L'intervento dietetico nel paziente diabetico con nefropatia

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Scuola Medica Salernitana

ERN working group
European Renal Nutrition

Nutritional approach in **CKD**

Goals

- Improve uremia
- Prevent PE-wasting
- Reduce CKD progression

Diet

low-protein

[high-carbohydrate]

normal/high-energy

Reduce Renal & CV risk

Glucose control in DKD ?

Nutritional approach in **DM**

Goals

- Body weight goal
- Glucose, BP, lipids goals
- Prevent diabetes compl.

Diet

low-carbohydrate

[high-protein]

low-energy

Reduce CV risk

CKD progression ?

Chronic Kidney Disease: Treatment (2).

11.5 For people with **non dialysis-dependent chronic kidney disease, dietary protein intake should be approximately 0.8 g/kg body weight per day** (the recommended daily allowance). For patients on dialysis, higher levels of dietary protein intake should be considered B

11.6 In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin-to-creatinine ratio (30-299 mg/g creatinine) B and is strongly recommended for those with urinary albumin-to-creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73m^2. A

Microvascular Complications and Foot Care:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019;42(S1)

American Diabetes Association.

Diabetes Care Volume 42, May 2019

Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report

Diabetes Care 2019;42:731–754 | https://doi.org/10.2337/dci19-0014

Alison B. Evert,[1] Michelle Dennison,[2] Christopher D. Gardner,[3] W. Timothy Garvey,[4,5] Ka Hei Karen Lau,[6] Janice MacLeod,[7] Joanna Mitri,[8] Raquel F. Pereira,[9] Kelly Rawlings,[10] Shamera Robinson,[11] Laura Saslow,[12] Sacha Uelmen,[11] Patricia B. Urbanski,[13] and William S. Yancy Jr.[14,15]

Diabetic Kidney Disease

Consensus recommendation

- In individuals with diabetes and non–dialysis-dependent diabetic kidney disease (DKD), reducing the amount of dietary protein below the recommended daily allowance (0.8 g/kg body weight/day) does not meaningfully alter glycemic measures, cardiovascular risk measures, or the course of glomerular filtration rate decline and may increase risk for malnutrition.

MNT: Energy Balance.

5.9 **Weight loss (>5%) achievable by the combination of reduction of calorie intake and lifestyle modification** benefits overweight or obese adults with type 2 diabetes and also those with prediabetes. Intervention programs to facilitate weight loss are recommended.

Lifestyle Management:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019;42(S1)

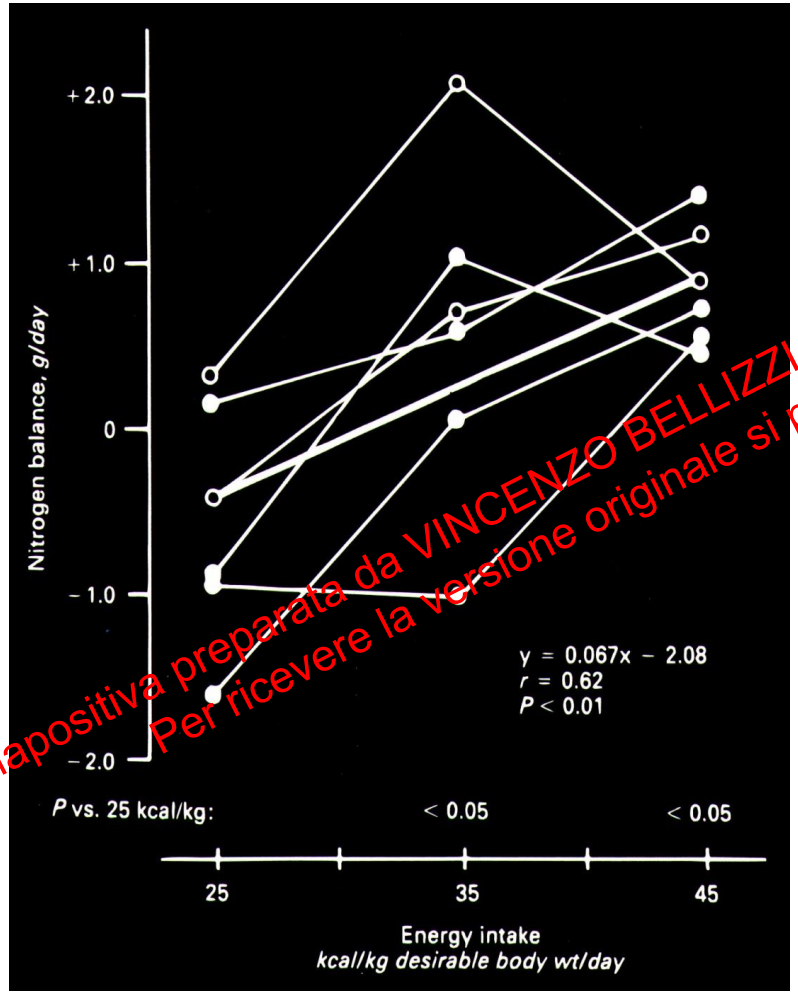
	Body Mass Index (BMI) Category (kg/m²)				
Treatment	25.0-26.9 (or 23.0-26.9*)	27.0-29.9	30.0-34.9 (or 27.5-32.4*)	35.0-39.9 (or 32.5-37.4*)	≥40 (or ≥37.5*)
Diet, physical activity & behavioral therapy	┼	┼	┼	┼	┼
Pharmacotherapy		┼	┼	┼	┼
Metabolic surgery			┼	┼	┼

* Cutoff points for Asian-American individuals.
┼ Treatment may be indicated for selected, motivated patients.

Obesity Management for the Treatment of Type 2 Diabetes:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019;42(S1)

American Diabetes Association.

Energy related Nitrogen Balance in CKD



GFR< 25 ml/min:

>60 years: 35 kcal/kg idBW/day

>60 years: 30-35 kcal/kg idBW/day

Slomovitz, *Kidney Int* 1989

Nutritional Treatment in **DKD** ?

which Diet ?

low-carbohydrate, low-energy diet

[high-protein]

or

low-protein, normal-energy diet

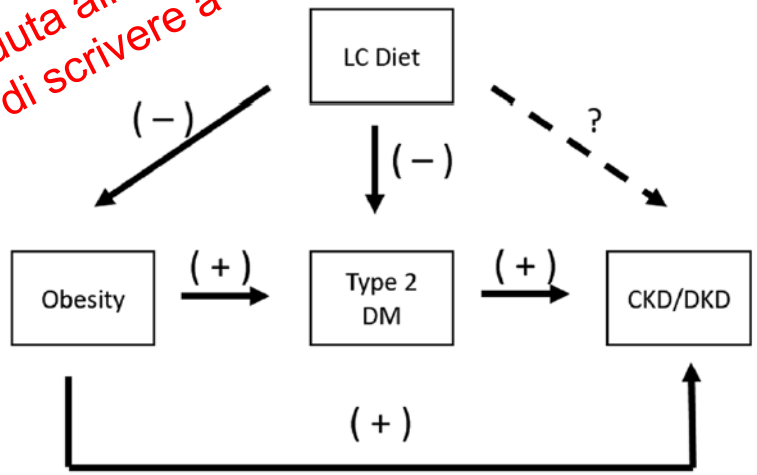
[high-carbohydrate]

AGENDA:

- Low-Carbohydrate diet in DKD
- Low-Protein diet & Glucose metabolism in DKD
- LPDs / Patterns & DKD outcomes
- The dark side of LPDs & DKD
- Summary

Low-carbohydrate diet and **DKD**

Diet	Daily protein (g)
Western diet	Women: 59–72 Men: 73–109[a]
KDIGO recommendation:	
Stages G1–3	Women: 68–107 Men: 71–124[b]
Stages G4/5	Women: 46–61 Men: 53–71[b]
LC diet	73–130
Postbariatric surgery diet	60–120[11]

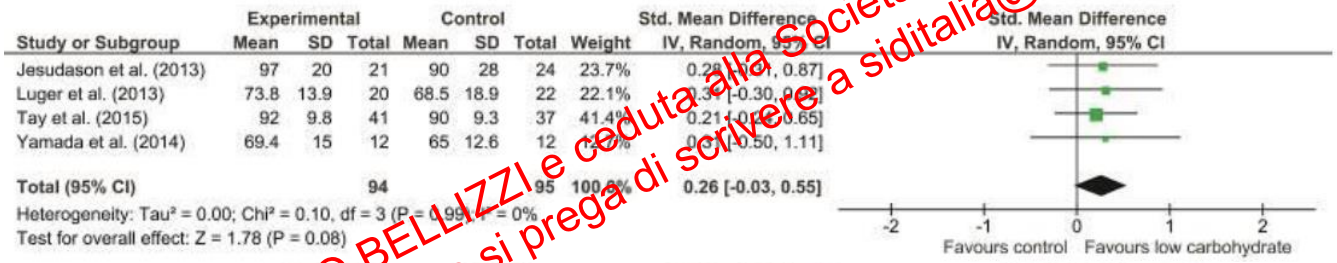


Mitchell, *Ann NY Acad Sci* 2019

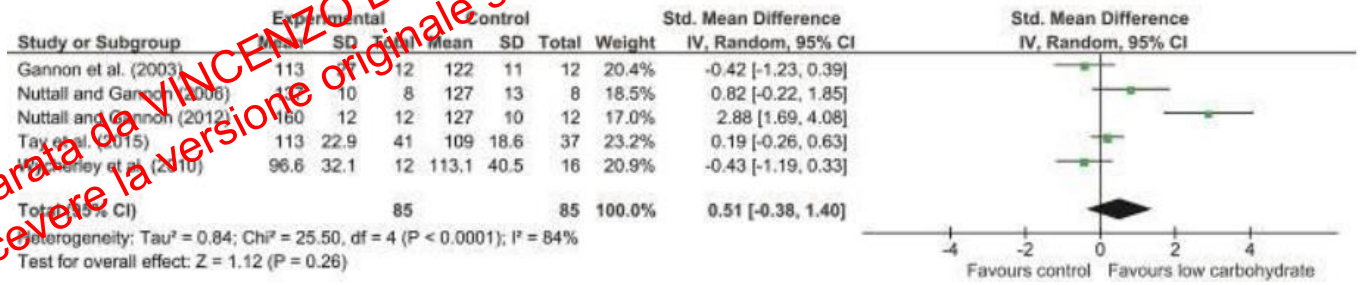
Low-carbohydrate diet and **DKD**

- **Meta-analysis, 12 RCT: 952 participants (**500 LCD and 442 control diets**)**
- **General population; Age, 44-63 y**
- ***Outcomes*: markers of renal function**

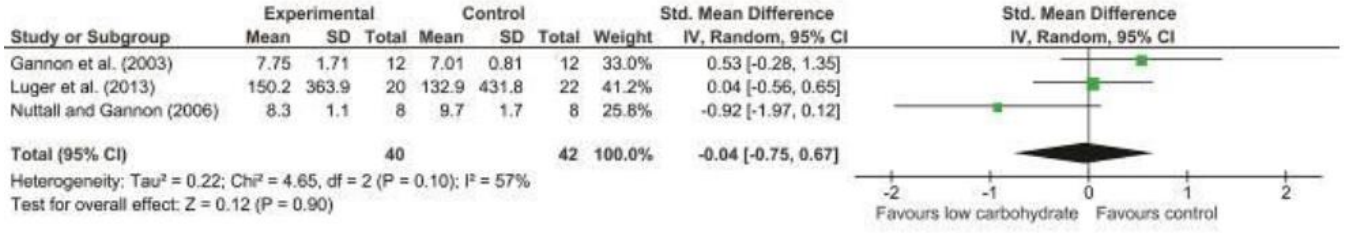
eGFR



Creat. Clear.



Albuminuria



Suyoto, *Diab Met Res* 2018

AGENDA:

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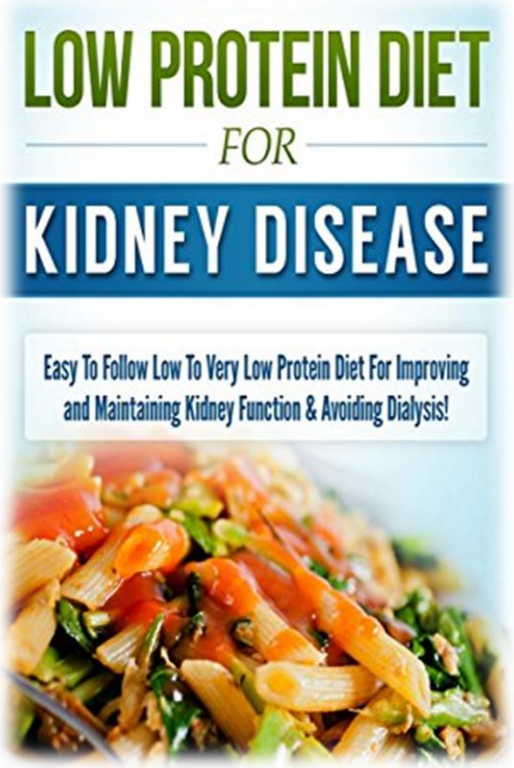


Glucose & Insulin homeostasis in CKD

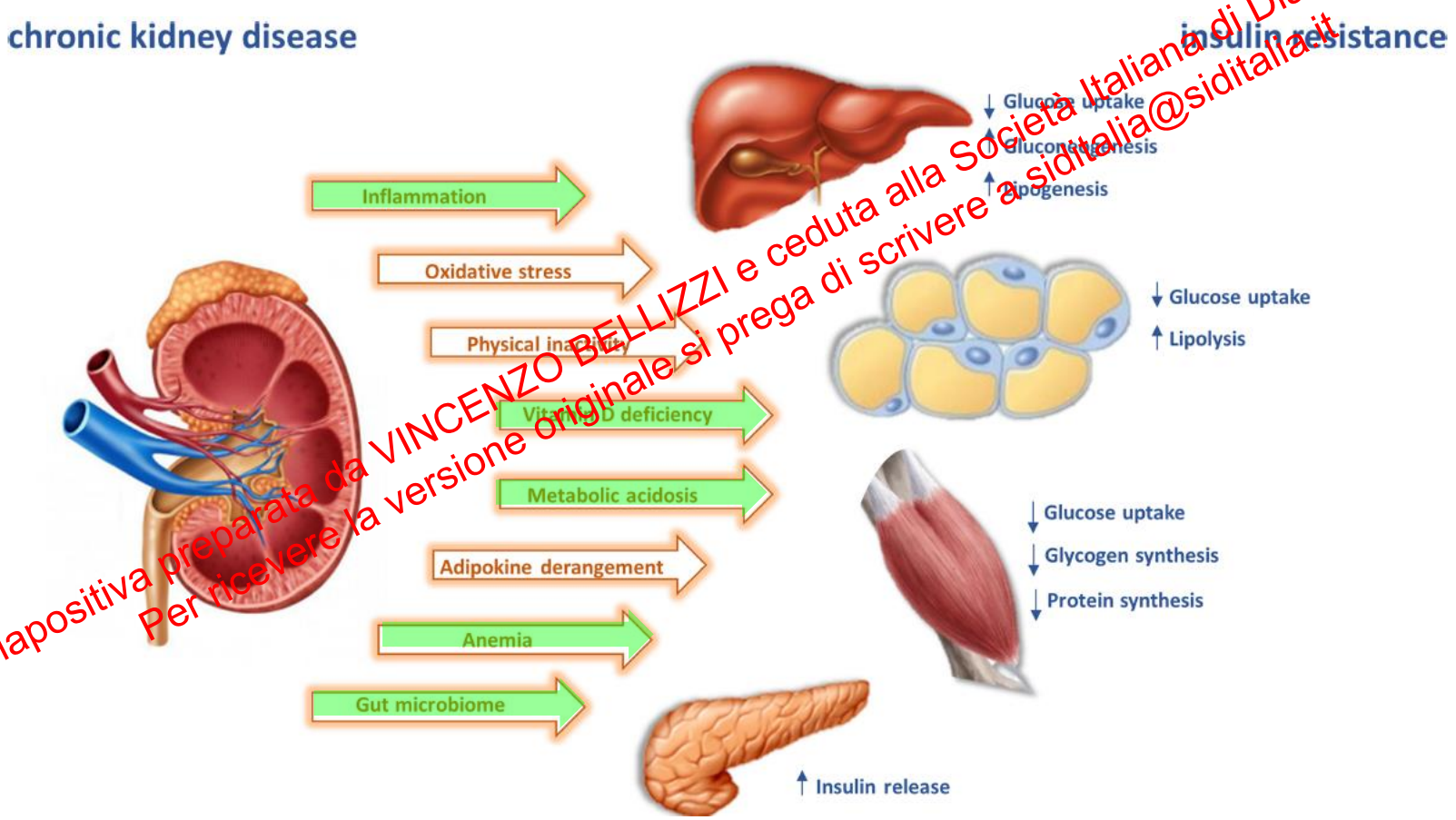
Study: cross-sectional; **CKD**: 59 non-diabetic CKD stage 4-5; **Controls**: 39 healthy subjects; **Methods**: euglycemic clamp & glucose test; **Outcome**: insulin sensitivity, clearance, and secretion and glucose tolerance

Measurement	eGFR<60 ml/min per 1.73 m^2, *n*=59	eGFR≥60 ml/min per 1.73 m^2, *n*=39	*P* Value
Fasting measurements			
Fasting glucose, mg/dl	102.7 (8.8)	100.1 (10.1)	0.19
Fasting insulin, μU/ml	10.1 (5.3)	7.3 (5.2)	0.01
Hemoglobin A1c, %	5.6 (0.4)	5.5 (0.4)	0.56
Hyperinsulinemic-euglycemic clamp measurements			
Steady-state insulin, μU/ml	190.0 (39.5)	162.0 (34.2)	<0.001
Glucose disposal rate, mg/min	857.1 (199.2)	739.1 (212.1)	0.06
Insulin sensitivity, mg/min per microunit per milliliter	3.9 (2.0)	5.0 (2.0)	<0.01
Insulin clearance, ml/min	876.1 (225.7)	998.3 (212.1)	<0.01
IVGTT measurements			
Acute insulin response, μU × min/ml	339.7 (241.3–529.4)	332.5 (197.5–546.7)	0.84
OGTT measurements[a]			
Matsuda index	4.2 (2.5)	6.6 (5.0)	<0.01
Insulinogenic index, μU/ml per milligram per deciliter	0.8 (0.5–1.4)	0.7 (0.4–1.0)	0.67
Glucose AUC, (mg × min)/ml	19,407 (17,512–21,680)	18,667 (16,930–21,661)	0.50
2-h plasma glucose, mg/dl, *N* (%)			0.30
<140	20 (35)	19 (49)	
140–199	31 (54)	15 (38)	
≥200	6 (11)	5 (13)	

- In CKD the glucose metabolism is impaired because of reduced insulin sensitivity (not related to GFR, only in part related to lifestyle and diet)

de Boer, *J Am Soc Nephrol* 2016

Insulin Resistance in CKD



Spoto, Am *J Physiol Renal Physiol* 2016

Insulin resistance in CKD: the culprit is Urea

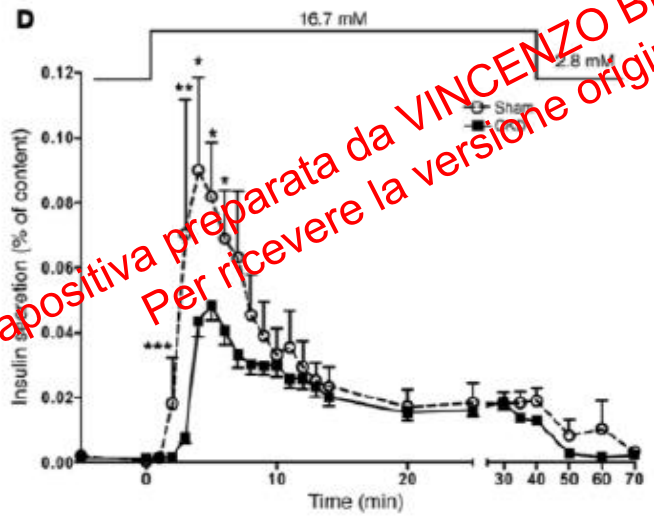
RESEARCH ARTICLE

The Journal of Clinical Investigation

Urea impairs β cell glycolysis and insulin secretion in chronic kidney disease

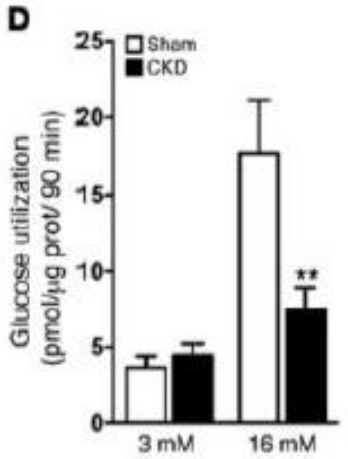
Laetitia Koppe,[1,2] Elsa Nyam,[1,2,3] Kevin Vivot,[1,2] Jocelyn E. Manning Fox,[4] Xiao-Qing Dai,[4] Bich N. Nguyen,[5,6] Dor
Camille Attané,[1,2] Valentine S. Moullé,[1,2] Patrick E. MacDonald,[4] Julien Ghislain,[1,2] and Vincent Poitout[1,2,3,7]

[1]Montreal Diabetes Research Center, Montreal, Quebec, Canada. [2]Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Montréal, Québec, Canada.
and Molecular Medicine, Université de Montréal, Montréal, Québec, Canada. [4]Department of Pharmacology and Alberta Diabetes Institute, University of Alberta, Edmonton, Al
[5]Department of Pathology, CHUM, Montréal, Québec, Canada. [6]Department of Pathology and Cell Biology, Université de Montréal, Montréal, Québec, Canada. [7]Departm
Université de Montréal, Montréal, Québec, Canada.



CKD mice islets exposed to glucose

normal mice islets exposed to urea



CKD mice islets

Koppe, *J Clin Invest* 2017

Insulin resistance in CKD: the culprit is Urea

RESEARCH ARTICLE

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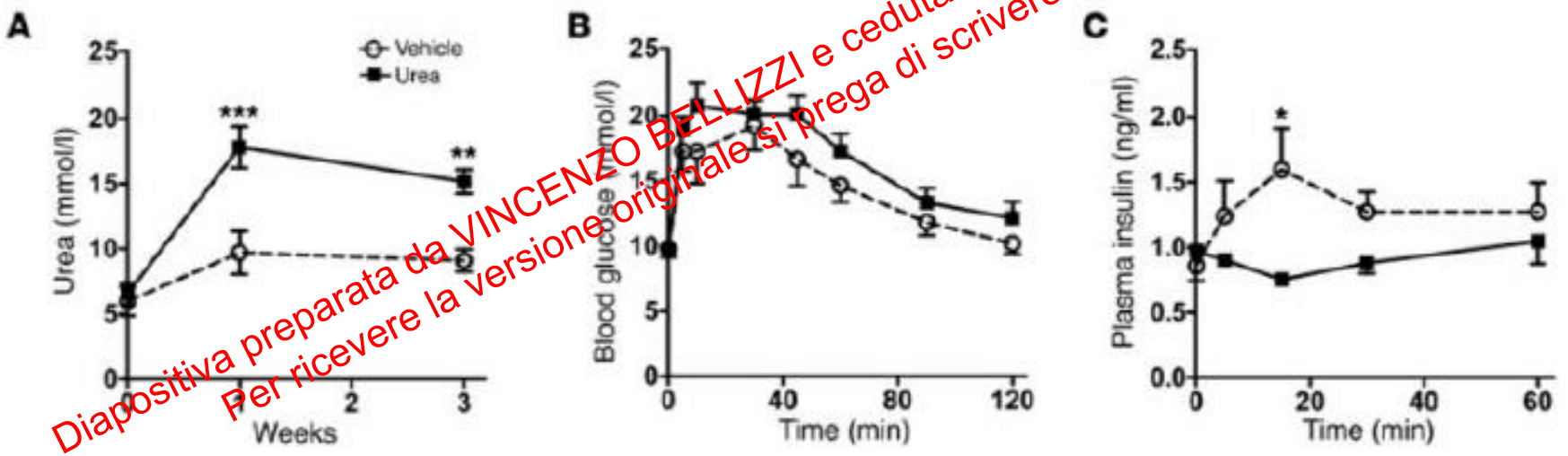


normal mice exposed to urea in tap water

- Insulin secretory defects in CKD arise from elevated circulating levels of urea

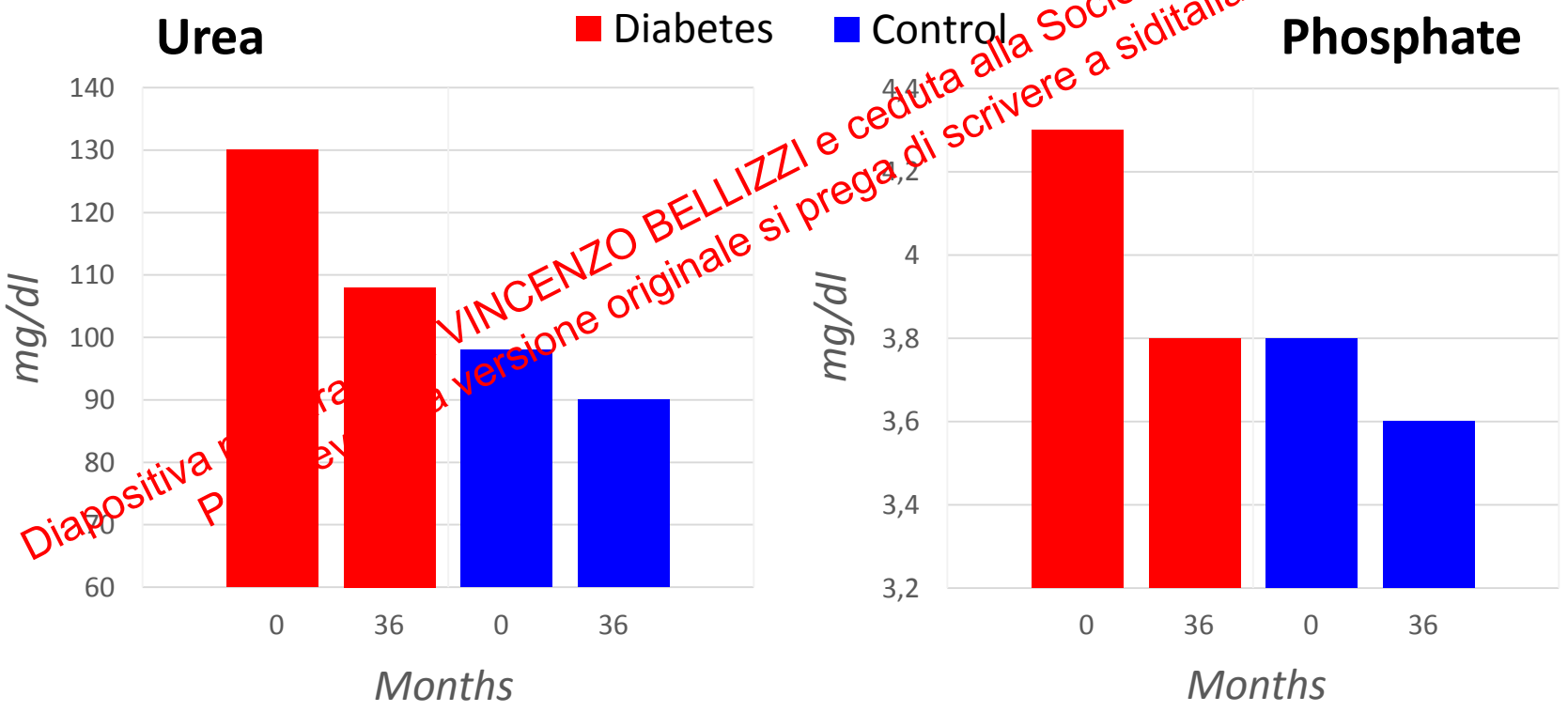
Koppe, *J Clin Invest* 2017

LPDs & Glucose homeostasis in CKD/DKD

- In CKD non-DM, plasma levels of **glucose and insulin decrease** after LPD, indicating restoring of insulin sensitivity and improving of glucose tolerance [Rigalleau, *Kidney Int* 1997]
- Small trial in CKD 3-4 type-2 DM → 1 year LPD *vs.* free diet → unchanged serum glucose and **decreased the glycated hemoglobin** [Meloni, *J Renal Nutr* 2002]
- Small trial in progressive CKD type-I DM → LPD **lowered the glycated hemoglobin** [Hansen, *Kidney Int* 2002]

KA-LPD & Metabolism in DKD

Study: prospective, controlled; **N**: 81 DM, 116 CON; **CKD**: stage 4-5; **Age**: 65 y; **Follow-up**: 6 mts to 3 years; **Diet**: 0.5-0.6 g/kg/d + ketoacids; **Outcome**: weight; albumin; body comp.



Bellizzi, *BMC Nephrology* 2016

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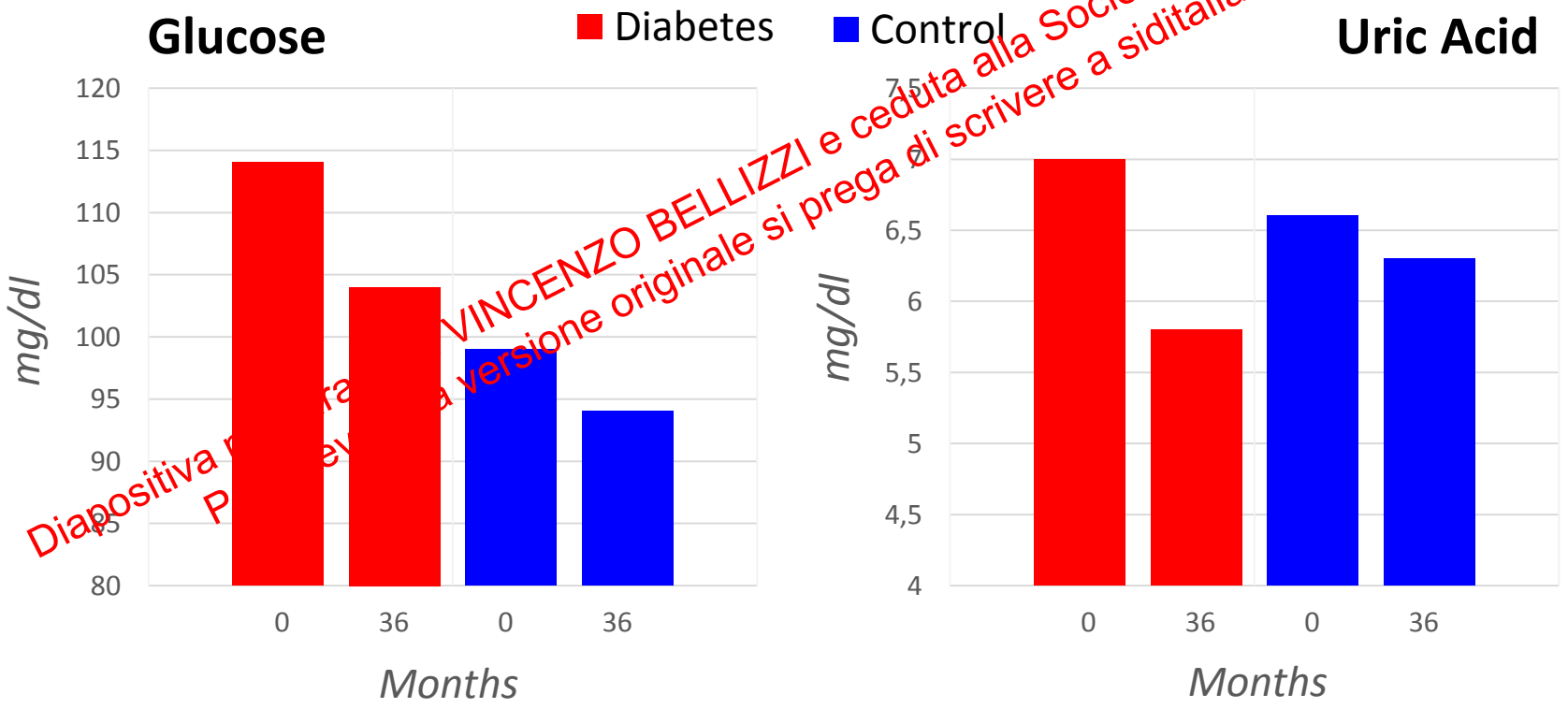

Bellizzi, *BMC Nephrology* 2016

Uric Acid & Insulin Resistance

- Hyper-uricemia may be associated to insulin resistance [**Avula,** *J Clin Diagn Res* 2016]
- Hyper-uricemia may be a consequence of insulin resistance (lower excretion) but uric acid has also a causal role in diabetes [**Facchini,** *JAMA* 1992; **Johnson,** *Diabetes* 2016]
- In models of metabolic syndrome, lowering the uric acid improves the insulin resistance [**Baldwin,** *Diabetes* 2011]
- Direct evidences in humans are limited. In diabetics treated with allopurinol it was observed an improvement of glycated hemoglobin [**Dogan,** *Blood Press* 2011]
- **KA-LPD → urea reduction → insulin resistance reduction (**lower uric acid**) → glucose profile improvement**

AGENDA:

- Low-Carbohydrate diet in DKD
- Low-Protein diet & Glucose metabolism in DKD
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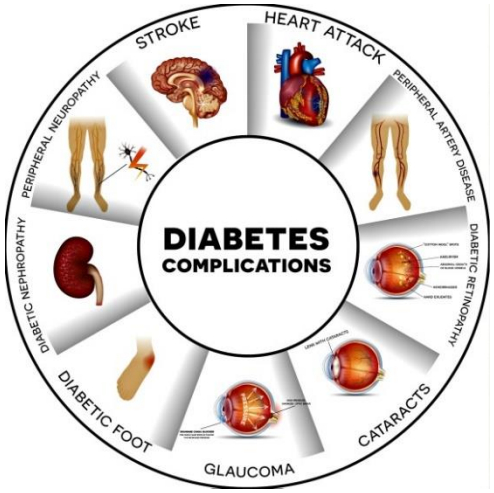


Effect of low-protein diet on kidney function in diabetic nephropathy: meta-analysis of randomised controlled trials

BMJ open 2013
accessible medical research

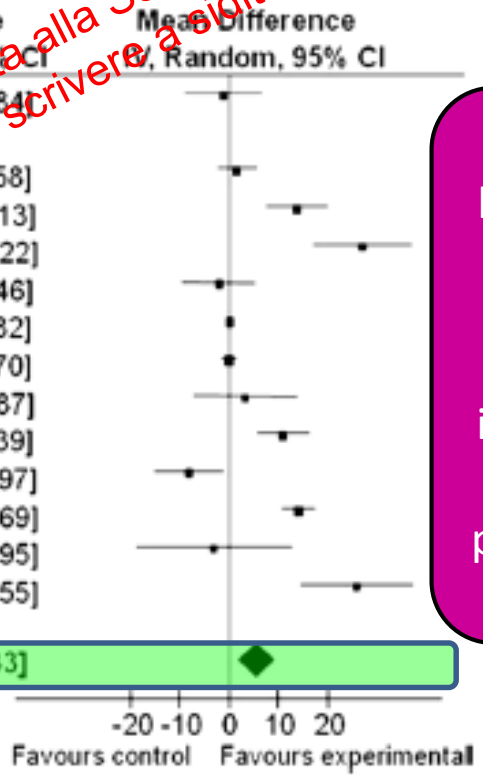
Uru Nezu,[1] Hiroshi Kamiyama,[2] Yoshinobu Kondo,[3] Mio Sakuma,[4] Takeshi Morimoto,[4] Shinichiro Ueda[1]

- **Age: 33-67 y**
- **GFR: 76 ml/min/1.73m²**
- **Diet: 0.6-0.8 g/kg/d *vs.* 1.0-1.6**

13 RCT, 779 DKD | ***Outcome*: GFR; U-prot; HbA1C; nutrition**

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Koya, 2009	-21.4	22.8	56	-20.3	20	56	7.1%	-1.10 [-8.84, 6.84]
Velàquez, 2008								
normoalbuminuria	-1.3	5.1	9	-2.9	3.5	10	9.7%	1.60 [-2.38, 5.58]
microalbuminuria	6.5	9	10	-7.3	5.3	12	8.1%	13.80 [7.47, 20.13]
macroalbuminuria	17.9	14.1	10	-9.3	7.5	9	5.6%	27.20 [17.18, 37.22]
Dussol, 2005	-7	11	22	-5	15	25	7.4%	-2.00 [-9.46, 5.46]
Meloni, 2004	-5.8	1.5	40	-6	1.3	40	11.0%	0.20 [-0.42, 0.82]
Hanasen, 2002	-3.8	3.2	38	-3.9	3.9	38	10.8%	0.10 [-1.50, 1.70]
Pijls, 2002	-11.6	29	63	-14.9	32.7	68	5.5%	3.30 [-7.27, 13.87]
Raal, 1994	3	6.4	11	-8	6.4	11	8.7%	11.00 [5.61, 16.39]
Dullart, 1993	-18	12.2	14	-10	6	16	7.6%	-8.00 [-15.03, -0.97]
Zeller, 1990	-11.8	4.5	20	-26	5.7	15	9.9%	14.20 [10.71, 17.69]
Brouhard, 1990	-28	10	8	-25	19.4	7	3.4%	-3.00 [-18.95, 12.95]
Ciavarella, 1990	15	14.6	7	-11	6.2	9	5.0%	26.00 [14.45, 37.55]
Total (95% CI)			308			316	100.0%	5.82 [2.30, 9.33]

Heterogeneity: Tau² = 29.24; Chi² = 143.11, df = 12 (P < 0.00001); I² = 92%
Test for overall effect: Z = 3.24 (P = 0.001)



Low-normal protein diet [< 0.9 g/kg] improves AbA1C, improves GFR, no effect on proteinuria, no malnutrition

Mild LPD improves the progression of diabetic nephropathy (in adherent patients**)**

Original Investigation

Diet and Kidney Disease in High-Risk Individuals With Type 2 Diabetes Mellitus

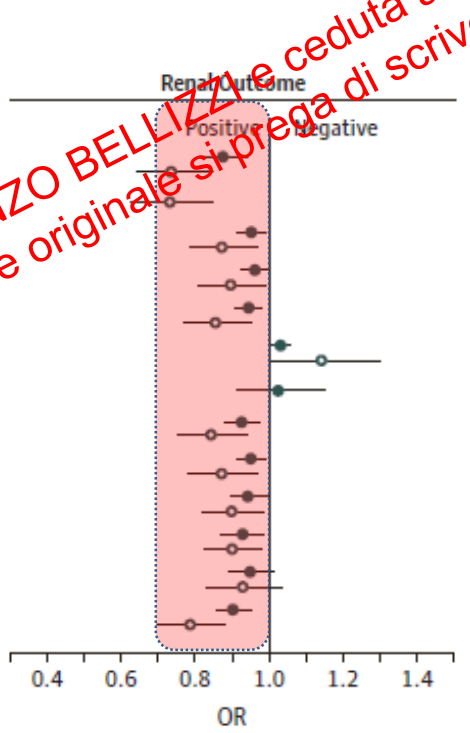
Daniela Dunkler, PhD; Mahshid Dehghan, PhD; Koon K. Teo, PhD; Georg Heinze, PhD; Peggy Gao, MSc; Maria Kohl, MSc; Catherine M. Clase, MB; Johannes F. E. Mann, MD; Salim Yusuf, DPhil; Rainer Oberbauer, MD; for the ONTARGET Investigators

- 6.213 T2-DM pts, no CKD
- FU = 5.5 y
- Renal outcomes

6200 pz T2-DM, NO microalbuminuria | ***Outcome***: Albuminuria or eGFR loss >3%/y

Figure 3. Forest Plot for Single-Variable Multinomial Logit Models Adjusted With Known Confounders

Independent Variable	Median of Tertile 1	2	3
mAHEI	18	25	33
Alcohol, drinks/wk	0		5
Animal protein, g/kg/d	0.27	0.47	0.81
Plant protein, g/kg/d	0.04	0.10	0.20
Total protein, g/kg/d	0.36	0.58	0.96
High-carbohydrate foods	2	9	21
Deep fried/snacks/fast food	No	Yes (46.8%)	
Fruits and fruit juices	1	9	18
Fruits	3	7	14
Vegetables	5	11	21
Leafy green vegetables	1	4	7
24-h Urinary sodium, g	3.46	4.89	6.41
24-h Urinary potassium, g	1.70	2.13	2.72



OBJECTIVE

To examine the association between **healthy diet**, alcohol, protein and sodium intake and incidence or progression of CKD among individuals with type 2 diabetes

CONCLUSIONS AND RELEVANCE

A healthy diet and moderate intake of alcohol may **decrease the incidence or progression of CKD** among individuals with type 2 diabetes. Sodium intake, within a wide range, and **normal protein intake are not associated with CKD**

Dunkler, *JAMA Intern Med* 2013

Nephrol Dial Transplant (2015) 30: iv76–iv85
doi: 10.1093/ndt/gfv086

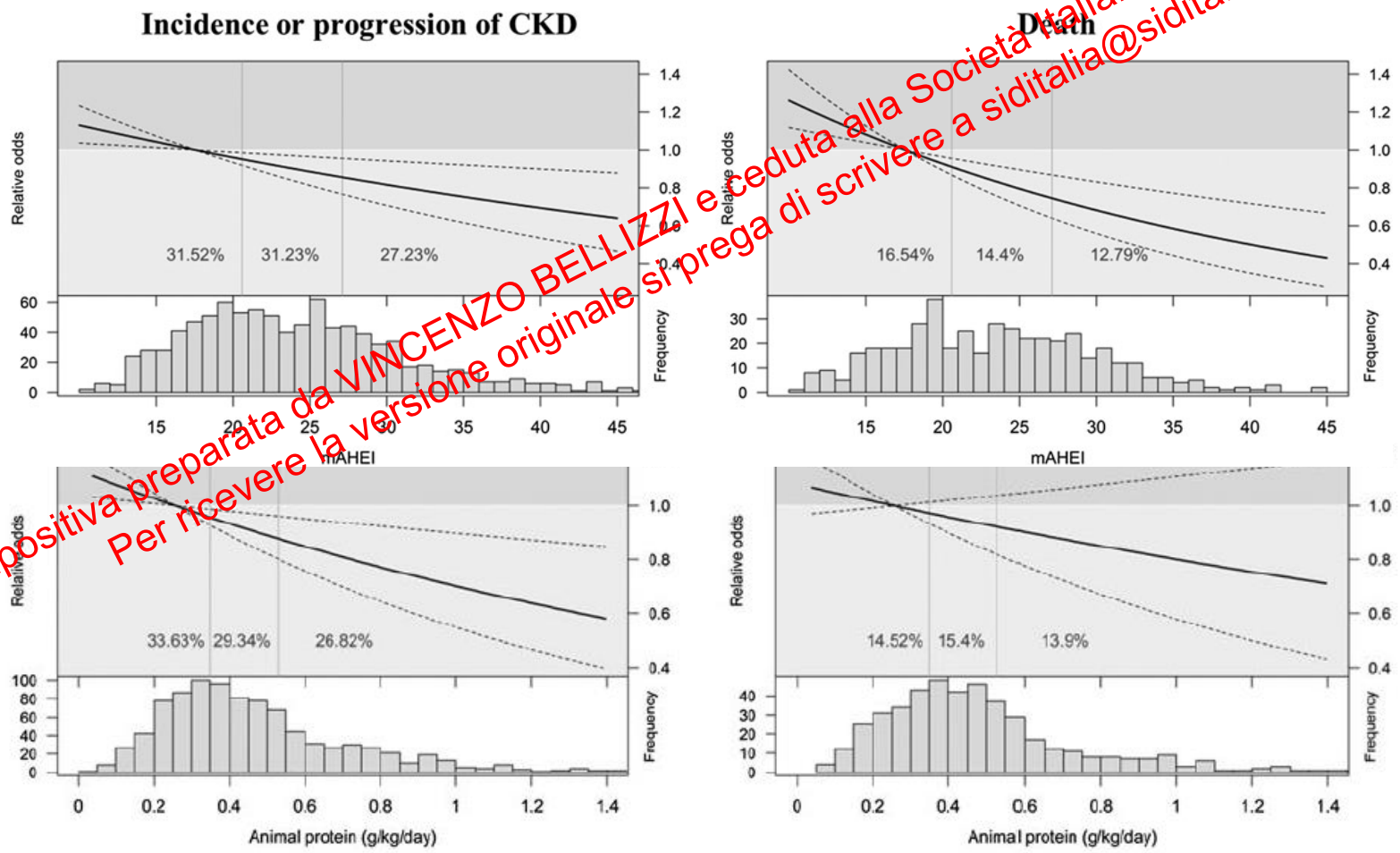
ndt Nephrology Dialysis Transplantation

Dunker, *Nephrol Dial Transpl*, 2015

Original Article

Dietary risk factors for incidence or progression of chronic kidney disease in individuals with type 2 diabetes in the European Union

- **3.088 DM, no CKD; FU 5,5 y**
- **Incidence or progression CKD and Death**



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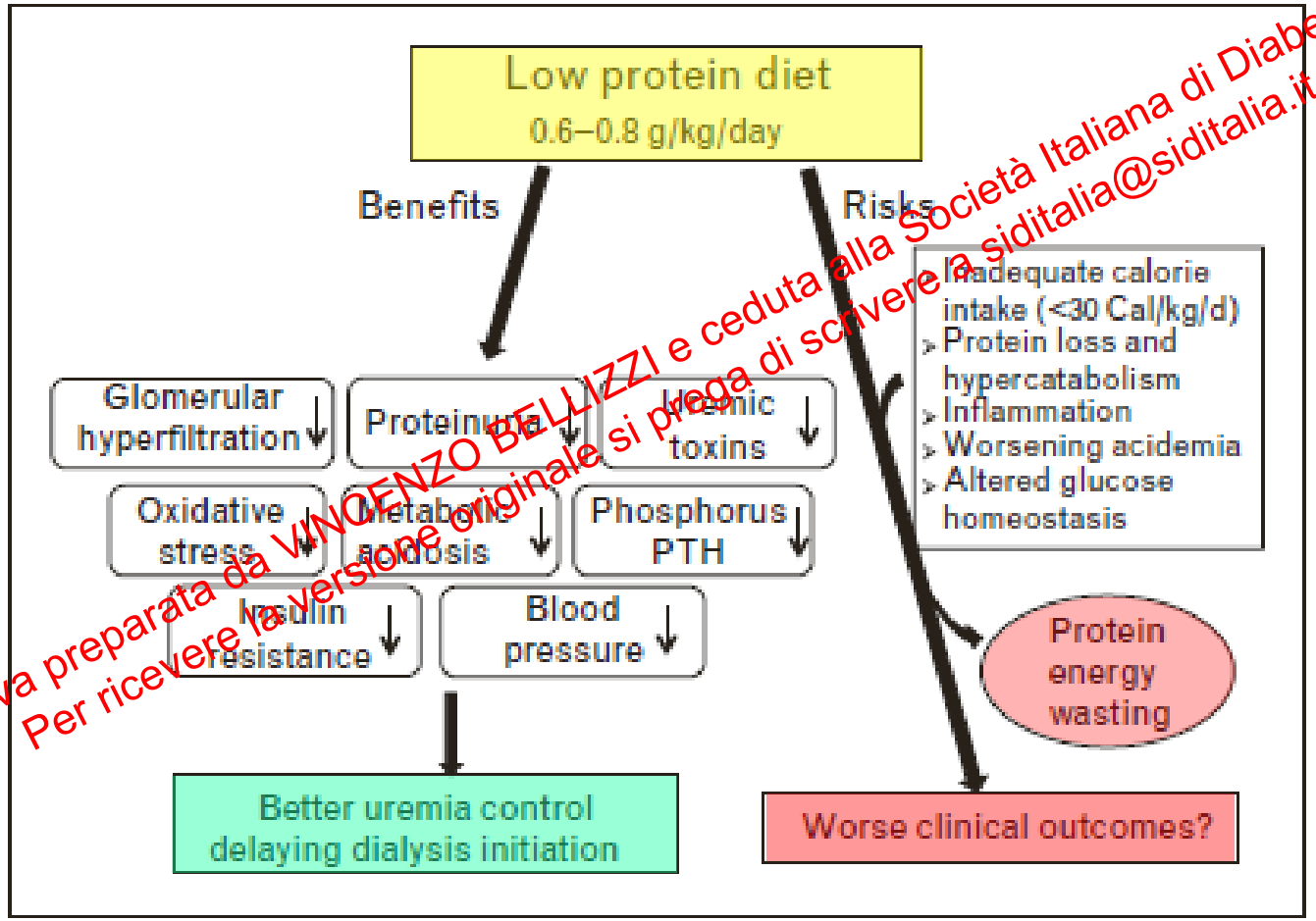
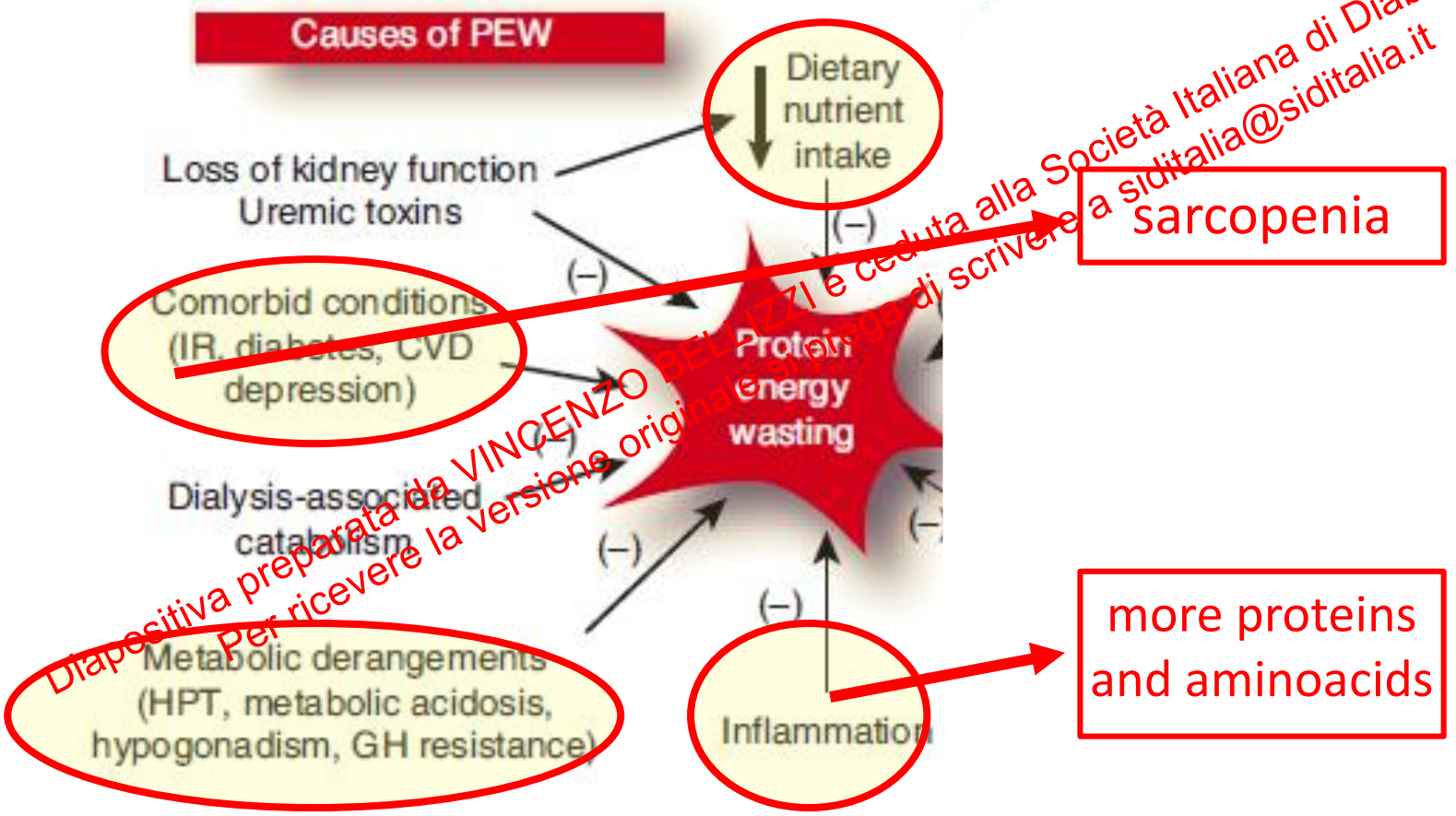
Protein Intake in CKD



Ko, Kalantar-Zadeh, *Curr Opin Clin Nutr*, 2016

Protein-Energy Wasting in ESRD



Ikizler, Kidney Int, 2013

Bellizzi *et al. BMC Nephrology*
https://doi.org/10.1186/s12882-018-0914-5

BMC Nephrology

RESEARCH ARTICLE Open Access

Safety and effectiveness of low-protein diet supplemented with ketoacids in diabetic patients with chronic kidney disease

Vincenzo Bellizzi[1*], Patrizia Calella[2], Julia Nava Hernández[3], Verónica Figueroba González[3], Silvia Moran Lira[3], Serena Torraca[1], Rocio Urbina Arronte[3], Pietro Cirillo[4], Roberto Minutolo[5] and Rafael A. Montúfar Cárdenas[3]

Study: prospective, controlled

Pts: 81 DM, 116 CON; 65 y

CKD: stage 4-5

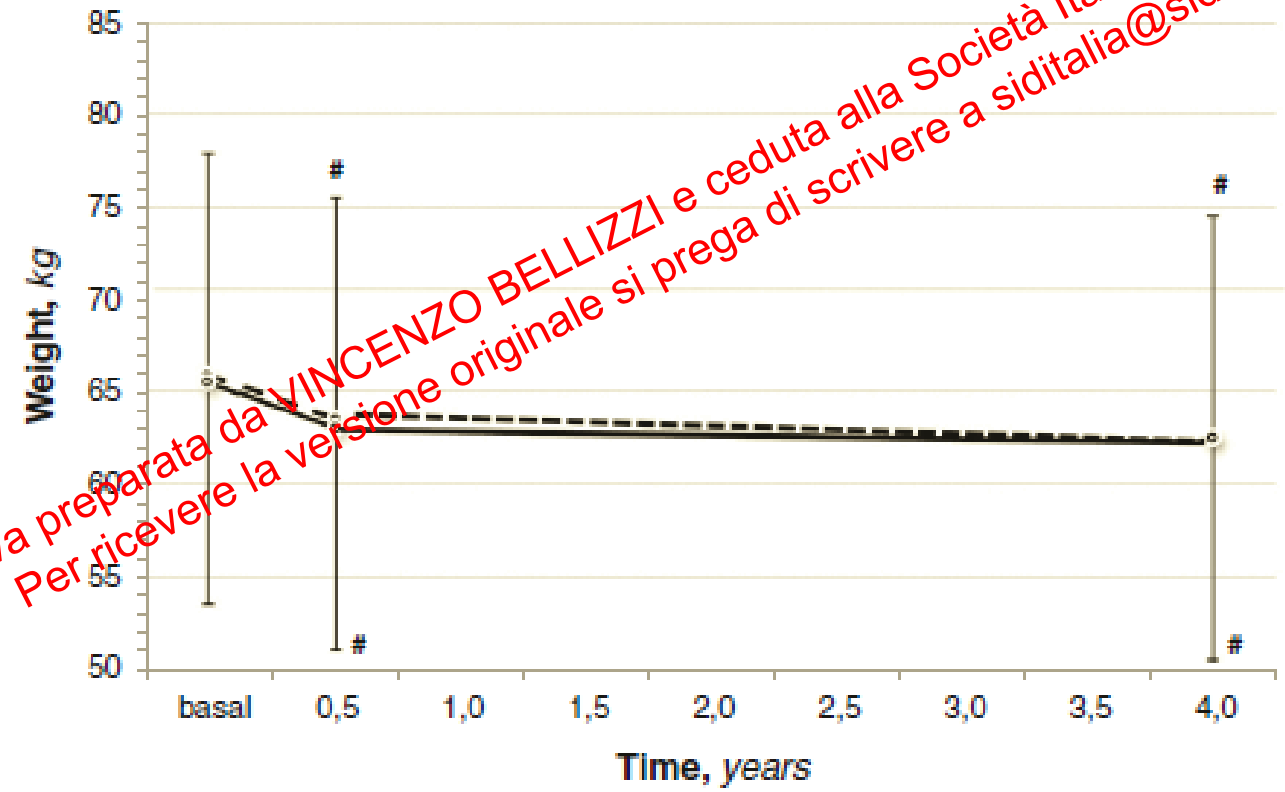
Follow-up: 6 mts to 3 years

Diet: 0.5-0.6 g/kg/d + ketoanalogs

Outcome: weight; albumin; body composition

KA-LPD & Weight in DKD

Study: prospective, controlled; **N**: 81 DM, 116 CON; **CKD**: stage 4-5; **Age**: 65 y; **Follow-up**: 6 mts to 3 years; **Diet**: 0.5-0.6 g/kg/d + ketoacids; **Outcome**: weight; albumin; body comp.



Bellizzi, *BMC Nephrology* 2016

KA-LPD & Body Comp. in DKD

Study: prospective, controlled; **N**: 81 DM, 116 CON; **CKD**: stage 4-5; **Age**: 65 y; **Follow-up**: 6 mts to 3 years; **Diet**: 0.5-0.6 g/kg/d + ketoacids; **Outcome**: weight; albumin; body comp.

Table 6 Nutritional follow-up of CKD patients on low-protein diet and ketoacids followed in the long-term (at least 2 years)

	Diabetes (*n* = 29)		non-DM (*n* = 35)	
	basal	final	basal	final
BMI, *kg/mt²*	25,5 ± 3,3	24,3 ± 2,5*	25,6 ± 3,8	24,3 ± 2,9#
Albumin, *g/dl*	3,8 ± 0,5	3,9 ± 0,4	4,0 ± 0,4	3,9 ± 0,5
Cholesterol, *mg/dl*	173 ± 34	164 ± 23*	170 ± 51	165 ± 33
Tryglicerides, *mg/dl*	168 ± 85	147 ± 52	176 ± 95	155 ± 85
W/H ratio	0,99 ± 0,08	0,90 ± 0,07	0,93 ± 0,09	0,92 ± 0,09
FM, *Kg*	17,1 ± 6,4	15,9 ± 6.0	18,4 ± 6,2	16,5 ± 4,9#
FM, *% bw*	27 ± 9	26 ± 9	28 ± 8	27 ± 8
FFM, *Kg*	47,9 ± 9,8	46,5 ± 9,7	47,2 ± 11,9	45,7 ± 10,1
FFM, *% bw*	73 ± 8	74 ± 11	72 ± 7	72 ± 7
Muscle strength, *kg*	20,8 ± 7,9*	21,2 ± 7,2*	25,0 ± 7,8	25,5 ± 7,8
Male	24,3 ± 7,3	24,1 ± 6,9°	27,8 ± 6,9	28,3 ± 7,1
Female	14,1 ± 3,3°	15,6 ± 3,4	18,2 ± 5,5	18,6 ± 4,8
Muscle strength changes, Δ	–	0,3 ± 3,2	–	0,5 ± 3,6

Bellizzi, *BMC Nephrology* 2016

KA-LPD & PE-Wasting in DKD

Study: prospective, controlled; **N**: 81 DM, 116 CON; **CKD**: stage 4-5; **Age**: 65 y; **Follow-up**: 6 mts to 3 years; **Diet**: 0.5-0.6 g/kg/d + ketoacids; **Outcome**: weight; albumin; body comp.

Table 7 Comprehensive protein-energy wasting – PEW, by mean of prevalence of major nutritional parameters during the follow-up in CKD patients on low-protein diet and ketoacids

	Groups	basal	6 months	38 months
BMI < 23 kg/m^2, %	DM	30	33	30
	non-DM	23	29	37
Albumin < 3.8 g/dl, %	DM	41	38	38
	non-DM	23	29	37
Cholesterol < 100 mg/dl, %	DM	3	0	0
	non-DM	0	0	0
Fat Mass < 10% weight, %	DM	7	7	3
	non-DM	3	3	3

Bellizzi, *BMC Nephrology* 2016

Safety of KA-LPD in DKD

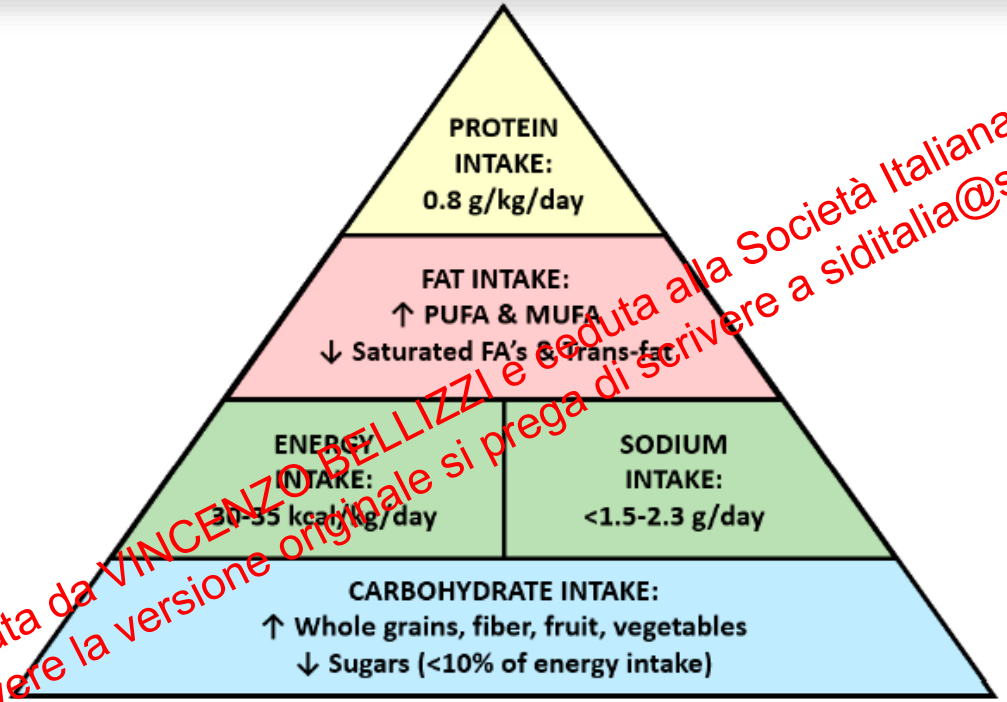
- The body weight declines after the start of KA-LPD, but remains stable in the long-term and is not associated with both **Sarcopenia** and **Dynapenia**
- A long-term KA-LPD has no impact on **PEW**
- In well-nourished, non-dialysis CKD 4-5 patients with diabetes and under regular nephrology and dietitian surveillance, a KA-LPD is **nutritionally safe**

Bellizzi, *BMC Nephrology* 2016

AGENDA:

- Low-Carbohydrate diet in DKD
- Low-Protein diet & Glucose metabolism in DKD
- LPDs / Patterns & DKD outcomes
- The dark side of LPDs & DKD
- Summary

Diabetic Kidney Disease Food Piramid



Nutrient	Guidance for Quantity	Guidance for Quality
Protein	<15% of total calories, or RDA of 0.8 g/kg BW/day for patients with DKD.	Emphasize vegan protein sources, and non-fat or low-fat dairy products are recommended.

Ko, *Nutrients* 2017; **Tuttle,** *Am J Kidney Dis, 2014* ; **KDOQI,** *Am J Kidney Dis, 2007*

Benefits and Risks of LPDs in DKD