SINut
Società Italiana di Nutraceutica

Ketogenic Diet Academy

EDIZIONE 2020

BOLOGNA
HOTEL RELAIS BELLARIA
SAVOIA HOTEL REGENCY

8/9.02.2020 | 7/8.03.2020 | 4/5.04.2020

Controindicazioni e safety della KD

Mikiko Watanabe MD PhD

Dipartimento di Medicina Sperimentale
Sezione di Fisiopatologia Medica
Endocrinologia e Scienza dell'Alimentazione

SAPIENZA
UNIVERSITÀ DI ROMA

Contraindications to VLCKD

ADI Associazione Italiana di dietetica e Nutrizione Clinica 2014	SIE Società Italiana di Endocrinologia 2019
Pregnancy and lactation History of mental disorders and behavioral problems, abuse of alcohol and other substances Hepatic or renal failure Type 1 Diabetes Porphyria, unstable angina, recent myocardial infarction	Type 1 diabetes mellitus Latent autoimmune diabetes in adults ß-cell failure in type 2 diabetes mellitus Use of sodium/glucose cotransporter 2 (SGLT2) inhibitors (risk for euglycemic diabetic ketoacidosis) Pregnancy and breastfeeding Kidney failure and moderate-to-severe chronic kidney disease Liver failure Hearth failure (NYHA III-IV) Respiratory failure Unstable angina, recent stroke or myocardial infarction (or myocardial infarction (or myocardial infarction (< 12 months) Cardiac arrhythmias Eating disorders and other severe mental illnesses, alcohol and substance abuse Active/severe infections Frail elderly patients 48 h prior to elective surgery or invasive procedures and perioperative period Rare disorders: porphyria, carnitine deficiency, carnitine palmitoyltransferase deficiency, carnitine-acylcarnitine translocase deficiency, mitochondrial fatty acid ß-oxidation disorders, pyruvate carboxylase deficiency

Mild Chronic Kidney Disease

nutrients MDPI

Article

Very Low-Calorie Ketogenic Diet: A Safe and Effective Tool for Weight Loss in Patients With Obesity and Mild Kidney Failure

Adriano Bruci [1], Dario Tuccinardi [2], Rossella Tozzi [3], Angela Balena [3], Silvia Santucci [1], Riccardo Frontani [1], Stefania Mariani [3], Sabrina Basciani [3], Giovanni Spera [3], Lucio Gnessi [3], Carla Lubrano [3,†] and Mikiko Watanabe [3,*,†]

	NKF (e GFR ≥ 90)			MCKD (eGFR 60–89)			
Variable	**Baseline**	**End of diet**	***p***	**Baseline**	**End of diet**	***p***	***P* ***
N	54		NA	38		NA	
Female gender *n* (%)	43 (80)		NA	22 (68)		NA	0.22
HTN treatment *n* (%)	20 (43.5)		NA	19 (44.2)		NA	
Diet length (weeks)	15.33 ± 7.98		NA	15.33 ± 7.98		NA	0.645
Age (years)	47.96 ± 12.97		NA	55.97 ± 9.30		NA	**<0.0001**
Weight (Kg)	94.21 ± 18.60	77.94 ± 15.67	<0.0001	89.92 ± 17.84	75.28 ± 13.95	<0.0001	0.510
BMI (kg/m2)	34.46 ± 5.69	28.67 ± 5.04	<0.0001	33.01 ± 6.01	27.56 ± 4.68	<0.0001	0.334
Fat Mass (Kg)	37.51 ± 9.57	25.93 ± 9.45	<0.0001	33.05 ± 9.96	22.31 ± 7.99	<0.0001	0.742
Fat Free Mass (Kg)	56.69 ± 14.10	52.01 ± 11.10	<0.0001	56.88 ± 12.55	52.97 ± 10.72	<0.0001	0.521
Skeletal Muscle Mass (Kg)	37.08 ± 10.05	33.58 ± 8.14	<0.0001	37.54 ± 9.00	34.40 ± 8.13	<0.0001	0.542
TBW (Lt)	42.04 ± 10.00	38.60 ± 7.86	<0.0001	42.98 ± 9.76	40.03 ± 8.47	<0.0001	0.494
ECW (Lt)	19.53 ± 4.49	18.42 ± 4.04	<0.0001	19.74 ± 4.50	18.78 ± 3.90	<0.0001	0.238
ICW (Lt)	22.51 ± 5.91	20.37 ± 4.78	<0.0001	23.20 ± 5.67	21.23 ± 5.19	<0.0001	0.561
SBP (mmHg)	136.6 ± 14.5	130.9 ± 10.8	<0.0001	137.6 ± 12.2	132.2 ± 9.2	<0.0001	0.998
DBP (mmHg)	82.6 ± 7.2	77.3 ± 5.2	<0.0001	81.4 ± 6.7	77.4 ± 4.6	<0.0001	0.841
Creatinine (mg/dL)	0.70 ± 0.11	0.71 ± 0.12	0.43	0.93 ± 0.16	0.88 ± 0.17	0.002	0.414
eGFR (ml/min/1.73m²)	107.22 ± 11.20	105.28 ± 14.32	0.263	76.32 ± 10.44	82.21 ± 15.14	0.002	0.901
BUN (g/L)	0.34 ± 0.08	0.38 ± 0.07	<0.0001	0.39 ± 0.11	0.41 ± 0.11	0.052	0.822

kidney function. Upon stratification based on kidney function, no differences in the efficacy and safety outcomes were found. Interestingly, 27.7% of patients with mild renal failure reported normalization of glomerular filtrate after dietary intervention. We conclude that, when conducted

Severe Chronic Kidney Disease

Table 2. Anthropometric and body composition measurements

Measurement	Week 0	Week 12	*P*
Anthropometrics			
Weight (kg)	118.5 (94.8, 140.0)	104.3 (85.0, 115.8)	0.03
Height (m)	1.76 (1.68, 1.83)	—	—
Body mass index (kg/m^2)	38.6 (32.8, 43.7)	34.0 (29.6, 37)	0.03

Parameter	Week 0	Week 12	*P*
Glomerular filtration markers			
Serum creatinine (mg/dl)	3.54 (1.97, 3.85)	3.13 (1.63, 3.63)	<0.05
Cystatin C (mg/L)	2.79 (1.94, 3.34)	2.46 (1.97, 2.97)	<0.05
Estimated GFR (ml/min per 1.73 m^2)[a]	21 (17, 35)	22 (19, 38)	<0.05
Urinary protein excretion			
Albuminuria (mg/d)	2124 (52, 3496)	1366 (32, 7739)	0.08
Proteinuria (mg/d)	2515 (125, 4761)	2039 (69, 3317)	0.12

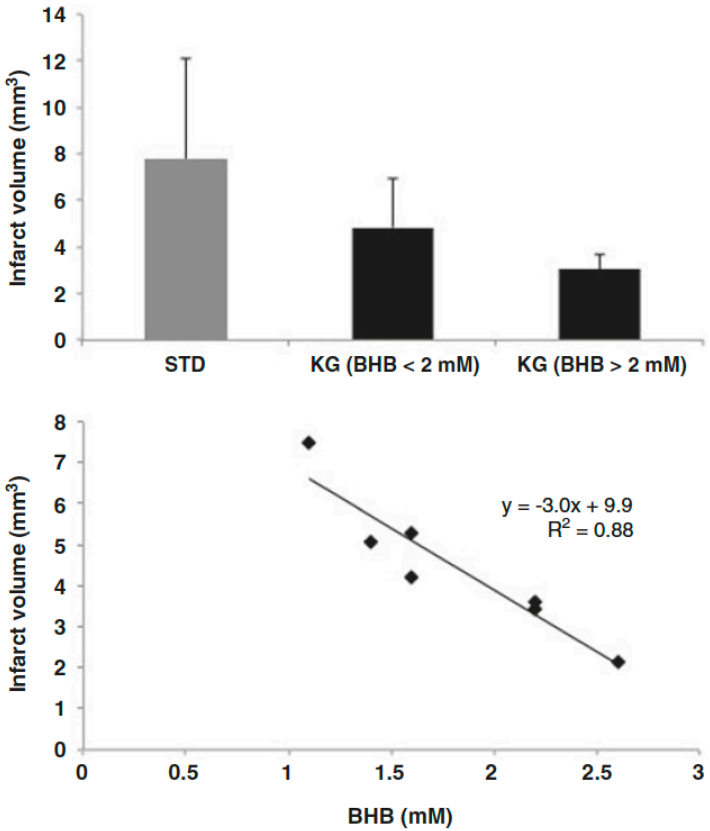
VLCKDs improve renal function in advanced diabetic nephropathy

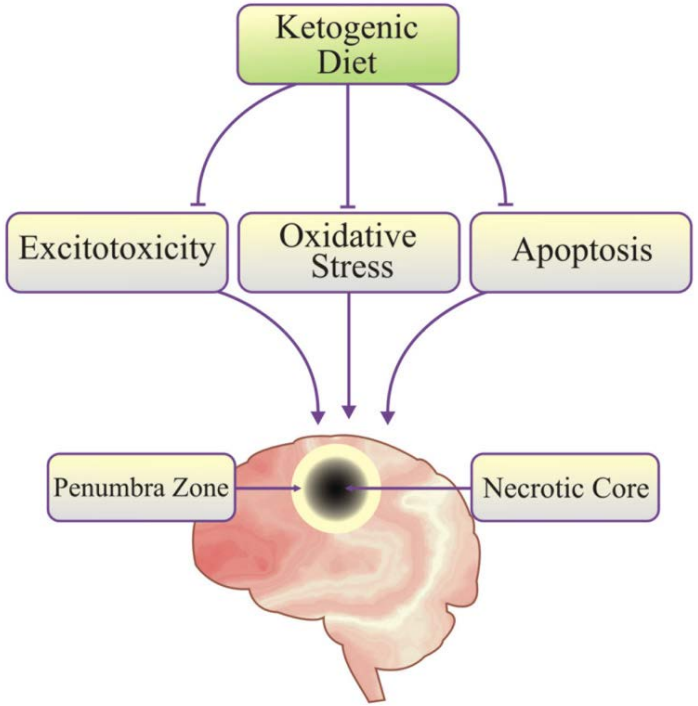
BUT
6 patients only

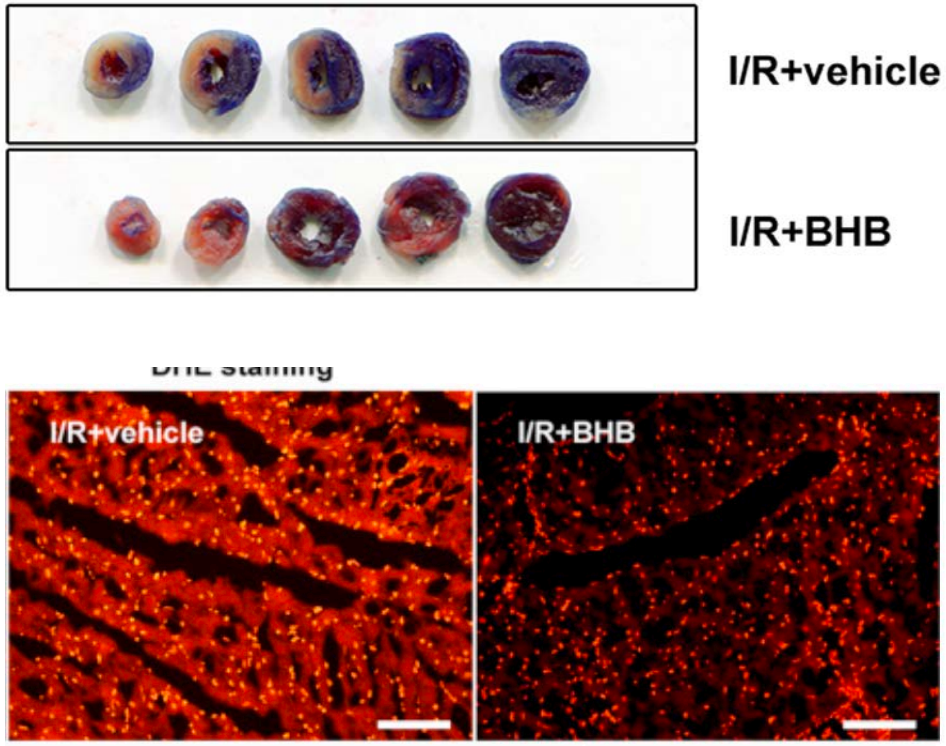
Friedman AN Clin J Am Soc Nephrol. 2013 Nov;8(11):1892-8.

Brain or heart ischemia

Pre clinical evidence suggests a protective role in recent stroke or heart ischemia







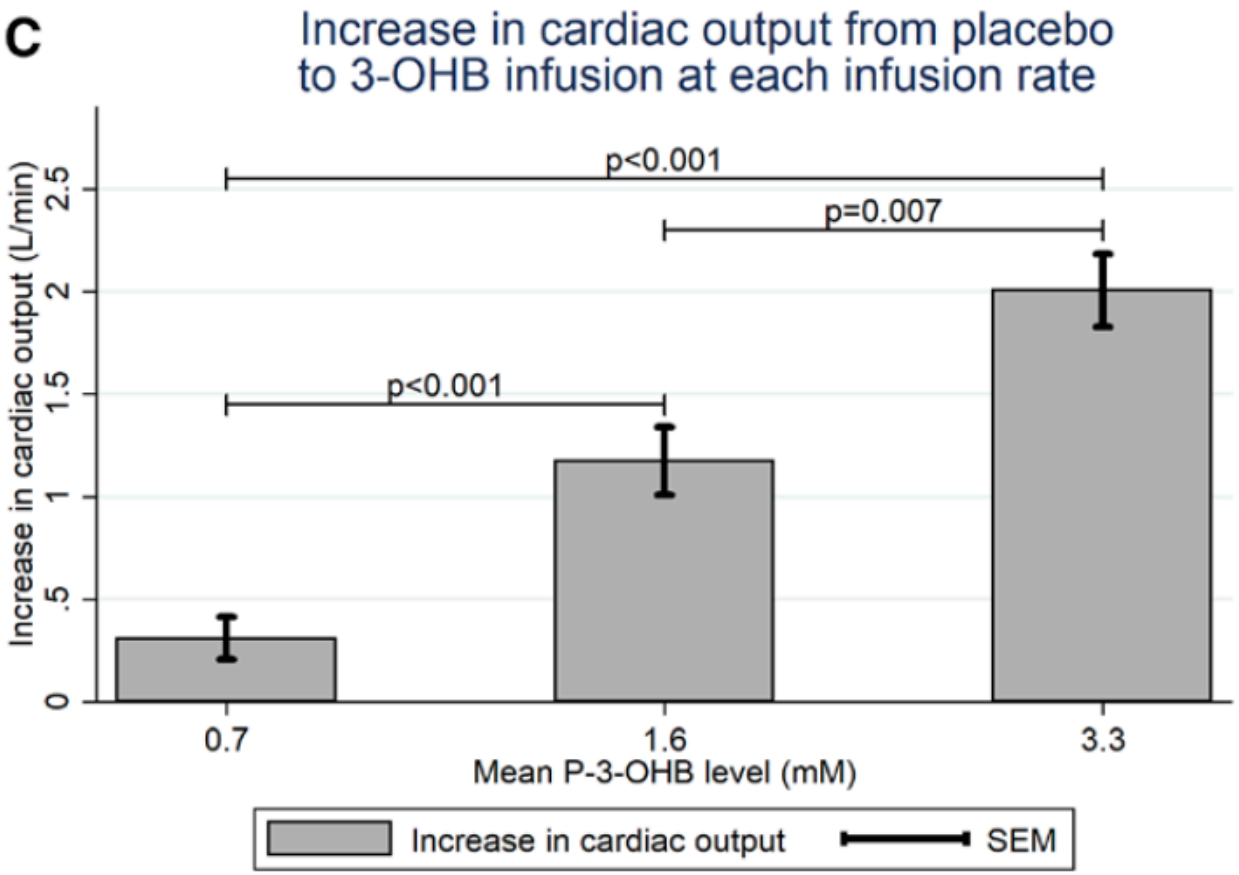
Shaafi S et al. Ketogenic Diet Provides Neuroprotective Effects against Ischemic Stroke Neuronal Damages. Adv Pharm Bull. 2014 Dec;4(Suppl 2):479-81

Yang Q et al. Ischemic preconditioning with a ketogenic diet improves brain ischemic tolerance through increased extracellular adenosine levels and hypoxia-inducible factors. Brain Res. 2017 Jul 15;1667:11-18

Yu Y et al. Treatment with D-β-hydroxybutyrate protects heart from ischemia/reperfusion injury in mice. Eur J Pharmacol. 2018 Jun 15;829:121-128

Heart failure (NYHA III-IV)

The failing heart shifts to ketone bodies as a significant fuel source for oxidative ATP production



NYHA II-III

Aubert G et al. The Failing Heart Relies on Ketone Bodies as a Fuel. Circulation. 2016 Feb 23;133(8):698-705.
Nielsen et al. Cardiovascular Effects of Treatment With the Ketone Body 3-Hydroxybutyrate in Chronic Heart Failure Patients. Circulation. 2019;139:2129–2141

Respiratory failure

Lean COPD patients (CHO 75 g/d)

TABLE VI.

MEASUREMENT OF LUNG FUNCTION*

Groups	n	RQ	V_{CO_2} (mL)	V_{O_2} (mL)	V_E (L/min)	FEV_1 (%predicted)	Airway resistance (%predicted)
Baseline							
Experimental	30	0.92 ± 0.07	308 ± 36	358 ± 46	12.5 ± 2.8	36 ± 12	265 ± 64
Control	30	0.91 ± 0.07	295 ± 37	347 ± 59	11.6 ± 2.3	39 ± 11	274 ± 76
3 wk							
Experimental	30	0.83 ± 0.06†	269 ± 24†	324 ± 37†	10.2 ± 1.9†	48 ± 9†	231 ± 38
Control	30	0.90 ± 0.05	301 ± 41	353 ± 42	12.1 ± 2.4	42 ± 11	238 ± 43

* Mean ± standard deviation.

† $P < 0.05$.

FEV_1, forced expiratory volume in 1s; RQ, respiratory quotient; V_E, minute ventilation; V_{CO_2}, carbon dioxide production per unit time; V_{O_2}, oxygen consumption per unit time.

Cai B et al. Effect of supplementing a high-fat, low-carbohydrate enteral formula in COPD patients. Nutrition. 2003 Mar;19(3):229-32

Severe infections

- Veterinary Medicine: peri-partum ketosis can impair leukocyte localization to infections, increase risk of mastitis, and impair leukocyte function.[1,2]
- Clinical Evidence: few small trials 1-12 w long with inflammation and immune cell counts or function outcomes with inconstant results.[3-5]

SCIENCE IMMUNOLOGY | REPORT

INFECTIOUS DISEASE

Ketogenic diet activates protective γδ T cell responses against influenza virus infection

Emily L. Goldberg[1,2], Ryan D. Molony[2,3], Eriko Kudo[2], Sviatoslav Sidorov[1], Yong Kong[4], Vishwa Deep Dixit[1,2,5]*, Akiko Iwasaki[2,6,7]*

In lung - preclinical data

1 Grinberg N, et al. Infect Immun 2008;76(6):2802–7.
2 Zarrin M et al. J Dairy Sci 2014;97(6):3531–41.
3 Schmidt M et l. Nutr Metab (Lond) 2011;8 (1):54.
4 Urbain P et al. Nutr Metab (Lond) 2017;14:309. eCollection 2017.
5 Kossoff EH et al. Epilepsia 2006;47(2):421–4.

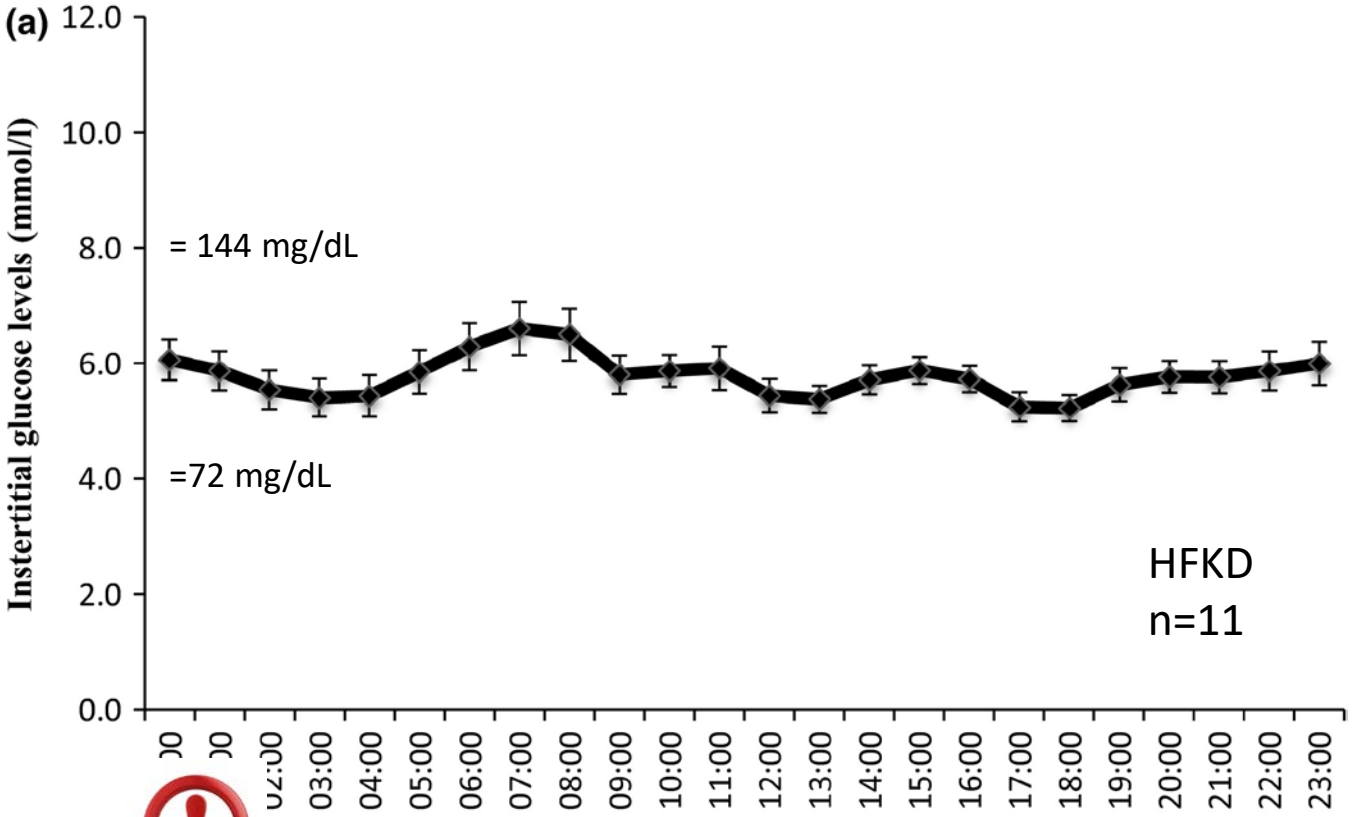
Frail elderly patients

- Possible Hypotension/Dehydration→**Increased risk of falls**
- **Supplements and correct understanding of the diet** are crucial in VLCKDs→if impaired cognitive ability this can be a safety issue
- **Wound healing** may or may not be impaired→this aspect may be important if patient has limited mobility and is therefore at risk of decubitus [1,2]

Chakravartty S et al. Preoperative liver shrinking diet for bariatric surgery may impact wound healing: a randomized controlled trial. Surg Obes Relat Dis. 2019 Jan;15(1):117-125.
Kesl et al. Sustaining dietary ketosis to improve blood flow and wound healing in young and aged Fisher rats The FASEB Journal 2014 28:1_supplement

Insulin dependent Diabetes

Leow ZZX et al. **The glycaemic benefits of a very-low-carbohydrate ketogenic diet in adults with Type 1 diabetes mellitus may be opposed by increased hypoglycaemia risk and dyslipidaemia**. Diabet Med. 2018 May 8



Hypoglycemia episodes/d 0.9 (0.0–2.0)

Case reports

Nolan J, Rush A, Kaye J. **Glycaemic stability of a cyclist with Type 1 diabetes: 4011 km in 20 days on a ketogenic diet.** Diabet Med. 2019 Nov;36(11):1503-1507

Dressler A et al. **Type 1 diabetes and epilepsy: efficacy and safety of the ketogenic diet**. Epilepsia. 2010 Jun;51(6):1086-9

excellent glycemic control without severe side effects (children with T1DM and epilepsy, one athlete with T1DM undergoing strenuous exercise

Concomitant use of SGLT2 Inhibitors

Reported Cases of **Euglycemic Diabetic Ketoacidosis**

- Yamamoto M et al. **Risk of Euglycemic Diabetic Ketoacidosis Due to Low-carbohydrate Diet While Taking Empagliflozin: a Case Report.** Yakugaku Zasshi. 2019;139(11):1479-1483.
- Tougaard et al. **Very low carbohydrate diet and SGLT-2-inhibitor: double jeopardy in relation to ketoacidosis**. BMJ Case Rep. 2019 Apr 5;12(4). pii: e227516.
- Bonikowska K et al. **Life-threatening ketoacidosis in patients with type 2 diabetes on LCHF diet**. Lakartidningen. 2018 Jun 29;115. pii: E4AD

Liver Failure

European Association for the Study of the Liver Guidelines 2018

- Most of what you have heard/read on the relationship between food and the liver has limited scientific evidence to support it. Generally, healthy eating of a variety of foods is advisable for all patients.
- Virtually no food other than alcohol actually damages the liver and/or is genuinely contraindicated in patients with chronic liver disease.
- In most patients with chronic liver disease, eating an adequate number of calories and protein is much more important than avoiding specific types of food, so it is important that you have a good, varied diet that you enjoy.
- You should try to split your food intake into 3 main meals (breakfast, lunch and dinner) and 3 snacks (mid-morning, mid-afternoon, late evening). The late-evening snack is the most important, as it covers the long interval between dinner and breakfast.
- You should try to eat as many fruit and vegetables as you can. If you feel that this makes you feel bloated, and that it makes you eat less, please report to your doctor or dietician.
- You should try not to add too much salt to your food. It may take some time to adjust, but it usually gets easier with time. However, if you keep feeling that this makes your food unpleasant to eat, and that it makes you eat less, please report to your doctor or dietician.
- A limited proportion of patents with liver disease have a complication called hepatic encephalopathy, which may make them tolerate animal protein (meat) less well than vegetable protein (beans, peas etc.) and dairy proteins. Before you make any changes to your protein intake, you should always ask your doctor or dietician. Please do not reduce your total protein intake as it is not advisable in cirrhosis.
- Some patients with liver disease have other diseases, for example diabetes or overweight/obesity, which require dietary adjustments. Please remember to tell your doctor about all your illnesses and about any dietary advice you have already received from other doctors, nurses or dieticians.

OPEN

Citation: Nutrition & Diabetes (2013) **3**, e95; doi:10.1038/nutd.2013.36
© 2013 Macmillan Publishers Limited All rights reserved 2044-4052/13
www.nature.com/nutd

SHORT COMMUNICATION

Very low calorie ketogenic weight reduction diet in patients with cirrhosis: a case series

JC Temmerman[1,3] and AN Friedman[2]

with a stable MELD score. VLCDs were well tolerated by both patients without adverse effects. In conclusion, under close medical supervision VLCDs in patients with ESLD can be safe and effective in reducing weight, facilitating liver transplantation listing, and possibly improving liver damage.

Severe mental illness and substance abuse

- Severe mental illness may increase the risk of side effects due to reduced compliance (water, supplements)
- Substance and alcohol abuse may induce acidosis under certain circumstances→+ KD→ increased risk
- Carbohydrate counting typical of KDs may trigger eating disorders in predisposed subjects

BUT

- KD was recently proposed as a possible treatment for anorexia to avoid starvation[1]

1. Scolnick B. Ketogenic diet and anorexia nervosa. Med Hypotheses. 2017 Nov;109:150-152

48 h prior to elective surgery or invasive procedures and perioperative period

- Most evidence on diabetic patients on SGLT2-Inhibitors[1]
- Pathophysiology: acute stress may require large glucose amounts→ketosis
- Perioperative ketosis approximately 5% not affect safety outcomes, not inducing acidosis

Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland
Anaesthesia, 2009, **64**, pages 903–907 doi:10.1111/j.1365-2044.2009.05940.x

CASE REPORT

Recurrent torsades de pointes in association with a very low calorie diet

E-J. T. Crawford[1] and D. Cochran[2]

1 Specialist Trainee, 2 Consultant, Department of Anaesthesia, Royal Bolton Hospital, Bolton, UK

1 Bardia A et al. Sodium-glucose cotransporter-2 inhibitors: an overview and perioperative implications. Curr Opin Anaesthesiol. 2019 Feb;32(1):80-85

2 Ohkawa H, Iwakawa T, Ohtomo N, Kitayama M, Miyahara A, Ishihara H, Matsuki A. [Clinical study on intraoperative hyperketonemia in non-diabetic surgical patients under general anesthesia]. Masui. 1993 Dec;42(12):1803-7.

Breastfeeding

Table 1 Review of reported cases of lactation ketoacidosis

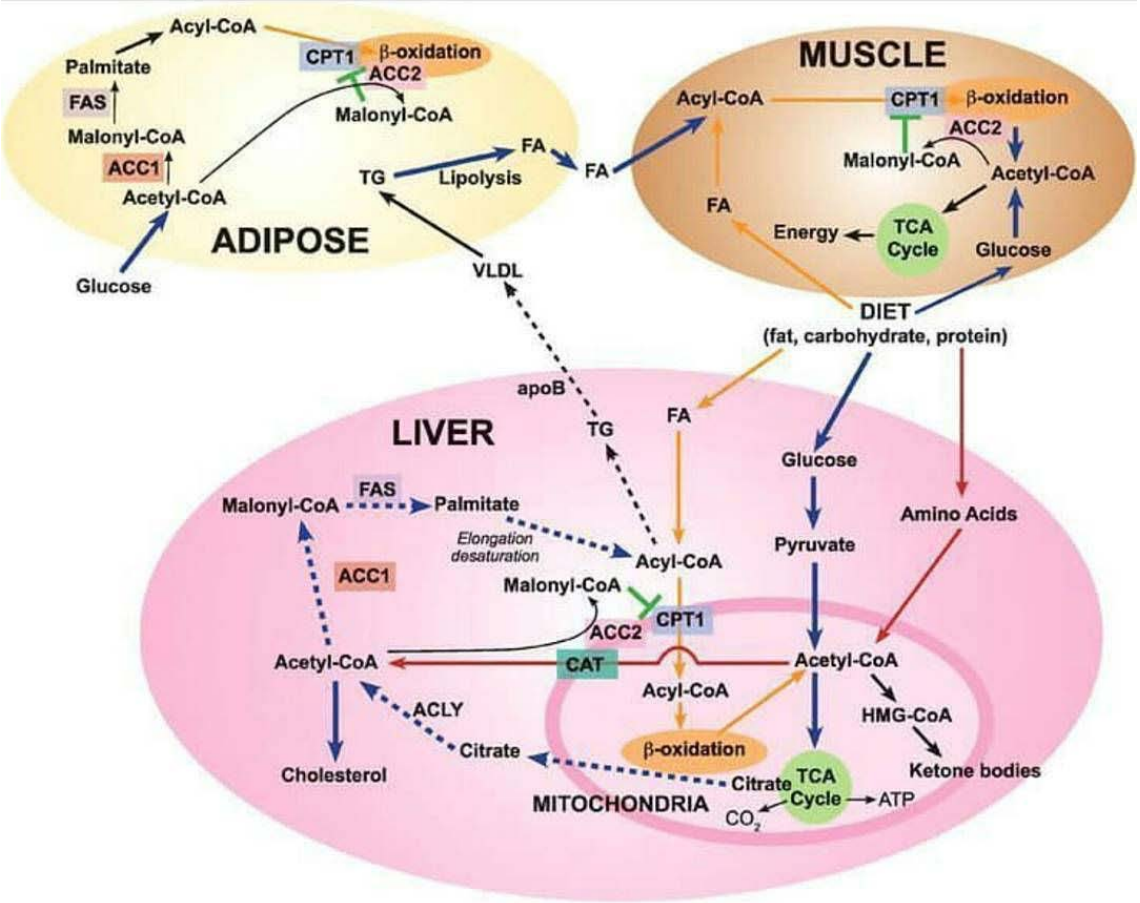
First author, year	Country	Age of mother (years)	Age of child (weeks)	pH	P-glucose (mmol/L)	Ketones	Precipitating factors
Chernow 1982[6] (3)	USA	19	30.4	7.25	11	Urine ketones +	Weight reduction diet
Altus 1983[11] (9)	USA	30	14	7.07	4.2	Urine ketones +	High protein, low carbohydrate diet
Heffner 2008[12] (10)	USA	35	12	7.24	3.8	Serum ketones +	Altered diet
Sandhu 2009[13] (11)	USA	36	5	6.9	7.4	Urine ketones +	High-protein carbohydrate-free meals
Szulewski 2012[9] (6)	Canada	35	3	7.15	6.3	Serum ketones +	Preoperative prolonged fasting
Von Geijer 2015[16] (14)	Sweden	32	43.5	7.2	3.8	Serum ketones +	Low carbohydrate, high-fat diet
Wuopio 2015[15] (13)	Sweden	21	6	6.92	4.4	Serum ketones +	Low carbohydrate diet
Hudak 2015[14] (12)	Germany	32	3	6.99	3.8	Urine ketones +	Reduced oral intake, nausea and vomiting
Greaney 2016[17] (15)	Ireland	36	9	6.88	5.7	Serum ketones +	High protein and low carbohydrate Skipped meals
Gleeson 2016[2] (8)	New Zealand	31	43.5	7.26	3.8	Serum ketones +	None identified
Sloan 2017[8] (5)	UK	27	8	7.02	3.6	Serum ketones +	Low carbohydrate diet
Al Alawi (2018)	Australia	35	21.7	7.13	2.9	Serum ketones +	Altered diet, skipping meals and exercise
		32 (IQR=6.5)	10.5 (IQR=23)	7.1 (0.27)	4.0 (IQR=2.2)	—	—

Al Alawi AM, Falhammar H. *BMJ Case Rep* 2018. doi:10.1136/bcr-2017-223494

of continuous fasting.[3 4] Lactation ketoacidosis or 'bovine ketoacidosis' is a well-described condition in cows which occurs in early lactation when high demand of glucose creates negative energy balance that leads to fat mobilisation, ketosis and ketoacidosis.[5] Lactation ketoacidosis is a rare phenomenon in humans with the first case reported in 1982.[6] We

Rare Genetic Conditions

- **Porphyria:** the lack of carbohydrates in the KD can exacerbate acute intermittent porphyria
- **Carnitine deficiency, carnitine palmitoyltransferase deficiency, carnitine-acylcarnitine translocase deficiency, mitochondrial fatty acid β-oxidation disorders, pyruvate carboxylase deficiency** → defective ketogenesis→ coma, death



Adverse events: true or false? And if true, what to do?

Short Term

- Hypotension
- GI side effects
- Electrolyte Imbalance
- Hyperuricemia
- Metabolic acidosis

Medium-long Term

- Bone damage
- Hair loss
- Urolithiasis
- Gallstones
- Muscle mass loss
- Dyslipidemia
- NAFLD
- Kidney Damage

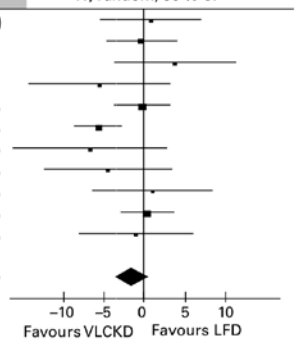
Short term

Hypotension

- Natriuresis occurs due to ketone bodies urinary excretion
- It is transient and ends typically in the first week of dieting
- This can also be an efficacy outcome in hypertensive patients[1]

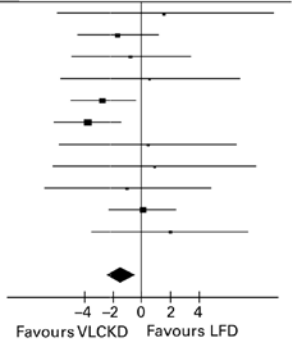
(a) SBP (mmHg) Study	VLCKD Mean, SD and total			LFD Mean, SD and total			Weight (%)	Mean difference (95 % CI)
Brinkworth *et al.* [28]	−13·8	14·36	33	−14·6	12	36	7·5	0·80 (−5·47, 7·07)
Dansinger *et al.* [50]	0·2	12	40	0·5	7·7	40	12·0	−0·30 (−4·72, 4·12)
Davis *et al.* [51]	0·2	15·6	55	−1·8	22·6	50	5·6	3·80 (−3·70, 11·30)
Foster *et al.* [53]	−1·9	15	33	3·6	20	30	4·3	−5·50 (−14·30 3·30)
Foster *et al.* [27]	−2·8	15·17	153	−2·59	15·67	154	15·8	−0·21 (−3·66, 3·24)
Gardner *et al.* [30]	−7·6	11	77	−1·9	7·7	76	17·8	−5·70 (−8·71 −2·69)
Iqbal *et al.* [29]	−11·2	30·28	67	−4·5	26·96	71	3·7	−6·70 (−16·29 −2·89)
Lim *et al.* [54]	−10·6	10·6	17	−6	13·3	18	5·1	−4·60 (−12·55 3·35)
McAuley *et al.* [55]	−5	15·9	24	−6	9·89	24	5·6	1·00 (−6·49, 8·49)
Shai *et al.* [49]	−3·9	12·8	109	−4·3	11·8	104	16·4	1·40 (−2·90, 3·70)
Stern *et al.* [26]	1	19	44	2	15	43	6·0	−1·00 (−8·18, 6·18)
Total (95 % CI)			652			646	100·0%	−1·47 (−3·44, 0·50)

Heterogeneity: τ^2= 3·33; χ^2 = 14·94, df = 10 (P=0·13); I^2 = 33 %
Test for overall effect: Z=1·46 (P=0·14)



(b) DBP (mmHg) Study	VLCKD Mean, SD and total			LFD Mean, SD and total			Weight (%)	Mean difference (95 % CI)
Brinkworth *et al.* [28]	−6·3	19·9	33	−7·9	9·6	36	2·0	1·60 (−5·88, 9·08)
Dansinger *et al.* [50]	−1·4	7·5	40	0·2	4·6	40	14·3	1·60 (−5·33, 1·13)
Davis *et al.* [51]	−2·9	9·4	55	−2·2	11·6	50	6·7	1·70 (−5·76, 3·36)
Foster *et al.* [53]	−4·6	12	33	−5·2	13	30	2·9	1·60 (−5·60, 6·80)
Foster *et al.* [27]	−3·19	9·24	153	−0·5	10·32	154	21·6	−2· 69 (−4·88, −0·50)
Gardner *et al.* [30]	−4·4	8·4	77	−0·7	6	76	19·6	−3·70(−6·01, −1·39)
Iqbal *et al.* [29]	−3·8	19·64	67	−4·3	16·85	71	3·0	0·50 (−5·62, 6 62)
Lim *et al.* [54]	−6·6	12·1	17	−7·5	8·7	18	2·3	0·90 (−6·12, 7 92)
McAuley *et al.* [55]	−4	9·81	24	−3	10·43	24	3·4	−1·00 (−6·73, 4·73)
Shai *et al.* [49]	−0·8	8·7	109	−0·9	8·1	104	20·4	0·10 (−2·16, 2·36)
Stern *et al.* [26]	3	15	44	1	10	43	3·9	2·00 (−3·35, 7·35)
Total (95 % CI)			652			646	100·0	−1·43 (−2·49, −0·37)

Heterogeneity: τ^2= 0·11; χ^2 = 10·33, df = 10 (P=0·41); I^2=3 %
Test for overall effect: Z=2·64 (P=0·008)



Educate the patient to drink at least 2 l water daily
Encourage tea and coffee consumption
If on HTN medication: stop diuretics, adjust other medication according to BP

1. Bueno et al. Br J Nutr 2013 (110)1178-1187

Gastrointestinal side effects

HFKD

- High-fat content
  - → increased gastric emptying time →Gastroesophageal reflux, nausea and vomit
  - →defective absorption and intolerance of fat →Diarrhea

VLCKD

- Low fat content, possible dehydration
  - Reduced stool lubrication and hydration →Constipation
- High fiber content
  - →dysbiosis→occasional diarrhea/bloating

Encourage water intake, adjust fat and fiber consumption
Probiotics
Inform the patient that symptoms are usually transient

Electrolyte Imbalance

Hypokalemia → Prolonged QT interval→Torsade de pointe→sudden cardiac death

Hyponatremia → Lethargy →Seizures→coma→death

Reviews in Endocrine and Metabolic Disorders
https://doi.org/10.1007/s11154-019-09514-y

Efficacy and safety of very low calorie ketogenic diet (VLCKD) in patients with overweight and obesity: A systematic review and meta-analysis

Marco Castellana[1] · Eleonora Conte[1] · Angelo Cignarelli[1] · Sebastio Perrini[1] · Andrea Giustina[2]
Luca Giovanella[3,4] · Francesco Giorgino[1] · Pierpaolo Trimboli[3]

Parameter	Number of patients (number of studies)	Estimate	I^2	p
Serum sodium (mEq/l)	269 (4)	1.6 (0.6 to 2.5)	73%	<0.001
Serum potassium (mEq/l)	269 (4)	0.0 (−0.2 to 0.2)	89%	0.70

Adequate electrolyte supplementation, screen patient for preexistent EKG abnormality

Torsade de Pointe

- VLCDs were very popular in the 1970s, but they declined when an increased risk of sudden death became apparent (60 ppl died)[1]
- They were not supplemented, protein were very low quality
- One case report with current VLCD and adequate supplementation (upon anesthesia induction)

Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland

Anaesthesia, 2009, **64**, pages 903–907 doi:10.1111/j.1365-2044.2009.05940.x

CASE REPORT

Recurrent torsades de pointes in association with a very low calorie diet

E-J. T. Crawford[1] and D. Cochran[2]

1 Specialist Trainee, 2 Consultant, Department of Anaesthesia, Royal Bolton Hospital, Bolton, UK

- Adequate supplementation
- Follow the 48h rule

Tsai AG, Wadden TA. The evolution of very-low-calorie diets: an update and meta-analysis. Obesity (Silver Spring). 2006 Aug;14(8):1283-93

Hyperuricemia

FALSE

Reviews in Endocrine and Metabolic Disorders
https://doi.org/10.1007/s11154-019-09514-y

Efficacy and safety of very low calorie ketogenic diet (VLCKD) in patients with overweight and obesity: A systematic review and meta-analysis

Marco Castellana[1] · Eleonora Conte[1] · Angelo Cignarelli[1] · Sebastio Perrini[1] · Andrea Giustina[2]
Luca Giovanella[3,4] · Francesco Giorgino[1] · Pierpaolo Trimboli[3]

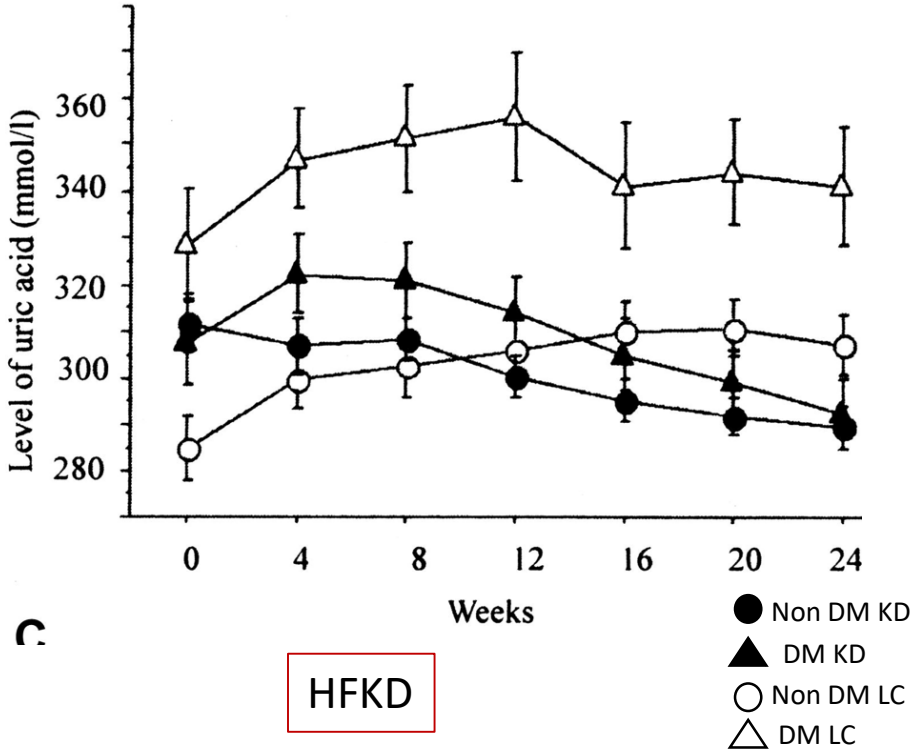
Parameter	Number of patients (number of studies)	Estimate	I^2	p
Fat mass (kg)	189 (7)	−8.5 (−11.1 to −6.0)	80%	<0.001
Lean mass (kg)	108 (6)	−4.4 (−5.3 to −3.6)	0%	<0.001
HbA1c (%)	185 (4)	−0.7 (−1.3 to −0.1)	87%	0.03
Total cholesterol (mg/dl)	485 (9)	−27.9 (−46.9 to −9.1)	96%	0.004
LDL cholesterol (mg/dl)	419 (8)	−6.4 (−14.8 to 1.9)	79%	0.13
HDL cholesterol (mg/dl)	419 (8)	−1.8 (−4.9 to −1.3)	66%	0.25
Triglycerides (mg/dl)	485 (9)	−29.8 (−40.1 to −19.6)	57%	<0.001
AST (U/l)	345 (6)	−7.2 (−12.1 to −2.3)	91%	0.004
ALT (U/l)	345 (6)	−7.7 (−13.2 to −2.2)	73%	0.006
GGT (U/l)	202 (4)	−8.0 (−11.3 to −4.7)	0%	<0.001
SBP (mmHg)	199 (4)	−8.5 (−11.4 to −5.6)	30%	<0.001
DBP (mmHg)	199 (4)	−7.2 (−8.9 to −5.5)	0%	<0.001
Serum creatinine (mg/dl)	293 (5)	0.0 (0.0 to 0.0)	0%	0.60
Serum uric acid (mg/dl)	293 (5)	−0.3 (−1.1 to 0.5)	92%	0.50

ELSEVIER
Nutrition
Volume 28, Issue 10, October 2012, Pages 1016-1021

Applied nutritional investigation

Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes

Talib A. Hussain M.B., Ch.B., R.C.G.P. [a], Thazhumpal C. Mathew M.Sc., Ph.D., F.R.C.Path. [b], Ali A. Dashti M.Sc., Ph.D. [b], Sami Asfar M.B., Ch.B., M.D., F.R.C.S., F.A.C.S. [c], Naji Al-Zaid B.Sc., Ph.D. [d], Hussein M. Dashti M.D., Ph.D., F.I.C.S., F.A.C.S. [c]



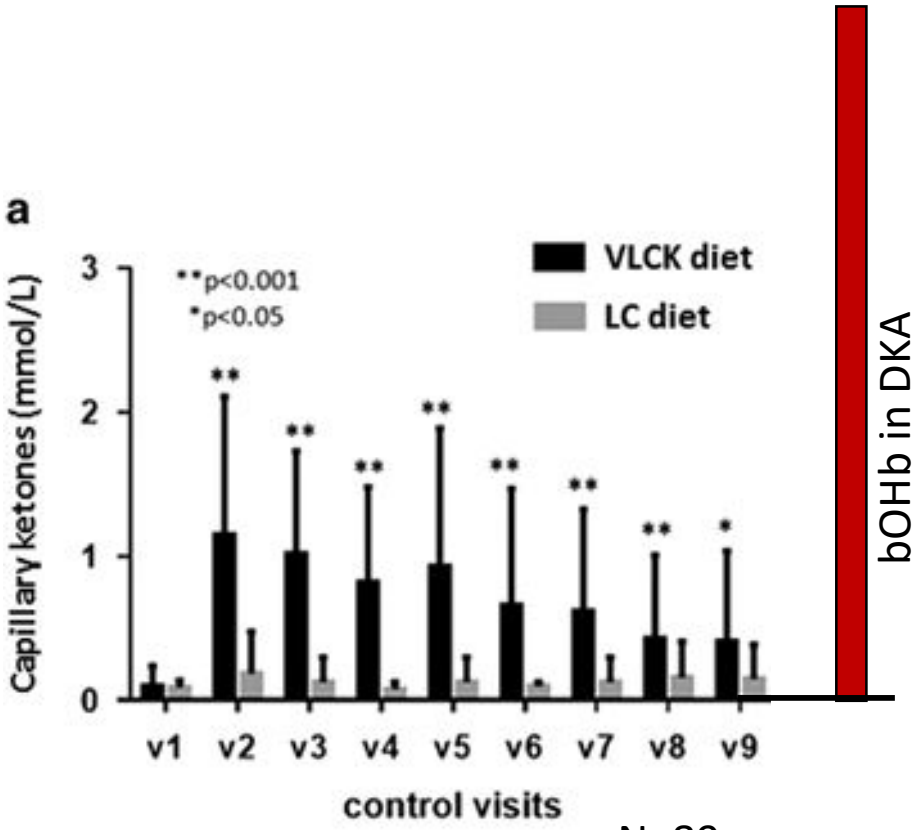
HFKD

Metabolic Acidosis

ORIGINAL ARTICLE

Short-term safety, tolerability and efficacy of a very low-calorie-ketogenic diet interventional weight loss program versus hypocaloric diet in patients with type 2 diabetes mellitus

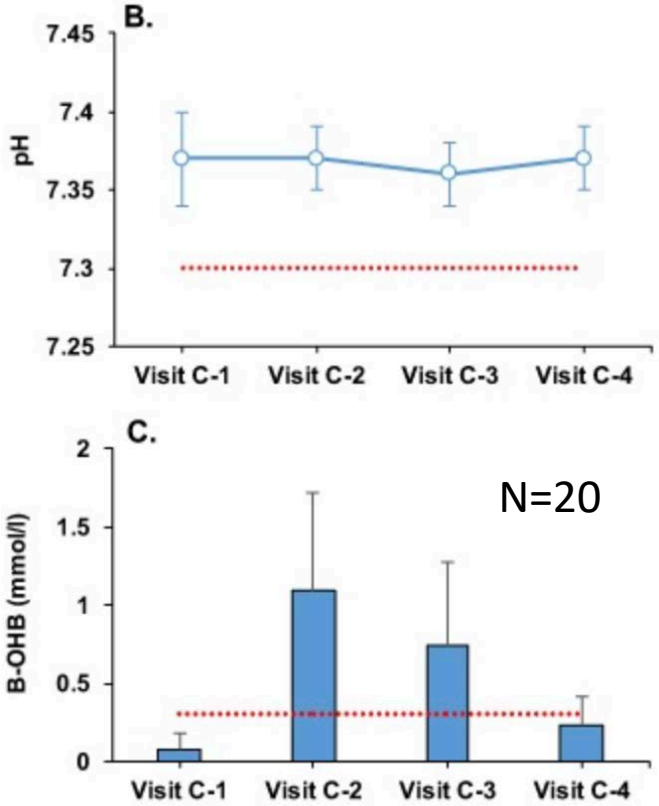
A Goday[1,2,3], D Bellido[4], I Sajoux[5], AB Crujeiras[6,7], B Burguera[8,9], PP García-Luna[10], A Oleaga[11], B Moreno[12] and FF Casanueva[6,7]



N=89

Nutr Diabetes. 2016 Sep 19;6(9):e230.

Gomez-Arbelaez D et al. **Acid-base safety during the course of a very low-calorie-ketogenic diet.** Endocrine. 2017 Oct;58(1):81-90



60 y.o. man with well controlled T2DM on metformin, HFKD+5 d fast

e-ISSN 1941-5923
© Am J Case Rep, 2019; 20: 1728-1731
DOI: 10.12659/AJCR.917226

Starvation Ketoacidosis due to the Ketogenic Diet and Prolonged Fasting – A Possibly Dangerous Diet Trend

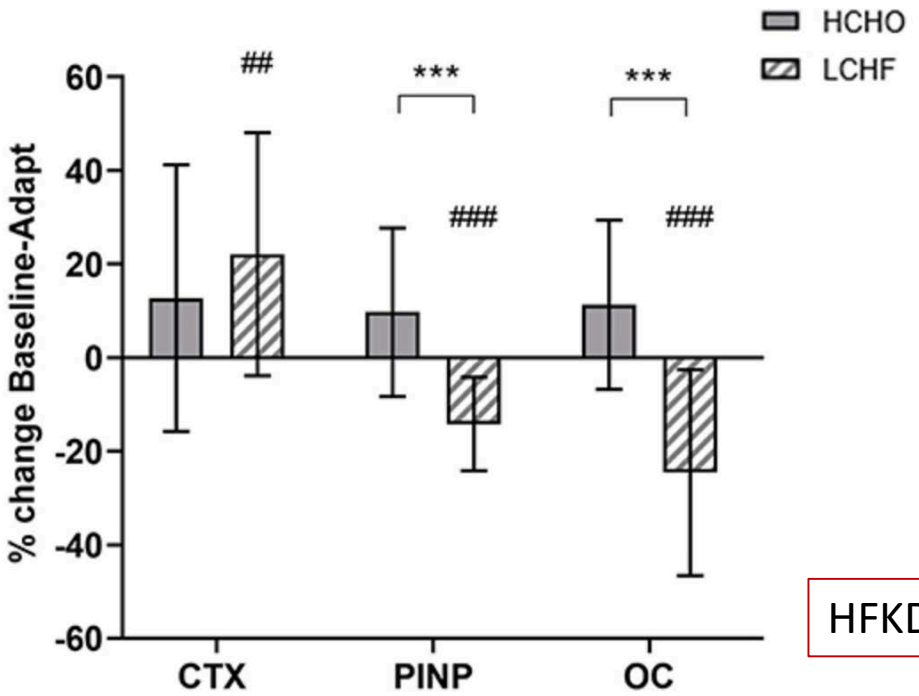
EF 1 Joanna C. Blanco
EF 1 Akshay Khatri
EF 1 Alina Kifayat
EF 1 Ronald Cho
EF 2 Wilbert S. Aronow

1 Department of Internal Medicine, Westchester Medical Center, New York Medical College, Valhalla, NY, U.S.A.
2 Department of Cardiology, Westchester Medical Center, New York Medical College, Valhalla, NY, U.S.A.

Medium-long term

Bone Mineral Density

Heikura et al. **A Short-Term Ketogenic Diet Impairs Markers of Bone Health in Response to Exercise** Front. Endocrinol., 21 January 2020



HFKD

Andersen et al. **Changes in bone mineral content in obese dieting women**. Metabolism. 1997 Aug;46(8):857-61

Table 2. Total and Regional BMC and BMD (mean ± SD) of Subjects on Diet Only and Diet Plus Resistance Training

	Diet Only			Diet + Resistance Training		
Variable	Baseline (n = 9)	24 Weeks (n = 8)	% Change	Baseline (n = 12)	24 Weeks (n = 11)	% Change
Total						
BMC (g)	2,781 ± 416	2,822 ± 396	1.2 ± 3.8	2,765 ± 344	2,707 ± 376	−0.6 ± 7.2
BMD (g/cm²)	1.22 ± 0.1	1.23 ± 0.1	0.8 ± 2.8	1.21 ± 0.1	1.22 ± 0.1	1.0 ± 3.5
Lumbar						
BMC (g)	52.3 ± 11	52.8 ± 12	0.8 ± 1.9	53.7 ± 10	53.7 ± 8	0.7 ± 5.6
BMD (g/cm²)	1.29 ± 0.2	1.28 ± 0.2	1.2 ± 1.8	1.29 ± 0.1	1.30 ± 0.1	0.7 ± 4.4
Femoral Neck						
BMC (g)	5.07 ± 0.84	4.39 ± 1.48*	−13.3 ± 19.8	5.30 ± .96	4.84 ± 1.13*	−7.8 ± 12.4
BMD (g/cm²)	1.09 ± 0.2	1.03 ± 0.2*	−2.9 ± 3.2	1.12 ± 0.1	1.06 ± 0.1*	−3.9 ± 5.2
Trochanter						
BMC (g)	11.78 ± 2.9	10.85 ± 2.4*	−7.2 ± 9.9	12.80 ± 2.3	10.48 ± 2.1†	−13.1 ± 14.0
BMD (g/cm²)	0.88 ± 0.2	0.87 ± 0.2	−1.4 ± 4.9	0.93 ± 0.1	0.87 ± .01†	−3.8 ± 3.4
Wards Triangle						
BMC (g)	2.33 ± 0.5	2.61 ± 0.7	12.0 ± 13.7	2.46 ± 0.7	2.58 ± 0.9	3.24 ± 16.6
BMD (g/cm²)	0.95 ± 0.2	0.95 ± 0.2	0.16 ± 6.7	1.00 ± 0.2	0.93 ± 0.2	−5.2 ± 7.4

*Significantly ($P < .05$) different from baseline.
†Significantly ($P < .01$) different from baseline.

VLCD

Adequate protein, calcium and Vitamin D Supplementation

Hair loss

- If protein[1] or micronutrient[2] intake is insufficient

→low priority of hair growth → telogen effluvium

Increase protein intake (with caution)
Ensure adequate supplementation of iron, vitamins, minerals i.e. zinc, copper

1. Blackburn GL, Bistrian BR, Hoag C. Letter: hair loss with rapid weight loss. JAMA. 1976;236:252
2. Almohanna HM, Ahmed AA, Tsatalis JP, Tosti A. The Role of Vitamins and Minerals in Hair Loss: A Review. Dermatol Ther (Heidelb). 2019 Mar;9(1):51-70. doi: 10.1007/s13555-018-0278-6

Urolithiasis

- Urinary acidosis, dehydration

→stones made of uric acid, calcium oxalate, or a mixture of calcium oxalate and calcium phosphate/uric acid

- Risk factors: young age, family history of kidney stones, and a urine Ca/Cr ratio of >0.2

Adequate daily fluid intake (at leat 2 L)
Alkalinize urine using oral potassium citrate.

Muscogiuri *et al. J Transl Med (2019) 17:356*

Gallstones

VLCKDs (rapid weight loss) increase risk of gallstones because of the increased mucin content and calcium concentration that promote cholesterol nucleation and stone formation [1,2]

Treatment	Intervention	Study
Diet	High dietary fiber intake **VLCKD: >7 gr fat/daily to ensure bile cycling**	European Association for the Study of the Liver (EASL)J Hepatol 2016; 65:146.
	Polyunsaturated and monounsaturated fats	Tsai CJ et al. Ann Intern Med 2004; 141:514.
	Coffee	Leitzmann MF et al JAMA 1999; 281:2106. Leitzmann MF, Stampfer MJ, Willett WC, et al Gastroenterology 2002; 123:1823. Zhang YP, Li WQ, Sun YL, Zhu RT, Wang WJ. Aliment Pharmacol Ther. 2015 Sep;42(6):637-48
	Nuts	Tsai CJ et al. Am J Epidemiol 2004; 160:961.
Exercise	Recreational physical activity	Leitzmann MF et al. Ann Intern Med 1998; 128:417. Leitzmann MF N Engl J Med 1999; 341:777
Medication	Ursodeoxycholic acid	Sugerman HJ et al. Am J Surg. 1995 Jan;169(1):91-6; discussion 96-7
	Statins	Bodmer M et al. JAMA 2009; 302:2001. Erichsen R et al. Am J Epidemiol 2011; 173:162
	Ascorbic acid supplementation	Gustafsson U et al. Eur J Clin Invest 1997; 27:387 Walcher T et al. BMC Gastroenterol 2009; 9:74 Simon JA et al. Arch Intern Med 2000; 160:931

1,2 Endocrinol Metab Clin N Am. 2003; 32: 761-786.; Johansson K et al. Int J Obes (Lond). 2014 Feb;38(2):279-84.

Dyslipidemia

- No evidence available relative to fat qualities in KDs
- Until then, safe to assume that unsaturated should be preferred
- HFKDs are overall **not associated to worse serum lipid profile**

Author, year	n	Duration	Intervention	Control	LDL	HDL	TRG
Johnstone et al.	20	6w	HFKD	LFD	worse	neutral	neutral
Volek et al.	40	12w	HFKD	LFD	neutral	better	better
Dashti et al.	66	56w	HFKD	n/a	better	better	better
Foster et al.	307	2y	HFKD	LFD	neutral	better	neutral
Yanci et al.	120	6m	HFKD	LFD	neutral	better	better
Mardinoglu et al.	10	2w	HFKD	n/a	better	n/a	better
Perez Guisado et al.	307	3m	HFKD	n/a	better	better	better
McAuley et al.	96	2w	HFKD	LFD	worse	better	better
Samaha et al.	130	6m	HFKD	LFD	neutral	neutral	better
Brehm et al.	53	6m	HFKD	LFD	neutral	better	neutral
Shei et al.	322	2y	HFKD+LCD	LFD	neutral	better	better
Schwenger et al.	139	1w	VLCD	n/a	better	better	neutral
Paoli et al.	68	6w	VLCKD+LCD	n/a	better	better	better
Bruci et al.	92	15w	VLCKD+LCD	n/a	neutral	neutral	better

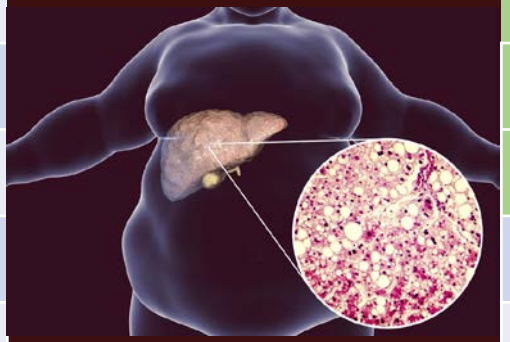
Non Alcoholic Fatty Liver Disease

RCT

Author, year	Country	n	Subjects	Duration	Intervention	kcal/d	cho/d (g)	fat/d (g)	Control	kcal/d	cho/d (g)	fat/d (g)	Biochemistry	Imaging
Kirk et al, 2009	USA	22	obese, NAFLD	11 w	HFKD	-1000	≤60	81	LFD	-1000	≥180	12	n/a	unchanged (MRS)
Browning, 2011	USA	18	obese, NAFLD	2 w	HFKD	1553	26	105	LCD	1325	169	49	n/a	improved (MRS)
Ministrini et al, 2019	Italy	52	obese	25 d	VLCKD	<800	<50	<30	Nutr. Adv.	n/a	n/a	n/a	unchanged	improved (US)

Observational

Author, year	Country	n	Subjects	Duration	Intervention	kcal/d	cho/d (g)	fat/d (g)	Biochemistry	Imaging	Histology
Tendler et al, 2007	USA	5	obese, NAFLD	6 m	HFKD	unr	< 20	unr	n/a	n/a	improved
Guisado et al, 2011	Spain	14	MS, NAFLD	3 m	HFKD	unr	< 30	n/a	improved	improved (US)	n/a
Schiavo et al, 2018	Italy	27	obese, NAFLD	1 m	HFKD	1200	12	91	improved	improved (US)	n/a
Mardinoglu et al, 2018	Sweden	17	MS, NAFLD	2 w	HFKD	3115	20-30	241	improved	improved (MRS)	improved
Paoli et al, 2011	Italy	106	obese	6 w	VLCKD	1098	34	63	unchanged	n/a	n/a
Paoli et al, 2013	Italy	81	obese	20 d	VLCKD	976	30	51	unchanged	n/a	n/a
Basciani et al, 2015	Italy	24	obese	6 m	VLCKD	700	50	10	improved	n/a	n/a
Leonetti et al, 2015	Italy	50	obese	10 d	VLCKD	577	15	24	unchanged	improved (US)	n/a
Colles et al, 2006	USA	32	obese	12 w	VLCKD	456	45	7	unchanged	improved (CT, MRI)	n/a



Take home messages

- Some contraindications are **deductive and not evidence based** (but still to be followed!)
- Ketogenic diets are **safe for most** patients
- Of the much feared side effects, **many are false**
- Many side effects can be easily avoided with **adequate supplementation** and **patient education**
- The association between KD and some adverse events is **yet to be fully elucidated**

Mikiko.watanabe@uniroma1.it