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Ketosteril®

Scientific information

Fouque and Laville.

Low Protein Diets for Chronic Kidney Disease in Non Diabetic Adults

Cochrane Database of Systematic Reviews 2009; 3: CD001892

Key message

Protein restriction in non-diabetic chronic kidney disease (CKD) patients reduces renal death by 32% compared to higher or unrestricted protein intake.

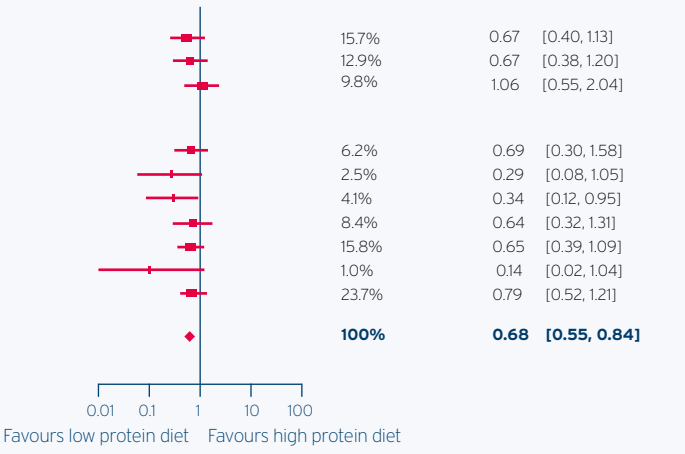

Figure 1: The risk ratio of renal death with protein restriction compared to a higher protein diet was 0.68 (95% Confidence interval [CI] 0.55 to 0.84).
* low protein diet supplemented with ketoanalogues

Key results

- Protein restriction reduced the relative risk of renal death by 32% *(Figure 1)*.
- The strongest effect on renal death was found for a protein intake of 0.3 to 0.6 g/kg body weight (BW)/d.
- A more liberal protein restriction (0.6 g/kg BW/d) showed no significant effect.

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Methods

The meta-analysis included studies comparing protein intake ≥ 0.8 g/kg BW/d with protein restriction to 0.6 g/kg/d and 0.3-0.6 g/kg/d regardless of supplementation with essential amino acids or ketoacids. Non-diabetic adults with moderate to severe CKD followed the diet for at least 12 months. Intention-to-treat analysis was performed. Renal death was defined as death during follow-up or need to start dialysis during follow-up or kidney transplant during the study.

Results

- 10 randomized controlled trials including 1,002 patients in the protein restriction group and 998 patients in the higher or unrestricted protein intake group were identified.
- The distribution of different kidney disease categories (glomerulopathy, interstitial nephritis, nephroangiosclerosis, polycystic disease) was similar in both groups.
- The actual reduction in protein intake based on urinary collection of protein waste products ranged from 0.2 g/kg BW/d (Locatelli 1991) to 0.35 g/kg BW/d (MDRD 1994, in Kopple 1997).
- Nine out of 10 studies showed a trend for a beneficial effect of protein restriction, and one study (Ihle 1989) found a statistically significant difference. The study results were homogeneous (X^2=8.20, df=9, p=0.51; I^2=0%).
- 113 renal deaths were observed with protein restriction and 168 events with unrestricted protein intake (Risk ratio [RR] 0.68, 95% CI 0.55 to 0.84).
- The relative renal death risk reduction of 32% in favour of a restricted protein intake was highly signifi cant (p=0.0002).
- The number of patients needed to be treated (NNT) during one year to avoid one renal death ranged from 2 (Di Iorio 2003) to 56 (MDRD 1994).
- Sub-analysis found the strongest effect on renal death for protein restriction of 0.3 to 0.6 g/kg BW/d (seven studies, RR 0.63, 95% CI 0.48 to 0.83, p=0.0009). In four of the seven studies low protein diet was supplied with ketoanalogues.
- The effect of a more liberal protein restriction (0.6 g/kg/d) was not statistically significant (three studies, RR 0.76, 95% CI 0.54 to 1.05, p=0.10).

Conclusion

This update of two previous meta-analyses (Fouque 1992; Pedrini 1996) demonstrates that protein restriction in CKD patients reduces the incidence of renal death by 32% compared with higher or unrestricted protein intake (p=0.0002). In half of the studies analysed low protein diet was supplemented with by ketoanalogues.

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, triacetine, titanium dioxide E171, povidone K 29-32. **Therapeutic indications:** Prevention and treatment of damages due to faulty or defi cient 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. A sufficient supply of calories should be ensured. No experience has been gained so far with the administration in paediatric patients. 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. **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 ciprofl oxacin 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 well as 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:** March 2009. Regarding further details, please refer to the national SmPC.
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Fresenius Kabi Deutschland GmbH
61346 Bad Homburg
Germany

Phone: +49 (0) 61 72 / 686-0
www.fresenius-kabi.com