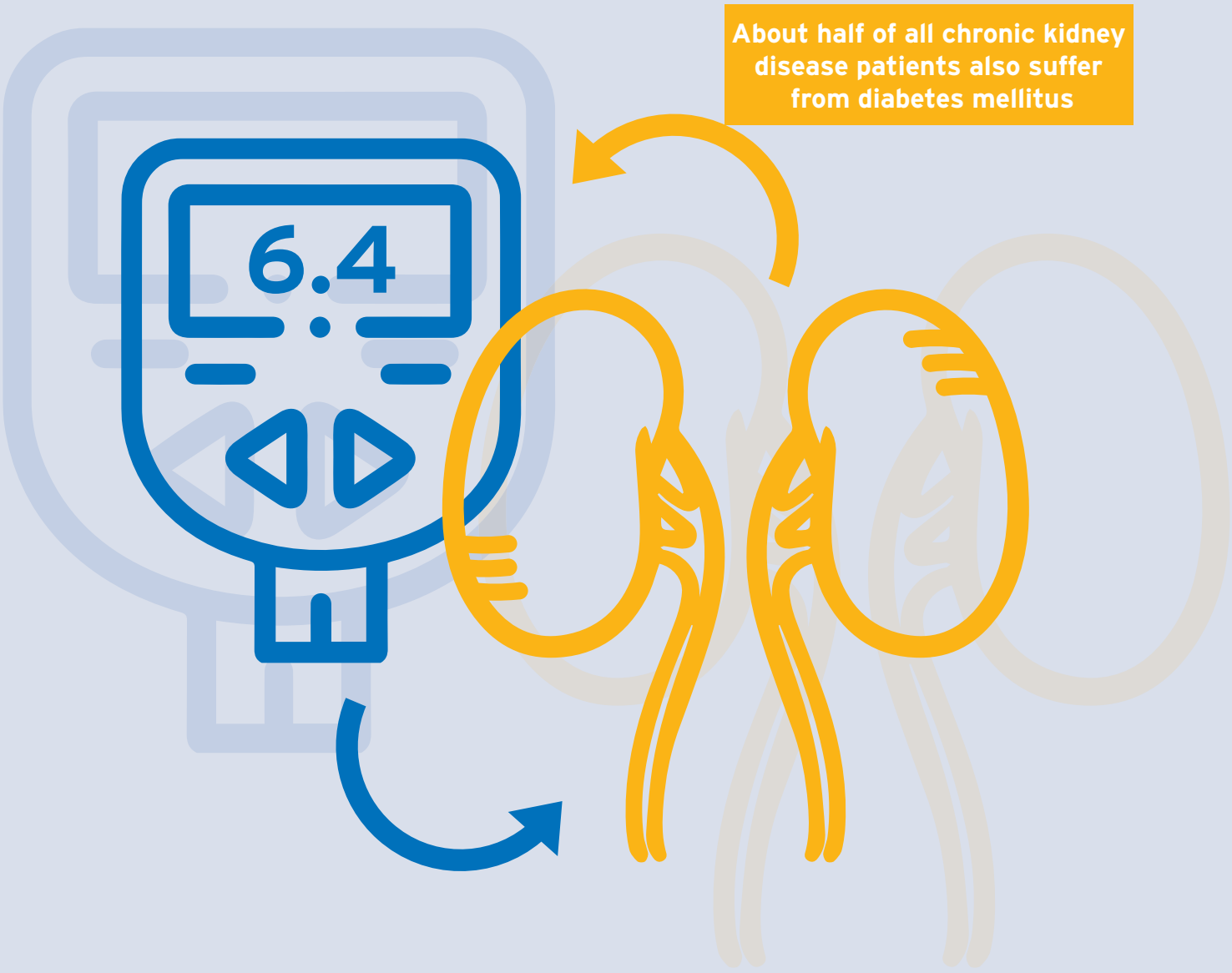
FRESENIUS KABI
caring for life

Protein reduction in chronic kidney disease patients with and without diabetes mellitus

Review of recent literature



Chronic kidney disease (CKD) and diabetes mellitus (DM) today

CKD with and without DM is common

- Approximately 700 million people worldwide suffer from CKD[1]
- Disorders of glucose homeostasis affect about 50% of CKD patients[2]
- 20-50% of individuals with DM develop as well CKD[3]

Combined CKD and DM increases health risks even further

- CKD patients with DM show faster decline of renal function compared to non-diabetic CKD patients[4]
- Once on dialysis, CKD patients with DM have, among others, an increased risk for:
  - cardiovascular death and all-cause mortality[5]
  - myocardial infarction and stroke[5]
  - ulceration and amputation[6]
  - complications of vascular access[7]

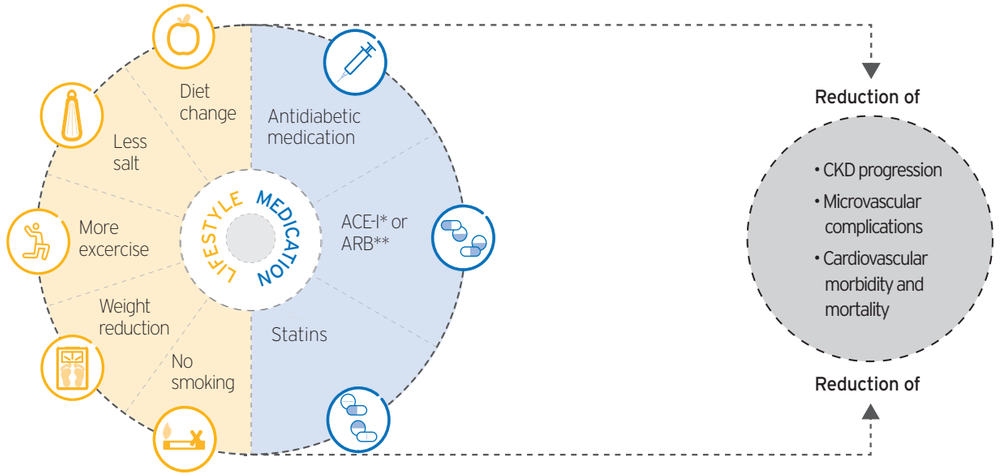
Slowing renal decline is more difficult in CKD patients stage 4+ with DM

- Impaired renal drug metabolism and excretion requiring dose adaptation[8]
- Increased risk for hypoglycemia due to compromised glucose homeostasis by kidney and liver[9]
- Uremic toxins exacerbating insulin resistance[2]

Patients who suffer both from CKD and DM need special attention to slow down progression of renal decline.[10,11]

Nutritional management is important for CKD treatment – also in CKD patients with comorbidities

Recommended treatments for CKD patients according to 2020 KDOQI and KDIGO guidelines:[8,12]



* ACE-I = angiotensin converting enzyme inhibitors; ** ARB = angiotensin-II receptor blockers

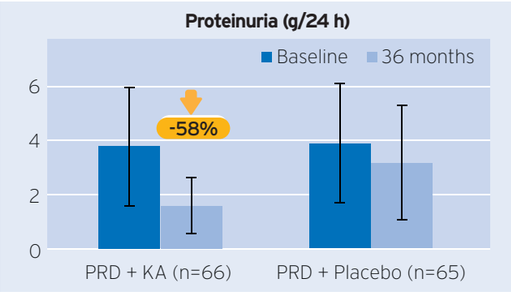
Nutritional management in CKD is based on three key interventions:[8,12]

Protein	Energy	Sodium
Protein reduction in CKD patients not on dialysis to maintain stable nutritional status and optimize glycemic control	Energy intake in all CKD patients adapted to metabolic state and comorbidities	Sodium cut in all CKD patients to reduce blood pressure, proteinuria, and improve volume control
KDOQI 2020 (Kidney Disease Outcome Quality Initiative)[12]		
CKD without DM: 0.55-0.60 g/kg body weight (bw)/day (d) or 0.28-0.43 g with keto acid/amino acid analogues **CKD with DM:** 0.6-0.8 g/kg bw/d	25-35 kcal/kg bw/d	<100 mmol/2.3 g sodium per day
KDIGO 2020 (Kidney Disease: Improving Global Outcomes)[8]		
CKD with DM: 0.8 g/kg bw/d	No intake level specified	<90 mmol/2 g sodium per day **or** <5 g sodium chloride per day

Influence of protein reduction supplemented with keto-analogues (KA) on parameters of CKD progression in CKD patients with and without DM

Effect on proteinuria

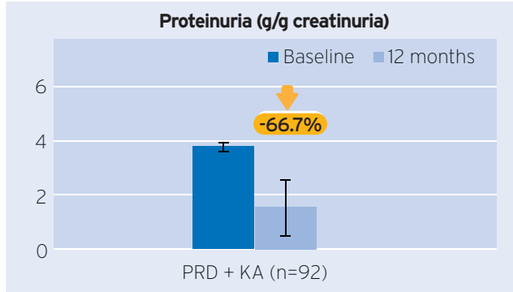
in CKD patients – mixed population



After 36 months, proteinuria was significantly lower with protein-reduced diet (PRD) supplemented with KA compared to PRD + Placebo (p<0.02).[13]

Study design: RCT; CKD patients stage 3-4, 40% with diabetes (none on insulin). Groups: 66/65 patients receiving 0.6 g protein/kg bw/d, <30 kcal/kg bw/d, + KA (1 tb/6 kg bw) or placebo.

in CKD patients with DM



After 12 months, proteinuria was significantly lower with PRD supplemented with KA compared to baseline (p<0.0001).[14]

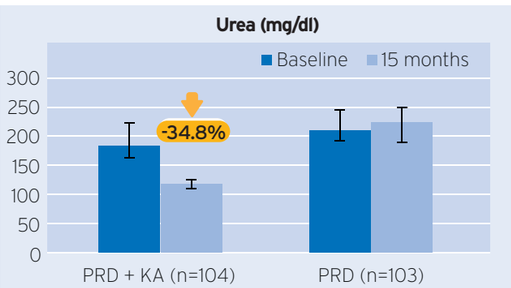
Study design: Open, interventional; 92 CKD patients stage 4-5 with diabetes (67% on insulin). Diet: 0.6 g protein/kg bw/d, 30 kcal/kg bw/d, + KA (1 tb/10 kg bw).

This result was confirmed in further clinical studies.[15,16]

A KA-supplemented PRD can ameliorate proteinuria from DM[14-16] or from a mixed origin in CKD patients[13]

Effect on uremia

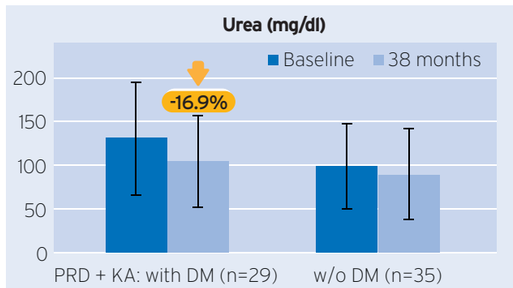
in CKD patients without DM



After 15 months, uremia was lower with PRD supplemented with KA vs. protein reduction alone (p<0.01).[17]

Study design: RCT; 207 patients CKD stage 4-5 without diabetes. Groups: PRD + KA: 0.3 g protein/kg bw/d + KA (1 tb/5 kg bw), or PRD: 0.6 g protein/kg bw/d; 30 kcal/kg bw/d in both groups.

in CKD patients - mixed population



After 38 months, there was a significant reduction of uremia with PRD supplemented with KA vs. baseline (p <0.05) in CKD patients with DM.[18]

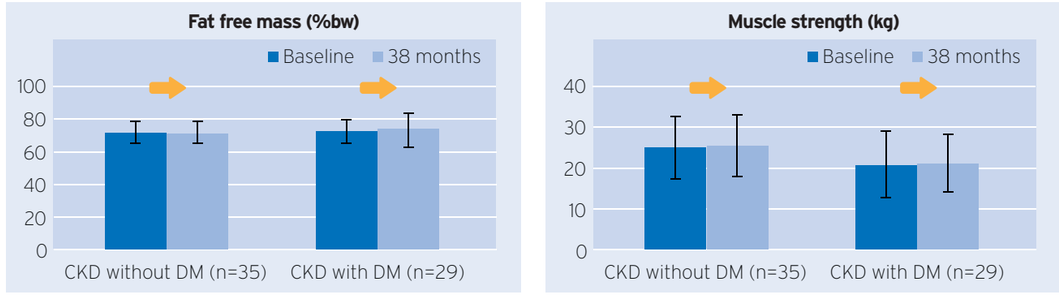
Study design: Open, observational; 64 long term patients CKD 3-5, (w/o diabetes). Diet: 0.5-0.6 g protein/kg bw/d, 30-35 kcal/kg bw/d + KA 1 tb KA per 5-7 kg bw/d.

This result was confirmed in another clinical study.[19]

A KA-supplemented PRD can significantly lower uremia in CKD patients with[18,19] and without DM[17]

Safety of protein reduction with supplementation of keto-analogues in CKD patients with and without DM

Effect of protein reduction on nutritional status in CKD patients with and without DM



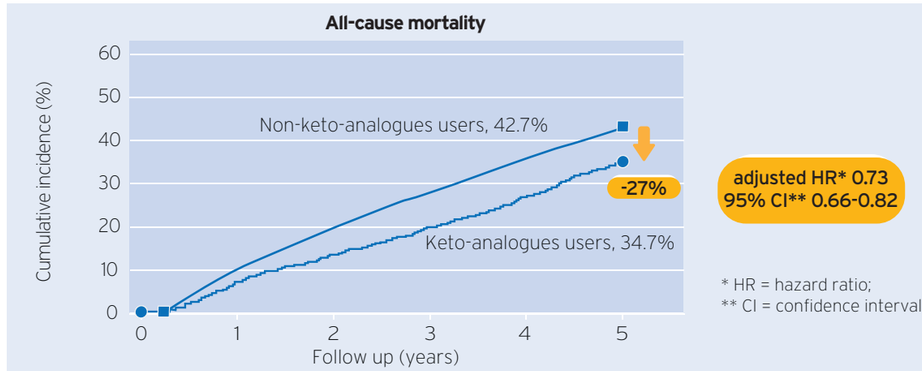
After 38 months, CKD patients treated with PRD + KA maintained fat free mass (muscle mass) and muscle strength vs. baseline irrespective if they also suffered from DM or not.[18]

Study design: Open, observational; 197 patients CKD 3-5, (81 with DM). 38 months follow up: 35 patients w/o DM and 29 patients with DM. Diet: 0.5-0.6 g protein/kg bw/d,, 30-35 kcal/kg bw/d with 1 tablet KA per 5-7 kg bw/d.

This result was confirmed in further clinical studies where KA-supplemented protein reduction maintained nutritional status, shown by maintained body weight, BMI and albumin levels.[16,19]

A KA-supplemented PRD can maintain nutritional status also in CKD patients with DM[16,18,19]

Results from a nationwide population based registry (Taiwan) on CKD patients with DM



In a retrospective analysis of the Taiwanese National Health Insurance Research Database, 1,001 **CKD patients with DM** not on dialysis taking KA in conjugation with a PRD were compared to 14,781 non-KA users for 5 years after reaching CKD stage 5.

Overall mortality adjusted for age, gender, geolocation, insurance level, comorbidities and medications was significantly lower in CKD patients with DM taking KA compared to the control group (see figure, adjusted HR 0.73, 95% CI 0.66-0.82).[20]

This study also reported slower progression to dialysis (1.6±1.5 vs. 1.0±1.4 years; HR 0.65, 95% CI 0.61-0.69) as well as a lower incidence of major adverse cardiovascular events (MACE; RR 0.76, 95% CI 0.67-0.86) in the KA group.[20]

Protein reduction in combination with KA has been shown to positively influence metabolic alterations in CKD patients with and without DM and represents a nutritionally safe treatment option.

Protein reduction in CKD patients should always be implemented step-by-step

Implementation should follow a stepped approach

1. Protein reduction is considered for patients with good nutritional status and appetite[21]
2. Stepwise reduction of protein intake with dietary counseling to support adherence and improve QoL[12,22]
3. Regular reassessment of metabolic parameters is mandatory[12,22]
4. Adequate energy intake substantially reduces nutritional risk in CKD patients[18]
5. CKD patients with and w/o DM following a PRD with KA under dietitians' advice have no increased risk of malnutrition[15,18] even after 7[23] to 10 years[24,25]
6. A protein reduced diet of 0.3-0.4 g/kg bw/d needs to be supplemented with KA to ensure supply with essential amino acids[12,18]

Protein reduced diet in CKD patients with and without diabetes mellitus

- is a guideline-recommended conservative CKD treatment[12]
- is able to ameliorate metabolic disturbances[13-19]
- is nutritonally safe[15,18,23-25]
- and should be introduced stepwise[12,22]

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Ketosteril®

Ketosteril® supplemented very low protein diet

- maintains nutritional status[25,26]
- reduces metabolic complications[17,18,26]
- postpones dialysis initiation[17,25,26]

Abbreviated prescribing information

Name of the medicinal product: Ketosteril® film-coated tablets..

Composition: One film-coated tablet contains: (RS)-3-methyl-2-oxovaleric acid (α-ketoanalogue to DL-isoleucine, Ca-salt) 67 mg; 4-methyl-2-oxovaleric acid (α-ketoanalogue to leucine, Ca-salt) 101 mg, 2-oxo-3-phenylpropionic acid (α-ketoanalogue to phenylalanine, Ca-salt) 68 mg, 3-methyl-2-oxobutyric acid (α-ketoanalogue to valine, Ca-salt) 86 mg, (RS)-2-hydroxy-4-methylthio-butyric acid (α-hydroxyanalogue to DL-methionine, Ca-salt) 59 mg, L-lysine acetate 105 mg (=75 mg L-lysine), L-threonine 53 mg, L-tryptophan 23 mg, L-histidine 38 mg, L-tyrosine 30 mg, total nitrogen content per tablet 36 mg, calcium content per tablet 1.25 mmol =50 mg.

Excipients: Maize starch, crospovidone type A, talc, silica (colloidal anhydrous), magnesium stearate (Ph.Eur) [vegetable], macrogol 6000, quinoline yellow E104, basic butylated methacrylate copolymer, triacetin, titanium dioxide E171, povidone K 29-32.

Therapeutic indications: Prevention and treatment of damages due to faulty or deficient protein metabolism in chronic kidney disease in connection with a limited dietary protein intake of 40 g/day or less (adult). Usually this applies to patients whose glomerular filtration rate (GFR) is less than 25 ml/min.

Posology and method of administration: If not otherwise prescribed the dose for adults (70 kg body weight) is 4 to 8 tablets three times daily during meals. The tablets must not be chewed. Ingestion during meals facilitates proper absorption and the metabolisation into the corresponding amino acids.

Contraindications: Hypersensitivity to the active substances or to any of the excipients, hypercalcaemia and disturbed amino acid metabolism.

Special warnings and precautions for use: The serum calcium level should be monitored regularly. Ensure sufficient calorie intake. In the presence of hereditary phenylketonuria, attention should be given to the fact that Ketosteril contains phenylalanine. Monitoring of the serum phosphate levels is needed in case of concomitant administration of aluminium hydroxide. No experience has been gained so far with the administration in paediatric patients.

Interaction with other medicinal products and other forms of interaction: Concomitant administration of calcium-containing drugs may cause or aggravate elevated serum calcium levels. Drugs that form hardly soluble compounds with calcium (e.g. tetracyclines, quinolines such as ciprofloxacin and norfloxacin as well as drugs containing iron, fluoride or estramustine) should not be taken at the same time with Ketosteril to avoid disturbed absorption of the active substances. An interval of at least two hours should elapse between the ingestion of Ketosteril and these drugs. The susceptibility to cardioactive glycosides, and hence the risk for arrhythmia will increase if Ketosteril produces elevated serum calcium levels. Uraemic symptoms improve under therapy with Ketosteril. Thus, in case of aluminium hydroxide administration, the dose of this drug has to be reduced if necessary. Serum phosphate levels should be monitored for a decrease.

Pregnancy and lactation: There are no adequate data from the use of Ketosteril in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. No experience has been made so far with the use during lactation.

Undesirable effects: The intake of Ketosteril may very rarely lead to hypercalcaemia. If hypercalcaemia occurs, the intake of vitamin D should be reduced. In case of persisting hypercalcaemia, the dose of Ketosteril as wellas the intake of any other calcium sources has to be reduced.

Overdose: No case of overdose has been reported.

Special precautions for handling/storage: Do not use Ketosteril after expiry date! Keep out of the reach of children! Do not store above 25°C. Store in the original package and keep the blisters tightly closed to protect contents from moisture.

Issue of information: Sep 2014.

Registered product information may differ in your country. Before prescribing, refer to nationally approved prescribing information.

Picture source of images with persons depicted and showing medicinal products: Fresenius Kabi Deutschland GmbH

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