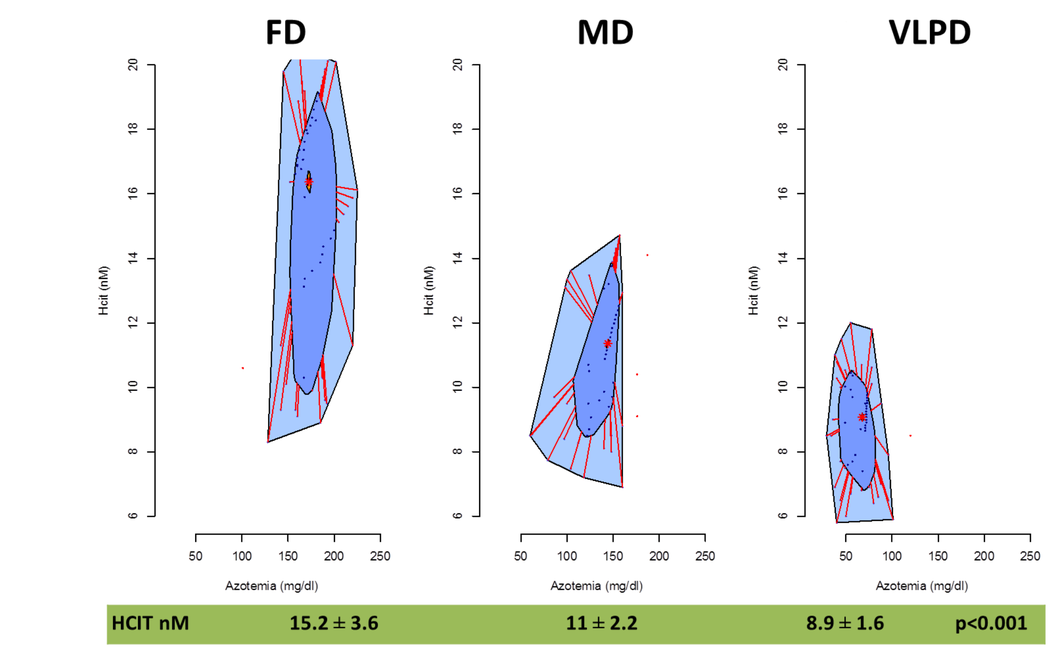

Figure 1. Bivariate relationship of azotemia with serum Hcit according to different nutritional regimens: free diet (FD), Mediterranean diet (MD) and very low protein diet (VLPD)

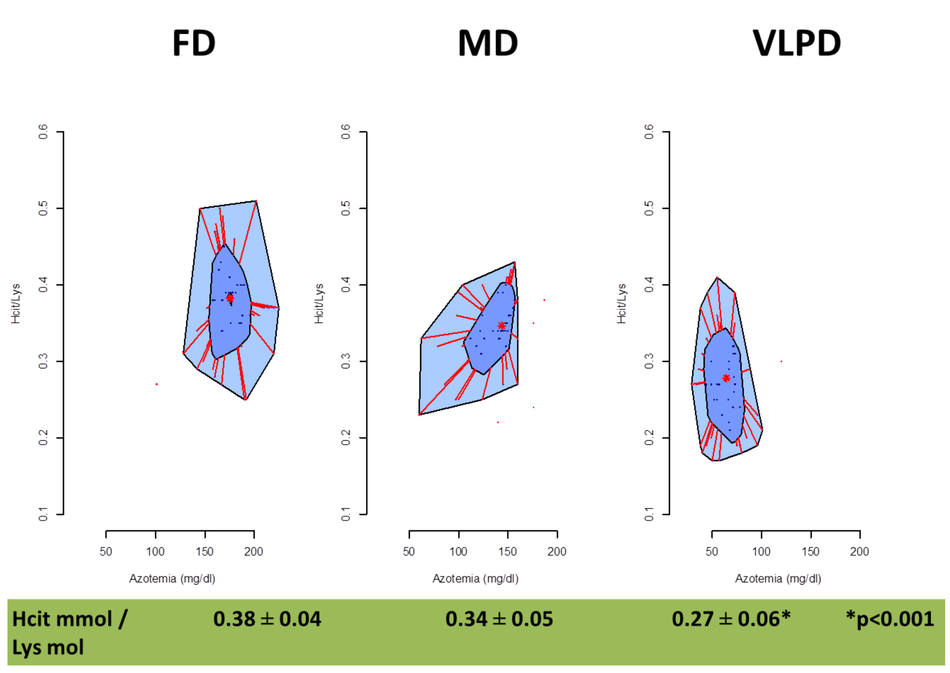

Figure 2. Bivariate relationship of azotemia with serum Hcit/Lys concentration ratio according to different nutritional regimens: free diet (FD), Mediterranean diet (MD) and very low protein diet (VLPD)

Results and Conclusions

MD and VLPD decrease serum urea by 20.5% and 58.3% as compared with FD ($p<0.001$), respectively. VLPD decreases Hcit and Hcit/Lys by 41.4% and 28.9% as compared with FD ($p<0.001$). MD lowers Hcit by 27.6% ($p<0.001$) and Hcit/Lys by 10.5% compared with FD (ns). VLPD was more effective than MD in lowering both carbamylation markers ($p<0.001$).

VLPD lowers diastolic blood pressure and serum levels of Na, P, PTH, homocysteine and increases serum bicarbonate and hemoglobin as compared to FD ($p<0.05$).

Moreover, Hcit, Lys and Hcit/Lys significantly correlate with serum urea ($r=0.7$, $r=0.7$ and $r=0.6$, respectively; $p < 0.0001$).

In conclusion, our study demonstrates that dietary regimens characterized by a reduced intake of animal proteins, such as VLPD and MD, are effective in reducing the levels of cyanates through urea reduction in CKD patients. Moreover we demonstrate, for the first time in our knowledge, that MD is capable of reducing urea and the cyanates, although to a minor extent than VLPD.

These findings suggest to consider urea as another therapeutic target in CKD, susceptible of modifications by a dietary approach.

	FD	MD	VLPD
Number	60		
Sex (M)	46		
Age, years	66±16		
Diabetes (n°)	24		
Body Weight, kg	70.0±12.8	69.8±13.1	70.0±12.9
Systolic Blood Pressure, mm Hg	129±19	128±19	124±10
Diastolic Blood Pressure, mm Hg	73±11	71±9	69±7 *
Urea, mg/dl	175±22	137±26#	64±19*
Uricemia	5.4±1.6	5.2±1.6	5.1±1.7
Na, mmol/L	141±2	141±2	138±4*
K, mmol/L	5.1±0.6	5.0±0.8	5.1±0.7
Phosphate, mg/dl	4.5±0.7	4.1±0.7	3.6±0.7*
Bicarbonates, mmol/L	20±3	23±3#	25±3*
PTH, pg/ml	200±123	180±105	165±111*
Hb, g/dl	11.4±1.0	11.7±1.7	12.1±0.7*
Albumin, g/dl	3.6±0.4	3.6±0.4	3.6±0.8
CRP, mg/L	3.4±3.3	3.0±2.9	2.7±2.9
Homocysteine, umol/L	35±7	34±9	25±7*
Na-u, mmol/day	164±47	151±50	127±48 *
K-u, mmol/day	44±16	49±17*	57±21 *
Cl-u,	115±28	112±22	94±16 *
P-u	706±198	499±201#	281±140 *
UUN, g/day	23±6	17±6#	8.2±2.9 *
Prot-u, mg/day	1587±1072	1543±1398	935±1059 *
Creatinine-u, mg/day	1.0±0.4	1.0±0.4	0.9±0.3
Creatinine Clearance, ml/min	22.1±13.9	23.7±13.1	23.2±16.7
Protein intake, g/kg/day	1.21±0.23	0.90±0.20#	0.48±0.14*
P intake, mg/day	989±271	799±264#	368±194*
Na intake, g/day	10.2±2.3	9.1±2.7	8.5±3.4
Urinary Pr/Cr ratio	1.5±1.2	1.5±1.4	1.0±0.91*

Table 1. Anthropometric, clinical and biochemical data of patients according to each nutritional intervention. **Legend**: Na = sodium, K = potassium, PTH= parathyroid hormone, Hb = hemoglobin, CRP = C-reactive protein, Na-U = urinary sodium, K-u = urinary potassium, UUN = urinary urea, Pr/Cr ratio = protein/creatinine ratio. *Bonferroni test $p<0.05$ versus FD and MD; #Bonferroni test $p<0.05$ versus FD.

Bibliography

1. Foley RN, Parfrey PS, Sarnak MJ: Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol 1998;9:S16–S23
2. Wang Z, Nicholls SJ, Rodriguez ER, et al. Protein carbamylation links inflammation, smoking, uremia and atherogenesis. Nat Med 2007;13:1176–1184

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