Dr. Liliana Garneata
Assistant Professor of Nephrology “Dr Carol Davila” Teaching Hospital of Nephrology, Bucharest, Romania

- Head of the 1st Nephrology Department, Dr. Carol Davila Teaching Hospital of Nephrology: since May 2015

**Special interests**
- Nutrition and metabolism in renal diseases
- Renal anaemia
- Epidemiology of Chronic Kidney Disease
- Focal segmental glomerulosclerosis
- Diabetic nephropathy
- Kidney and pregnancy
- IgA Nephropathy

- Over 55 publications in National and international journals. Recipient of many awards for clinical work.
- She has recently published clinical study in JASN titled **Ketoanalogue-supplemented vegetarian very low-protein diet and CKD progression** which provides latest evidence in with Ketoanalogues in CKD.
Nutritional management of CKD: Key-role of ketoanalogues with low protein diets

Liliana Garneata
"Dr Carol Davila” Teaching Hospital of Nephrology
Bucharest, Romania
• Why Ketoanalogues supplementation of protein-restricted diets?
Why Low Protein Diets?

1) Reduce intraglomerular pressure, avoid hyperfiltration and further glomerulosclerosis
2) Control metabolic disturbances of advanced CKD
3) Control uremic symptoms and signs
4) Postpone RRT
Hypoproteic diets: The alternatives

• Conventional low protein diets: 0.6 g/kg per day
• Very low protein diets (0.3-0.4 g/kg per day) supplemented with:
  – essential amino acids
  – ketoanalogues of essential amino acids (keto-diet, KD)
• Low protein diet – a simplified approach
Protein catabolism with ketoanalogues supplementation

ENDO/EXOGENOUS PROTEIN CATABOLISM

- Acid radicals
- Phosphates
- Aminoacids

Acidosis
Hyperparathyroidism
NH₃

Ketoacids
Energy

Ureogenetic cycle
The case against...

1) Debatable efficacy
2) Risk of malnutrition
3) Difficult implementation:
   – poor compliance to the diet
   – close nutritional monitoring required
   – high costs of ketoanalogues
# Consensus on LPDs in CKD

**Keto Acid Therapy in Predialysis Chronic Kidney Disease Patients: Final Consensus**

<table>
<thead>
<tr>
<th>Stage</th>
<th>eGFR (mL/minute/1.73 m²)</th>
<th>Considered Daily Protein Supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>Normal protein intake (RDA: 0.8 g protein/kg body weight/day)</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Normal protein intake (RDA: 0.8 g protein/kg body weight/day)</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>Normal protein intake (RDA: 0.8 g protein/kg body weight/day)</td>
</tr>
<tr>
<td>a. 45-59 (with increasing serum creatinine)</td>
<td>Protein restriction 0.6/0.7 g protein/kg body weight/day</td>
<td></td>
</tr>
<tr>
<td>b. 30-44 (with increasing serum creatinine)</td>
<td>Protein restriction 0.6/0.7 g protein/kg body weight/day</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15-29 (with increasing serum creatinine)</td>
<td>Protein restriction 1. 0.6 g protein/kg body weight/day 2. 0.3-0.4 g protein/kg body weight/day</td>
</tr>
<tr>
<td>5</td>
<td>&lt;10-15 (not on dialysis)</td>
<td>Protein restriction 1. 0.6 g protein/kg body weight/day 2. 0.3-0.4 g protein/kg body weight/day</td>
</tr>
</tbody>
</table>

**Consensus/Strategy**

- **Low-normal protein, lower sodium and phosphate, normal energy**
  - 1) Prevent CKD-MBD, BP, BW, Proteinuria
  - Slow Renal Progression

- **Low protein, moderately low sodium, low phosphate, low acids, high energy**
  - 1) Reduce of uremic toxicity
  - 2) Improve uremic symptoms
  - 3) Prevent Malnutrition

- **Delay Start of Dialysis**

*eGFR, estimated glomerular filtration rate; RDA, recommended daily allowance.*
Dietary Protein Restriction AND Ketoanalogues

NEW EVIDENCE
Reducing proteinuria in diabetic patients

Table 1: Comparison of proteinuria levels between Group I (LPD + KA + ACEi) and Group II (LPD + ACEi) over 12 months.

Graph a: Proteinuria levels over time for both groups. Group I consistently had lower proteinuria levels compared to Group II, with a statistical significance of p < 0.01-0.02.

Graph b: Changes in 

Bellizzi V et al (2007) – prospective study, 110 patients, stages 4-5 CKD, compared the effect on BP control of:

- very low protein diet supplemented with KA (KD, 0.35 g/kg/day)
- low protein diet (LPD, 0.60 g/kg/day)
- free diet (FD)

BP diminished only in KD group.
BP was independently related to urinary sodium excretion and KD prescription.
Postponing RRT initiation

  - RRT initiation could be delayed for about 1 year without increasing their risk of either death or hospitalization.

Postponing RRT initiation

- **Fouque D (2009)** - meta-analysis of 10 studies:
  - Reduction in the occurrence of renal death by 32% with hypoproteic diets as compared with higher or unrestricted protein intake.
Ketoanalogue-Supplemented Vegetarian Very Low-Protein Diet and CKD Progression

Liliana Garneata,*† Alexandra Stancu, † Diana Dragomir, † Gabriel Stefan,*† and Gabriel Mircescu*†

*Department of Nephrology and Internal Medicine, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania; and †Department of Nephrology, “Dr. Carol Davila” Teaching Hospital of Nephrology, Bucharest, Romania

Excluded (n=631)
- Not meeting inclusion criteria (n=393)
- Refuse to participate (n=191)
- Enrolled in other trial (n=47)

Excluded (n=575)
- Not meeting inclusion criteria (n=483)
- Refuse to participate (n=92)

Discontinued diet (n=3)

Reaching primary end-point (n=14)
- RRT initiation (n=11)
- >50% reduction in eGFR (n=3)

Randomized (n=207)

Allocated and receiving intervention (n=104)

Protein intake 0.3g/kg per day + ketoanalogues (KD) arm

Baseline

Assessment period

Run-in period

Protein intake 0.6g/kg per day (LPD) arm

Allocated and receiving intervention (n=103)

Reaching primary end-point (n=41)
- RRT initiation (n=22)
- >50% reduction in eGFR (n=19)

Discontinued diet (n=4)

14% of screened patients could be enrolled.

Patients requiring RRT initiation (%)

- RRT initiation was required in a lower proportion in the KD group.

Garneata L et al, under the 2nd review, J Am Soc Nephrol

* - statistically significant
Patients experiencing ESRD or 50% reduction in eGFR

- Lower percentage of patients in KD group reached the primary endpoint.

* - statistically significant

Garneata L et al, under the 2nd review, J Am Soc Nephrol
• Patients on KD experienced a significantly slower decline in eGFR.

Garneata L et al, under the 2nd review, J Am Soc Nephrol
Nitrogen waste products retention

- Serum urea significantly decreased only in the KD group.

* - statistically significant

Acid-base balance

- Serum bicarbonate significantly increased only in patients on KD.

* - statistically significant

• Serum calcium increased and phosphates decreased in KD arm.

* - statistically significant

How effective is the keto-supplemented vegetarian very low protein diet?

Numbers needed to treat

- **Antibiotics** for healing peptic ulcer: 5 weeks (6-10 wks)
- **Statins** for preventing 1 heart attack: 20
- **KD** for preventing 1 ESDR: 3

Compliance to protein-restricted diet

Protein intake (median and 95% CI) during the study

Garneata L et al, under the 2nd review, J Am Soc Nephrol
Keypoints for Compliance
Patients’ and their families education

• 3-times weekly evaluation of patient’s food diary (direct session or online):
  – estimation of the intake for:
    • Protein
    • Energy
    • Carbohydrates (in diabetic patients)
  – observations, comments
  – suggestions for diet improvement

• Principles of low protein diets

• Basics on KA supplementation
Incidence of ESRD in 2014 (pmp)

Percentage of incident patients with ESRD due to diabetes, 2014
Ketoanalogues supplemented LPD in patients with advanced Diabetic Kidney Disease and severe proteinuria
Patients Flowchart

Assessment

Assessed for eligibility (n=267)

Excluded (n=170)
- Not meeting selection criteria (n=94)
- Refuse to participate (n=32)
- Other reasons: Included in other clinical trials (n=44)

Included (n=97)

Assessment

Run-in period: LPD - 12 weeks (n=97)

Lost to follow-up (n=0)
Study discontinuation (n=2)
- RTx (upon availability) (n=2)

Assessment

Intervention period: KD - 48 weeks (n=95)

Lost to follow-up (n=0)
Study discontinuation (n=3)
- RTx (upon availability) (n=3)

Follow-up

End of Study (n=92)
Nutritional Intervention

• Low protein diet supplemented with ketoanalogues of essential aminoacids:
  – Protein intake: 0.6 g/kg per day, mostly vegetarian, plus Ketosteril 1 cps/5 kg dry body weight
  – Carbohydrate intake: 200 g/day
  – Energy intake: 30 kcal/kg per day
• The rate of decline in eGFR decreased almost 5 times during SLPD.

Garneata L, Mircescu G. Unpublished data
Blood pressure control was ameliorated.

Garneata L, Mircescu G. Unpublished data
Proteinuria during the study

Proteinuria significantly decreased.

Garneata L, Mircescu G. Unpublished data
Effects of ketoanalogue-supplemented low protein diet

- Ketoanalogue-supplemented LPD was associated with significant reduction in the rate of decline in eGFR and of proteinuria.

Garneata L, Mircescu G. Unpublished data
Supplemented LPDs seem to be effective and safe in postponing RRT initiation.
Survival is not enough: What about the quality of life?

Patients’ Testimonials
I was so afraid of dialysis that I became mad when it came to the diet. I ate only vegetables, I was hating proteins and rejected the animal ones; my body weight decreased, I was feeling fatigue, I had nausea in the morning...

...I've been taught about the minimum protein intake and the role of Ketosteril. It was much better. It was “just nothing” to follow this diet as compared to the restrictions before. Creatinine declined and the kidney function became stable. I was impressed and motivated of the results.

...I am feeling great: do my job, feel good with my family and friends. I am still afraid of dialysis....” (sep 2015)

“They called me for transplantation in Cluj. What is your opinion?”
(Received as text message, 15.10.2015, 21.50)

“Everything is fine. The graft is working. The diuresis is... My creatinine is....”
(Telephone conversation, 01.11.2015, 17.30)
PATIENT’S TESTIMONIAL
(OCT 2015, 95 YEARS OLD, FEMALE, 8 YEARS ON K-LPD)
DIABETIC, PREVIOUSLY ON KETO-SUPPLEMENTATION AND NON-CONTROLLED DIET

“I was not aware of the role of diet. I was thinking drugs would be enough. I was following all that recommended, I took the Keto, I didn’t understand protein restriction is crucial.

...I am leaving another life, like I was waked up, I am now aware that what I am eating is really important.

It was not difficult.

I skip the rule once in a while, but I know this should be an exception. Just in case, my son put a padlock on the fridge...

...I don’t think anymore of dialysis. I am on a stable creatinine. My GFR stays around 13-14 for 8 years, my diabetes is OK, I am feeling fine ....”
Conclusions

• Ketoanalogue-supplemented protein-restricted diets seem to be effective and safe in compliant pre-dialysis CKD patients, both diabetics and non-diabetics, in postponing RRT initiation.

• Close nutritional monitoring and counseling are of paramount importance.
Integrated nutritional intervention in CKD