Le diete chetogeniche in cardiologia: dal rischio cardio-metabolico allo scompenso cardiaco

Massimiliano Caprio

Università San Raffaele
Roma

Il sottoscritto Massimiliano Caprio
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

- ❑ *che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario*
- ❑ *X che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:*

- *New Penta*
- *Therascience SAM*
- *Bayer AG*
- *Novo Nordisk*

Outline of the talk

. VLCKD e rischio cardiometabolico

. Corpi chetonici e cuore: cenni di fisiologia

. VLCKD e scompenso cardiaco: dati preclinici e clinici

Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-019-01061-2

CONSENSUS STATEMENT

Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE)

M. Caprio[1,2] · M. Infante[3] · E. Moriconi[1,4] · A. Armani[1] · A. Fabbri[3] · G. Mantovani[5] · S. Mariani[4] · C. Lubrano[4] · E. Poggiogalle[4] · S. Migliaccio[6] · L. M. Donini[4] · S. Basciani[4] · A. Cignarelli[7] · E. Conte[7] · G. Ceccarini[8] · F. Bogazzi[9] · L. Cimino[10] · R. A. Condorelli[10] · S. La Vignera[10] · A. E. Calogero[10] · A. Gambineri[11] · L. Vignozzi[12] · F. Prodam[13] · G. Aimaretti[13] · G. Linsalata[14] · S. Buralli[14] · F. Monzani[14] · A. Aversa[15] · R. Vettor[16] · F. Santini[8] · P. Vitti[9] · L. Gnessi[4] · U. Pagotto[11] · F. Giorgino[7] · A. Colao[17] · A. Lenzi[4] on behalf of the Cardiovascular Endocrinology Club of the Italian Society of Endocrinology

Table 2 Indications for the use of VLCKD in metabolic diseases

Strong recommendations	Strength of recommendations and quality of evidence according to GRADE system
Severe obesity	(1 ØØØO)
Management of severe obesity before bariatric surgery	(1 ØØØO)
Sarcopenic obesity	(1 ØØØO)
Obesity associated with type 2 diabetes (preserved beta cell function)	(1 ØØØO)
Obesity associated with hypertriglyceridemia	(1 ØØØO)
Obesity associated with hypertension	(1 ØØØO)
Pediatric obesity associated with epilepsy and/or with a high level of insulin resistance and/or comorbidities, not responsive to standardized diet	(1 ØØØO)

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Weak recommendations	
Obesity associated with dysbiosis of the gut microbiota	(2 ØØØO)
Obesity associated with high levels of LDL-cholesterol and/or low levels of HDL-cholesterol	(2 ØØØO)
Obesity associated with non-alcoholic fatty liver disease (NAFLD)	(2 ØØØO)
Obesity associated with heart failure (NYHA I–II)	(2 ØOOO)
Obesity associated with atherosclerosis	(2 ØOOO)
Male obesity secondary hypogonadism	(2 ØØØO)
Obesity associated with polycystic ovary syndrome (PCOS)	(2 ØOOO)
Menopausal transition-related obesity	(2 ØOOO)
Neurodegenerative disorders associated with sarcopenic obesity	(2 ØOOO)

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Massimiliano Caprio, Marco Infante

VLCKD, cardiovascular risk factors and diseases

Recommendations

- We recommend VLCKD for a rapid reduction of cardiovascular risk factors in obese patients, not responsive to standard diets (1 ØØØO).
- We recommend VLCKD in obese hypertensive patients, not responsive to standard diets (1 ØØØO).
- We suggest VLCKD as an option for rapid reduction in body weight and cardiac overload in obese patients with heart failure (NYHA I-II), upon careful examination of cardiac function and fluid balance (2 ØOOO).

European Guidelines for Obesity Management in Adults with a Very Low-Calorie Ketogenic Diet: A Systematic Review and Meta-Analysis

Giovanna Muscogiuri[a, b] Marwan El Ghoch[c] Annamaria Colao[a, b]
Maria Hassapidou[d] Volkan Yumuk[e] Luca Busetto[f] Obesity Management
Task Force (OMTF) of the European Association for the Study of Obesity (EASO)

VLCKD is associated with a significant reduction in body weight and BMI at 1, 2, 4, 6, 12, and 24 months, and appears to be associated with larger weight loss rates compared to other diets with a different energy content (i.e., LCD and VLCD) of the same duration

VLCKD is associated with a significant reduction of WC (an expression of central fat) and FM, and this reduction is significantly larger than those achieved with other weight loss interventions of the same duration

VLCKD was associated with a reduction of the HOMAIR index and an improvement in insulin sensitivity, and this effect was superior to that of other weight loss programs

A significant reduction in TG from baseline was associated with a VLCKD and it was shown to be superior compared to other diets

Multidisciplinary Treatment of Obesity with a Protein-sparing Modified Fast: Results in 668 Outpatients

AVIVA PALGI, PHD, J. LEIGHTON READ, MD, ISAAC GREENBERG, PHD, MARTHA A. HOEFER, BA, BRUCE R. BISTRIAN, MD, PHD, AND GEORGE L. BLACKBURN, MD, PHD

Abstract: Six hundred sixty-eight obese outpatients, 71 per cent (± 34) in excess of ideal weight, were enrolled in a multidisciplinary weight control program. The major components of the program included nutrition, education, behavior modification, and exercise. Rapid weight loss was accomplished using a very low calorie (less than 800 kcal) ketogenic diet. Patients adhered to the protein sparing modified fast (PSMF) for 17 ± 12 weeks and averaged 9 ± 17 weeks in a refeeding/maintenance program. Mean weight loss was 47 ± 29 lb (21 ± 13 kg) at the point of minimum weight and 41 ± 29 lb (19 ± 13 kg) at the end of the maintenance period. Systolic and diastolic blood pressure and serum triglycerides fell significantly in men and women. Success in weight loss was greatest in the heaviest patients, those who adhered the longest to the PSMF, and those who stayed the longest in the maintenance program. (*Am J Public Health* 1985; 75:1190–1194.)

attualità - rigore scientifico - sicurezza – efficacia (maggiore nei pazienti più obesi) – pleiotropia di effetto - durability

Palgi A, Blackburn GL, Am J Public Health 1985; 75:1190-1194

Definition of obesity

Obesity is a chronic relapsing progressive disease[1]

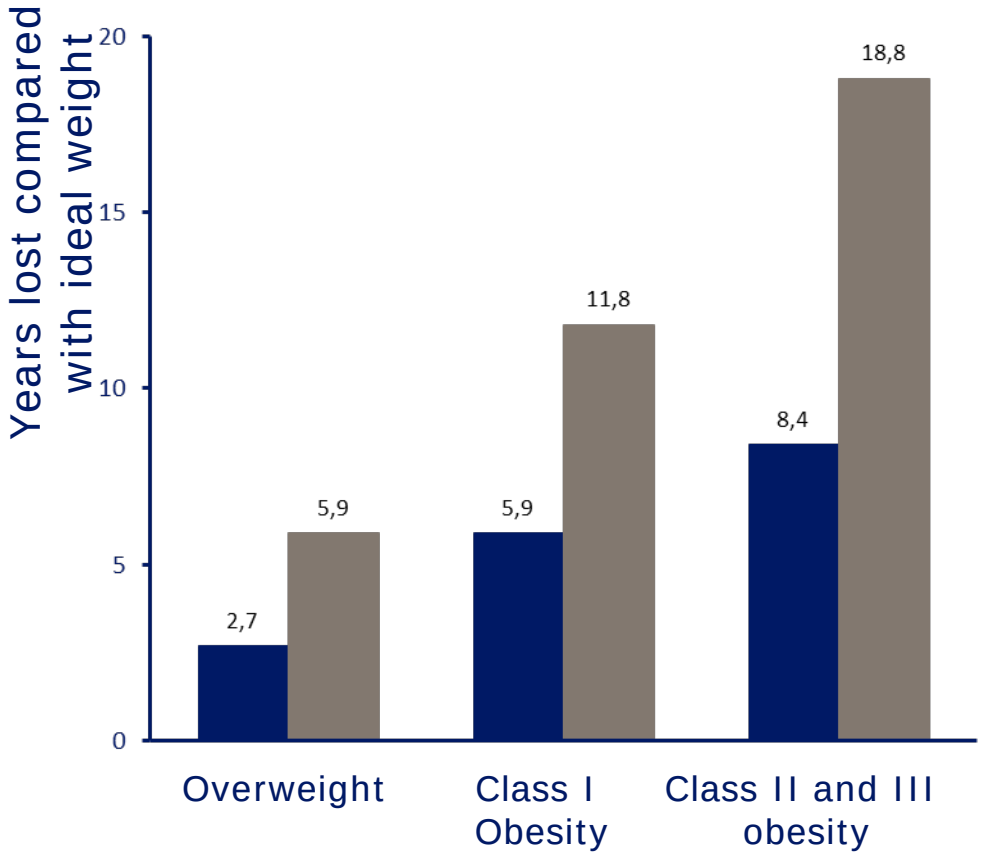
Obesity is a multifactorial disease[2]

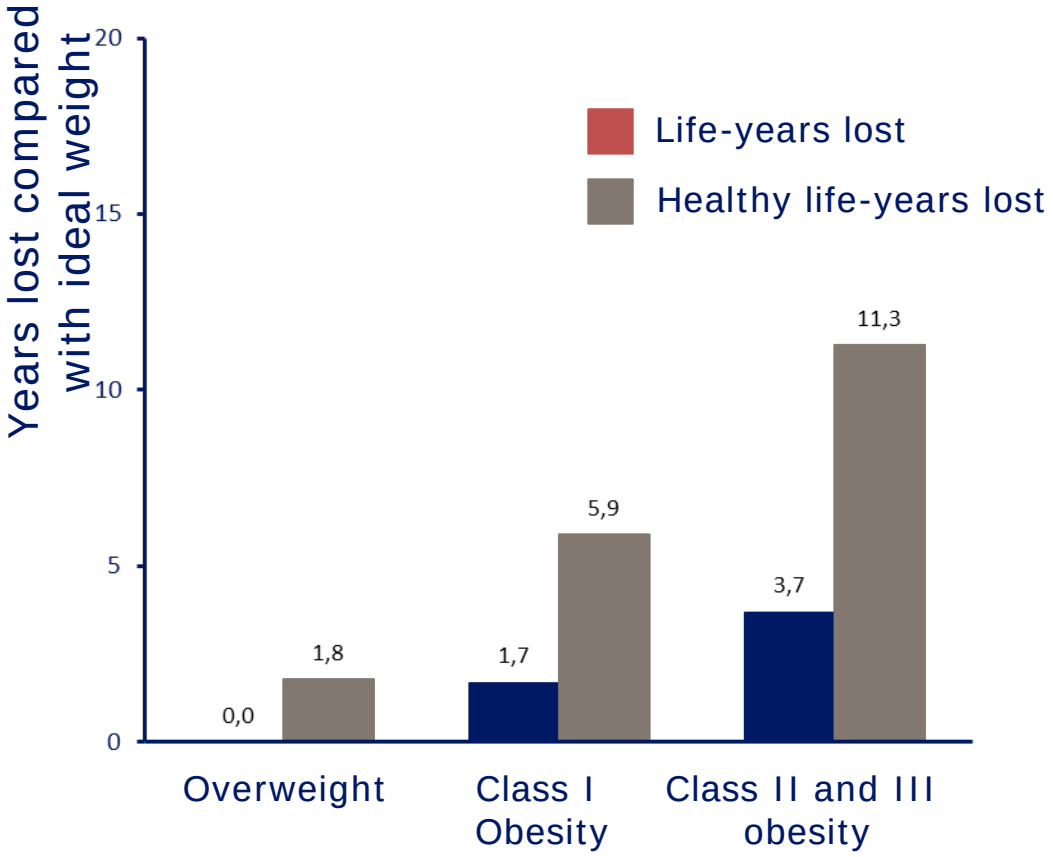
Obesity is a social disease, involving the overcoming of stigma, discrimination, and generalization[2]

1. WOF Position Statement, G. Brey et al. Obesity Reviews 18, 715–723, July 2017; 2. A. De Lorenzo et al. / Nutrition 71 (2019) 110615

Obesity increases both mortality and morbidity

More life-years and healthy-life years lost with increasing weight

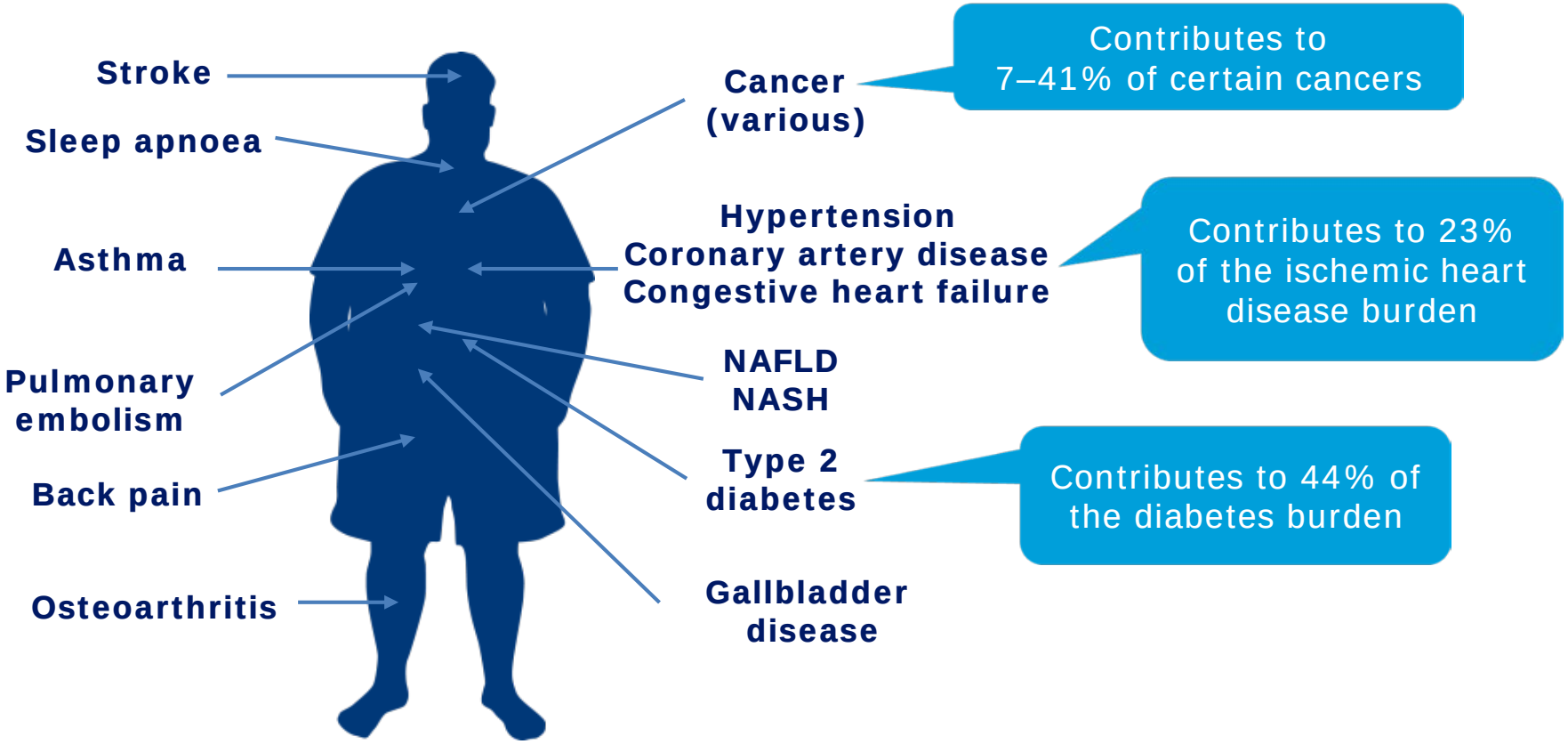




Grover *et al*. *Lancet Diabetes & Endocrinology*. 2015;3:114-122

Obesity is associated with multiple complications

Obesity-related complications include:

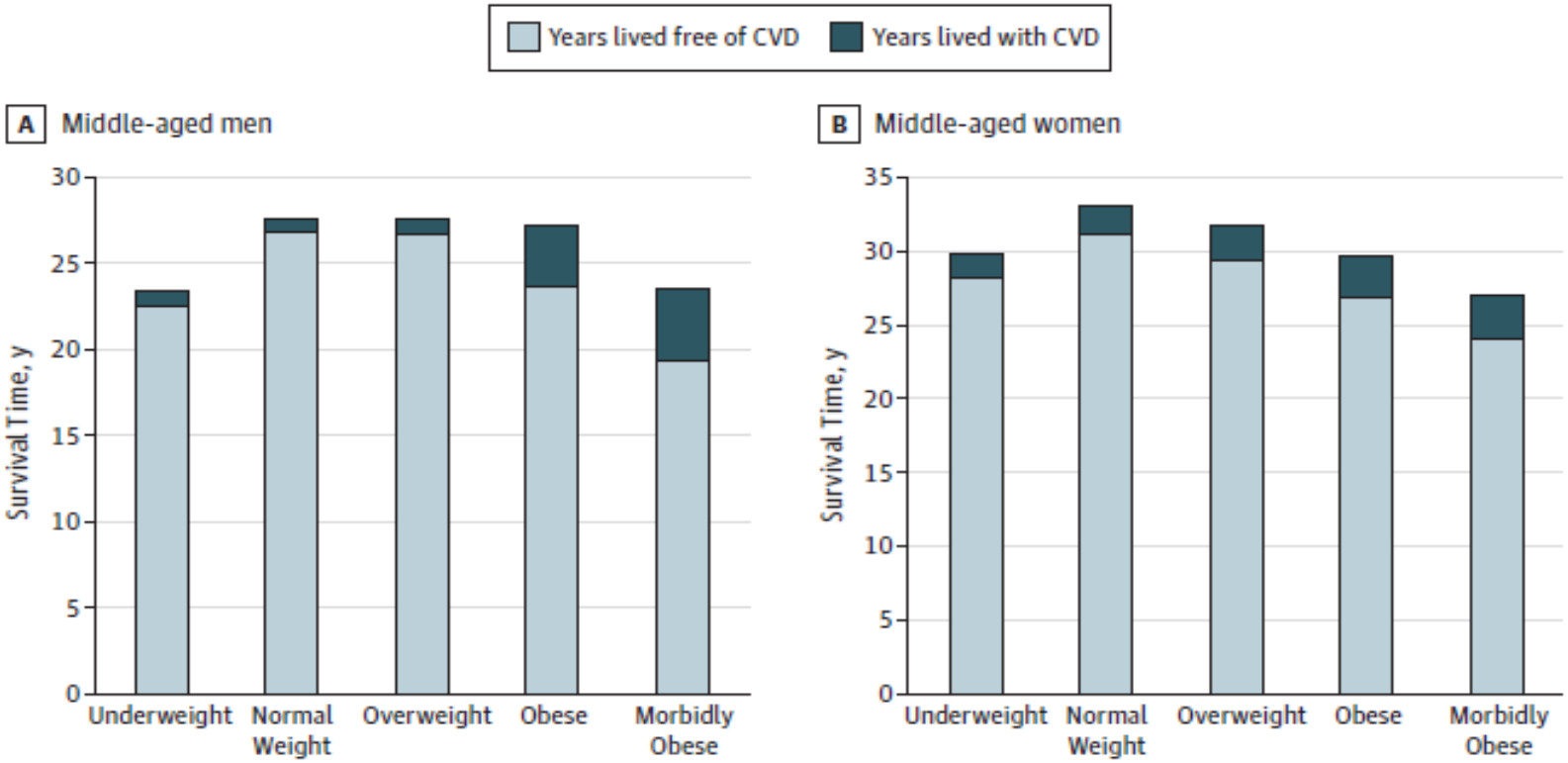


JAMA Cardiology | Original Investigation

Association of Body Mass Index With Lifetime Risk of Cardiovascular Disease and Compression of Morbidity

Sadiya S. Khan, MD, MS; Hongyan Ning, MD, MS; John T. Wilkins, MD, MS; Norrina Allen, PhD; Mercedes Carnethon, PhD; Jarett D. Berry, MD; Ranya N. Sweis, MD, MS; Donald M. Lloyd-Jones, MD, ScM

Figure 2. Years Lived Free of and With Cardiovascular Disease (CVD) Among Middle-aged Individuals



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VLCKD, insulin resistance and type 2 diabetes

Recommendations

- VLCKD should be considered to obtain an early efficacy on glycemic control, particularly in obese patients with short duration of the disease (1 ØØØO).
- VLCKD should be considered to reduce the use of glucose-lowering agents, including insulin (1 ØØØO).

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]

Although the recommended dietary allowance for carbohydrate for adults without diabetes (19 years and older) is 130 g/day and is determined in part by the brain's requirement for glucose, **this energy requirement can be fulfilled by the body's metabolic processes, which include glycogenolysis, gluconeogenesis (via metabolism of the glycerol component of fat or gluconeogenic amino acids in protein), and/or ketogenesis in the setting of VLCKD**

For select adults with type 2 diabetes not meeting glycemic targets or where reducing antiglycemic medications is a priority, reducing overall carbohydrate intake with low- or very low carbohydrate eating plans is a viable approach

STOP DIABETES

American Diabetes Association

nutrients

MDPI

Article

Very-Low-Calorie Ketogenic Diet as a Safe and Valuable Tool for Long-Term Glycemic Management in Patients with Obesity and Type 2 Diabetes

Eleonora Moriconi [1,2], Elisabetta Camajani [2,3], Andrea Fabbri [4], Andrea Lenzi [5] and Massimiliano Caprio [1,3,*]

- Primary outcome:
  - To evaluate the superiority of VLCKD to reduce HbA1c plasma levels after 3 months.

- Secondary outcomes:
  - To compare the effects of VLCKD and LCD upon **on weight loss and metabolic parameters** after 3 months.
  - To investigate the potential role of VLCKD in **T2DM reversal** and weight maintenance after 12 months.
  - To assess the **reduction in pharmacological therapy** after VLCKD or LCD after 12 months.
  - To compare **changes in quality of life and eating behaviors** in patients following VLCKD or LCD after 12 months.

Moriconi et al. Nutrients 2021

Variation of pharmacological therapy at baseline and after 12 months

	VLCKD group		LCD group	
	Baseline	After 12 months	Baseline	After 12 Months
Subjects	15			
Men	8			
Women	7			
Diabetes Duration (years)				
Diet				
Metformin			15	8
Sulphonylurea			0	0
Metformin + GLP-1 agonist			0	6
Metformin + SGLT2 inhibitor	3	0	0	1
DD4-inhibitor	2	0	0	0

26.6% stopped antidiabetic drugs

73.3% were taking Metformin at the end of the study

46.6% increased antidiabetic medications

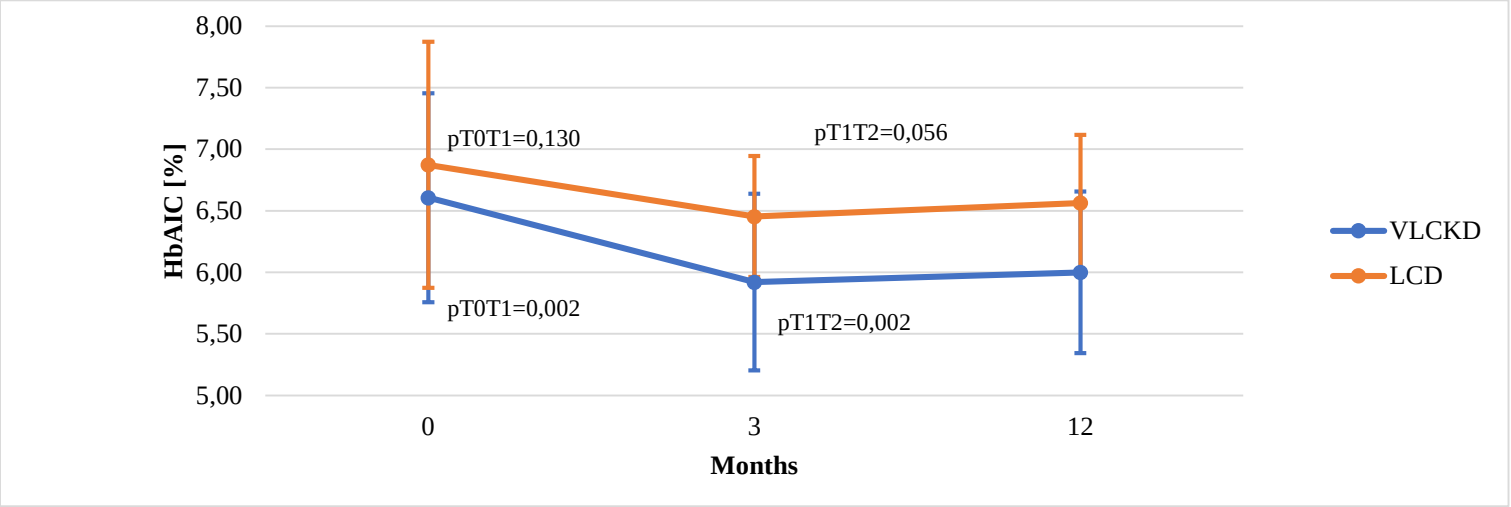
Moriconi et al. Nutrients 2021

Article

Very-Low-Calorie Ketogenic Diet as a Safe and Valuable Tool for Long-Term Glycemic Management in Patients with Obesity and Type 2 Diabetes

Eleonora Moriconi [1,2], Elisabetta Camajani [2,3], Andrea Fabbri [4], Andrea Lenzi [5] and Massimiliano Caprio [1,3,*]

Kinetics of HbA1c % in patients following a VLCKD vs a LCD



	ΔT0-T1 (mean ± DS)		P-value	ΔT2-T0 (mean ± DS)		P-value
	VLCKD	LCD		VLCKD	LCD	
HbA1c%	0,69 ± 0,65	0,42 ± 1,01	0,533	0,61 ± 0,54	0,13 ± 0,76	0,070

Moriconi et al. Nutrients 2021

Variation of SF-36 score over the study: VLCKD group

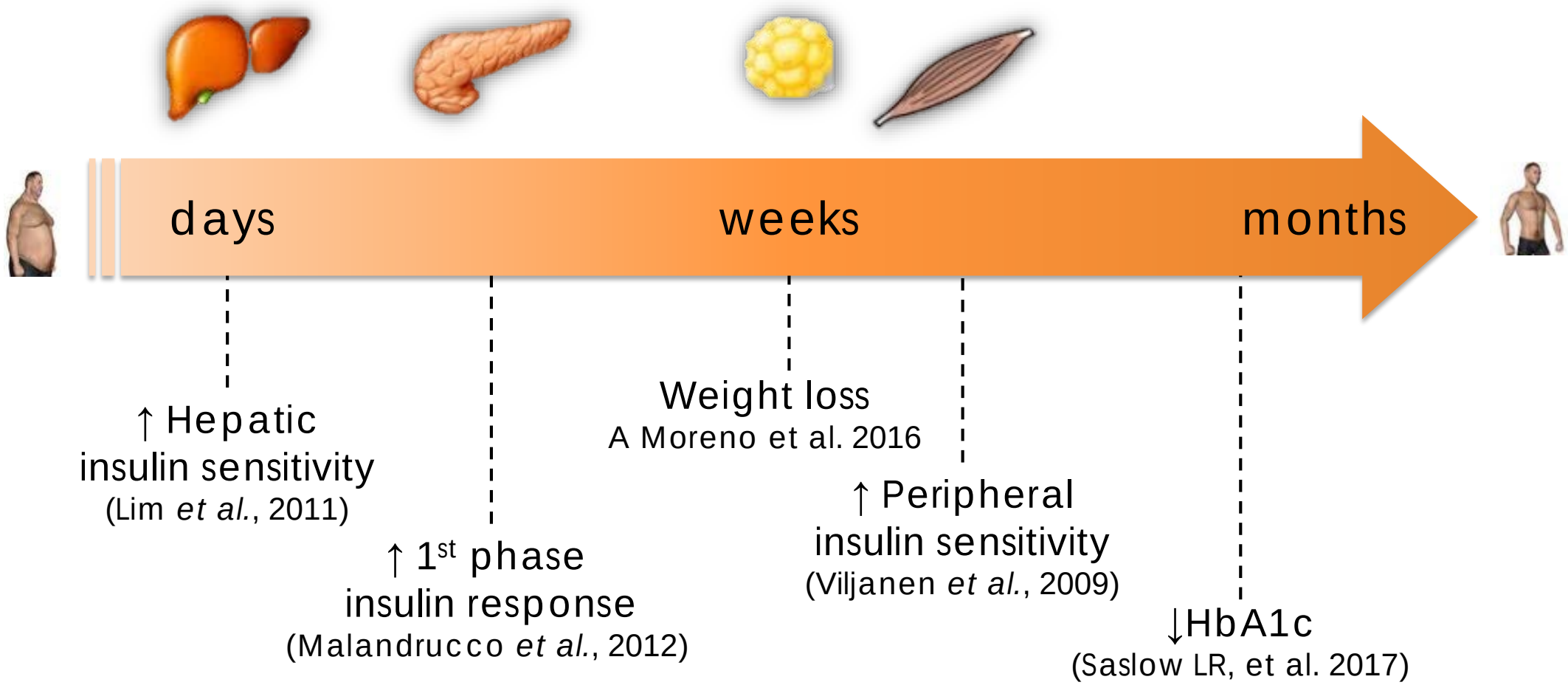
SF-36	VLCKDT0	VLCKDT1	p-value T0T1	VLCKDT2	p-value T0T2
Physical Functioning	43,4 ± 14,2	56 ± 12,4	**0,005**	69,6 ± 9,12	**0,000**
Role physical	41,4 ± 14,8	61,6 ± 11,7	**0,000**	72 ± 5,4	**0,000**
Bodily pain	41,7 ± 14,8	59,3 ± 12,7	**0,001**	62,8 ± 12,4	**0,000**
General health	49,9 ± 47,5	66 ± 11,7	**0,000**	73,6 ± 7,4	**0,000**
Vitality	47,5 ± 14,0	68,3 ± 11,7	**0,001**	68,7 ± 10,6	**0,001**
Social functioning	45,6 ± 10,7	65,7 ± 8,0	**0,000**	68,8 ± 10,1	**0,000**
Role emotional	57,3 ± 9,2	69,8 ± 11,4	**0,005**	72,2 ± 8,5	**0,000**
Mental Health	51,6 ± 12,1	66,4 ± 12,4	**0,000**	70,2 ± 9,7	**0,002**

Adherence diet score at T1 and T2 in VLCKD and LCD group

	Score T1		*p*-Value	Score T2		*p*-Value
	VLCKD	LCD		VLCKD	LCD	
Mean ± DS	10.3 ± 2.4	8.4 ± 2.1	0.025	9.9 ± 1.9	7.8 ± 1.6	0.004

Moriconi et al. Nutrients 2021

VLCKD effects on glucose metabolism in obese subjects

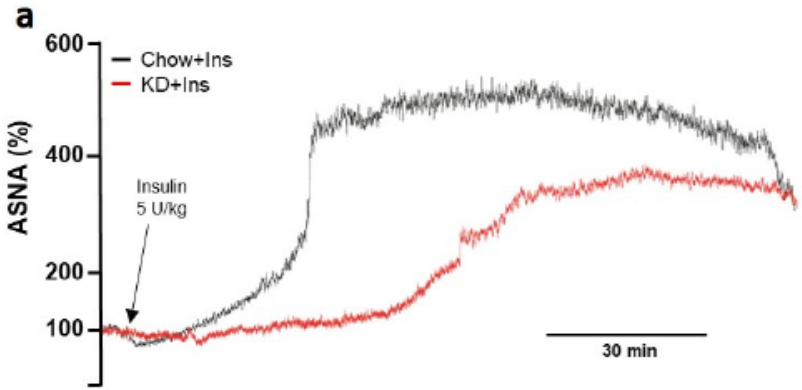


Caprio M, Infante M et al. J Endocrinol Invest 2019 May 20

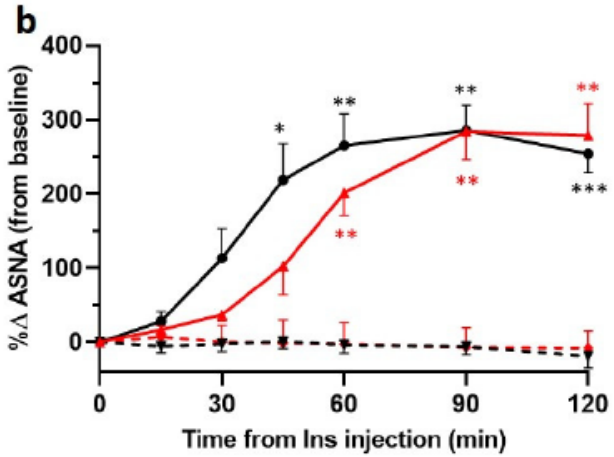
Communication

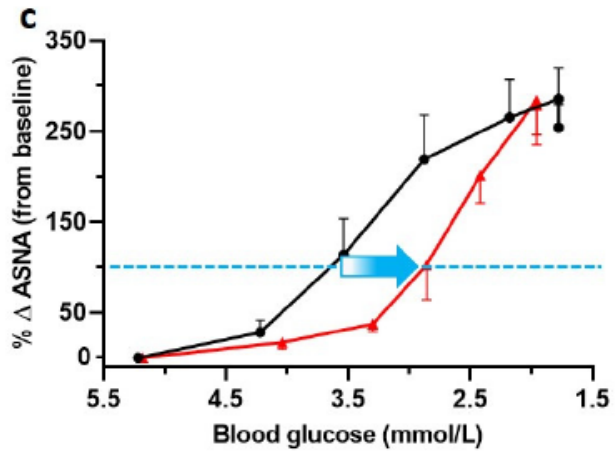
Slow but Steady—The Responsiveness of Sympathoadrenal System to a Hypoglycemic Challenge in Ketogenic Diet-Fed Rats

Polina E. Nedoboy [1,2], Myfanwy Cohen [1] and Melissa M.-J. Farnham [1,2,*]



All KD rats responded to hypoglycemia with a robust increase in ASNA, which was initiated at significantly lower BG levels compared to Chow-fed rats.



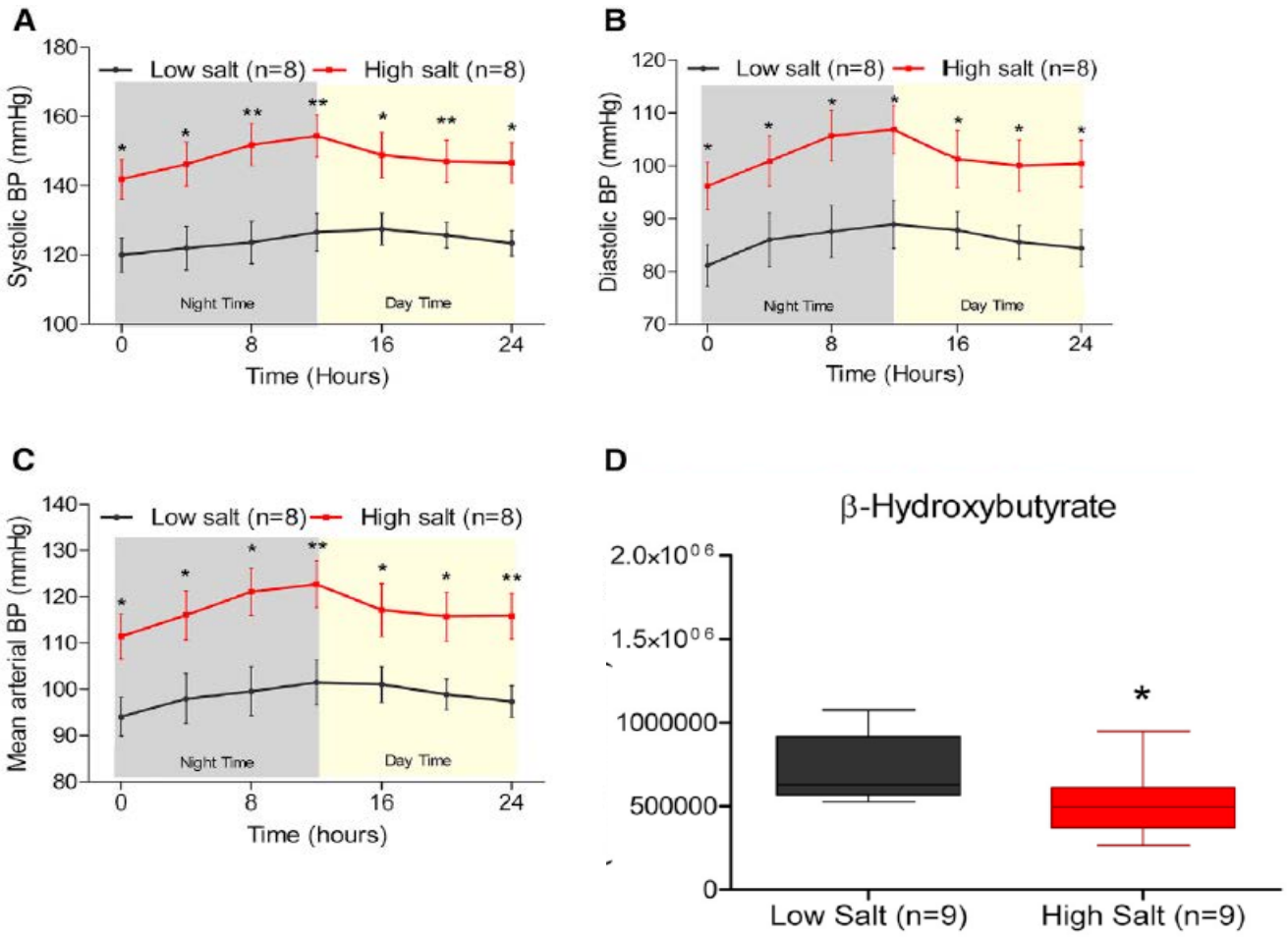


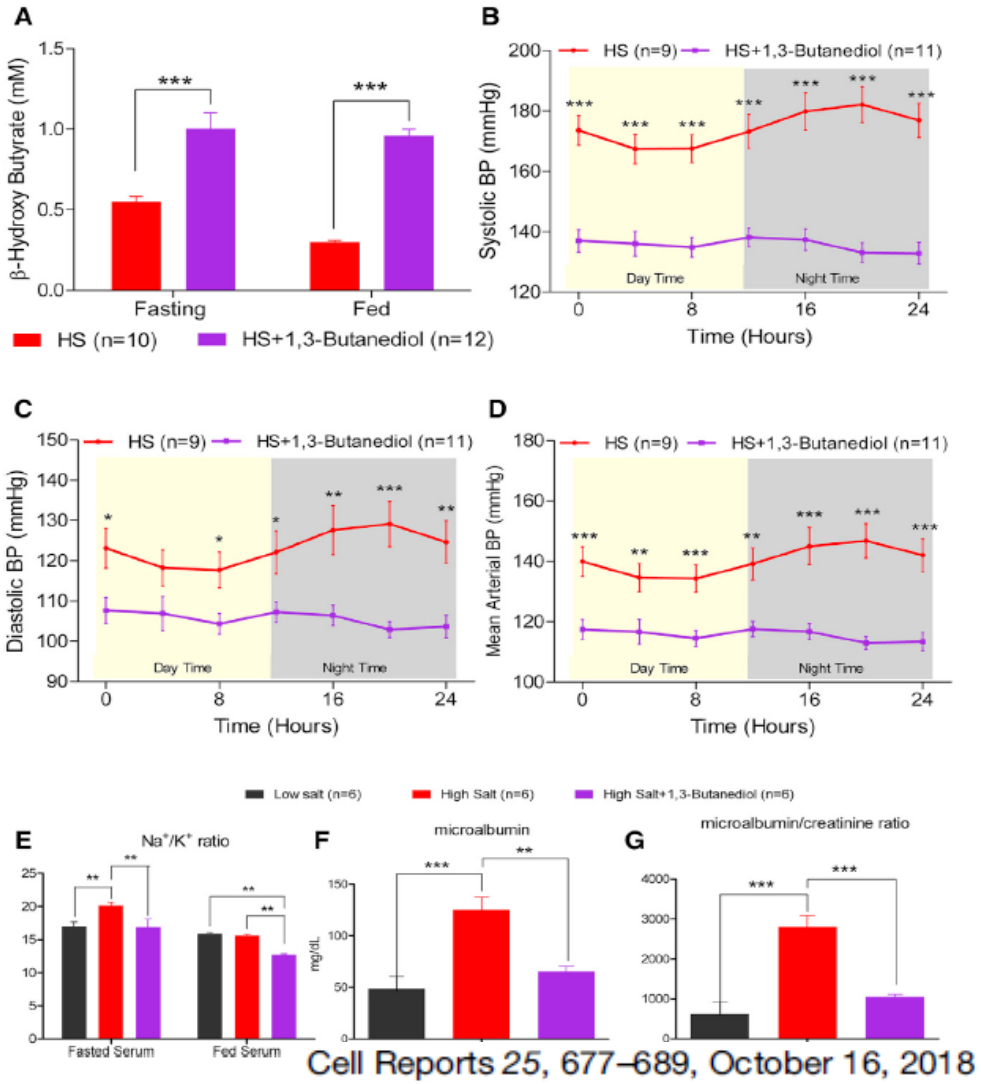
Salt-Responsive Metabolite, β-Hydroxybutyrate, Attenuates Hypertension

Saroj Chakraborty,[1] Sarah Galla,[1] Xi Cheng,[1] Ji-Youn Yeo,[1] Blair Mell,[1] Vishal Singh,[1] BengSan Yeoh,[1] Piu Saha,[1] Anna V. Mathew,[2] Matam Vijay-Kumar,[1] and Bina Joe[1,3,*]

[1]Program in Physiological Genomics, Microbiome Consortium, Center for Hypertension and Personalized Medicine, Department of Physiology and Pharmacology, University of Toledo College of Medicine and Life Sciences, Toledo, OH, USA

[2]Department of Internal Medicine-Nephrology, University of Michigan, Ann Arbor, MI, USA





Cell Reports 25, 677–689, October 16, 2018

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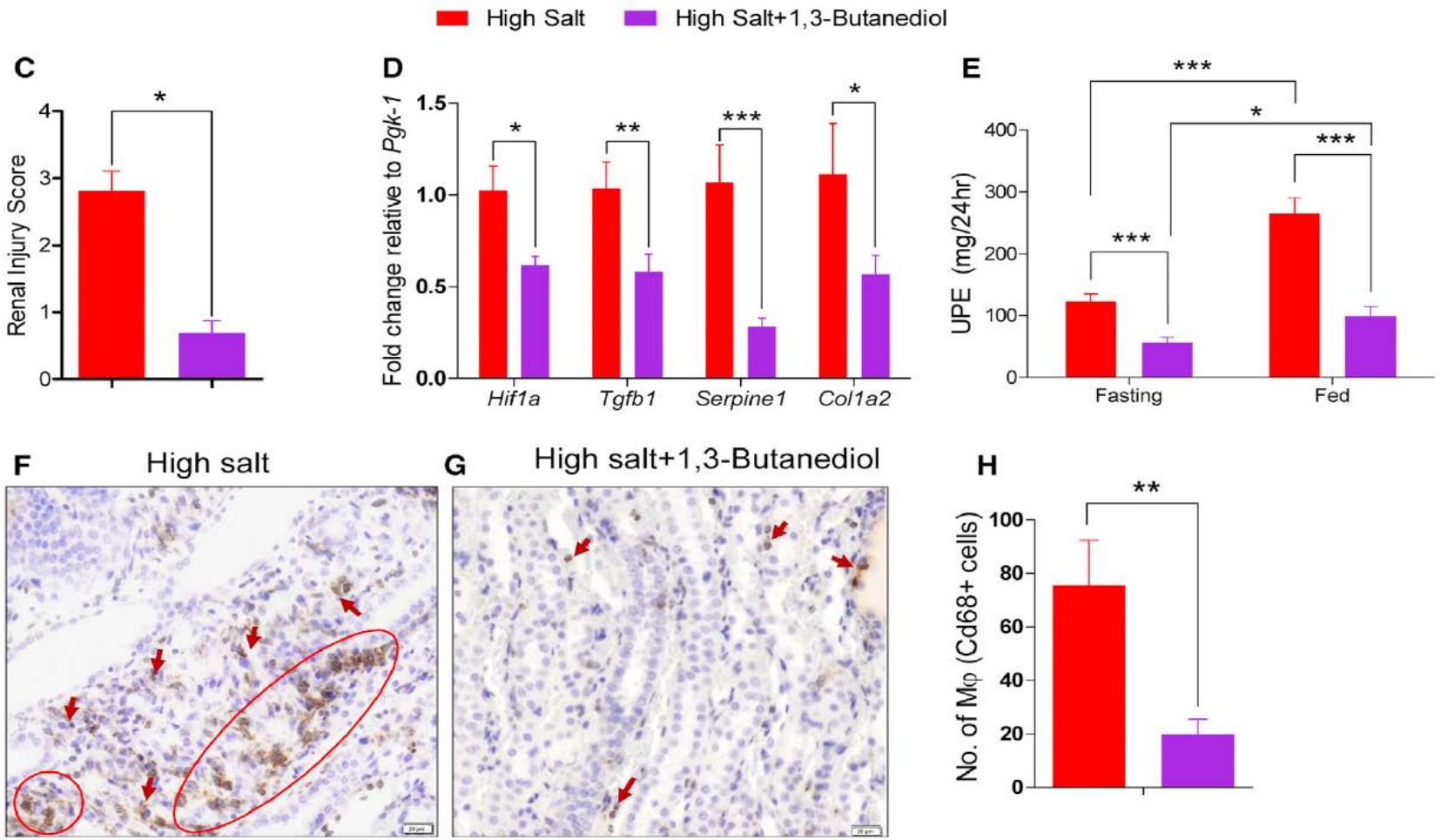
[1]Program in Physiological Genomics, Microbiome Consortium, Center for Hypertension and Personalized Medicine, Department of Physiology and Pharmacology, University of Toledo College of Medicine and Life Sciences, Toledo, OH, USA
[2]Department of Internal Medicine-Nephrology, University of Michigan, Ann Arbor, MI, USA



Cell Reports 25, 677–689, October 16, 2018

Trends in Endocrinology & Metabolism

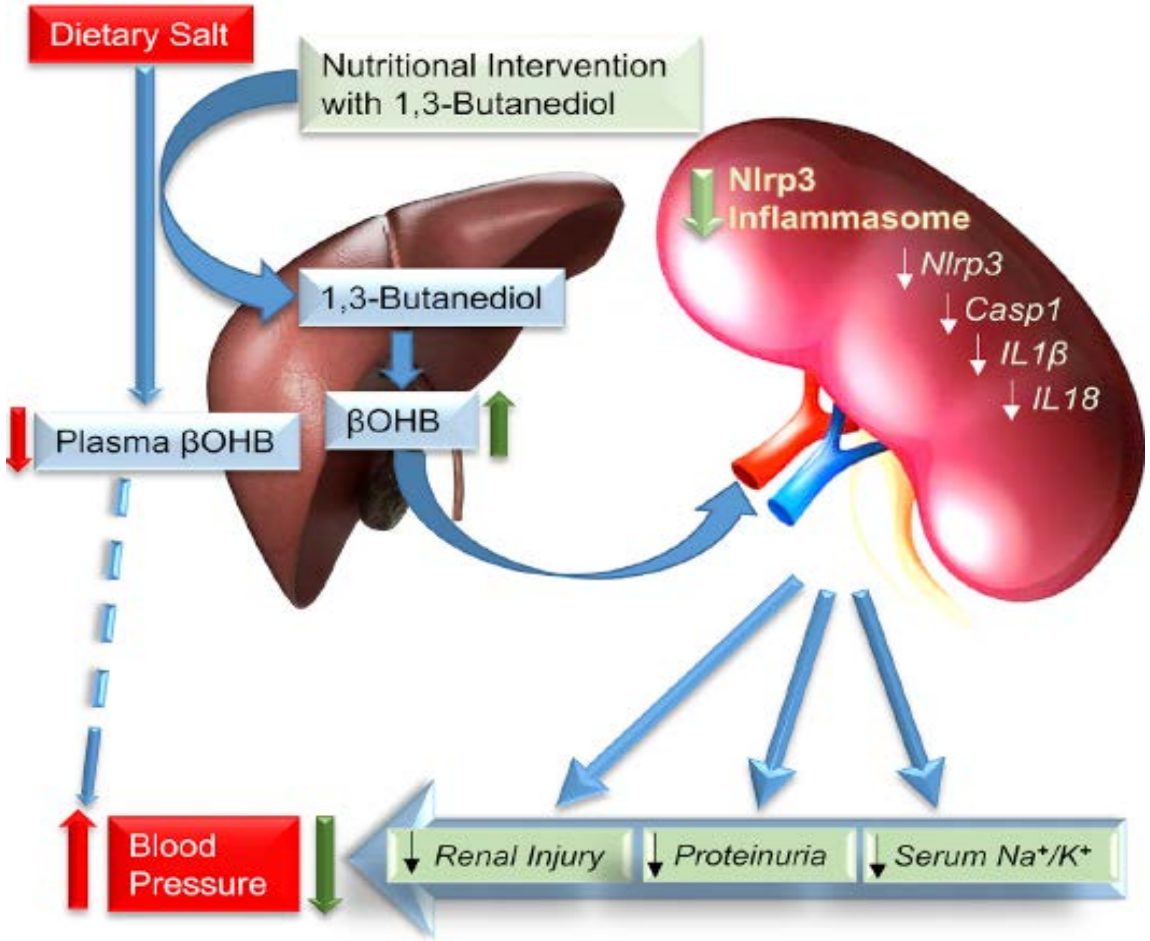
CellPress REVIEWS

Spotlight

Fueling Ketone Metabolism Quenches Salt-Induced Hypertension

David E. Place[1] and Thirumala-Devi Kanneganti[1,*]

Excercise
Fasting
Ketogenic diets



*

Key facts about the hypertension pandemic

- **Hypertension - or elevated blood pressure - is a serious medical condition that significantly increases the risks of heart, brain, kidney and other diseases.**

- **An estimated 1.13 billion people worldwide have hypertension, most (two-thirds) living in low- and middle-income countries.**

- **In 2015, 1 in 4 men and 1 in 5 women had hypertension.**

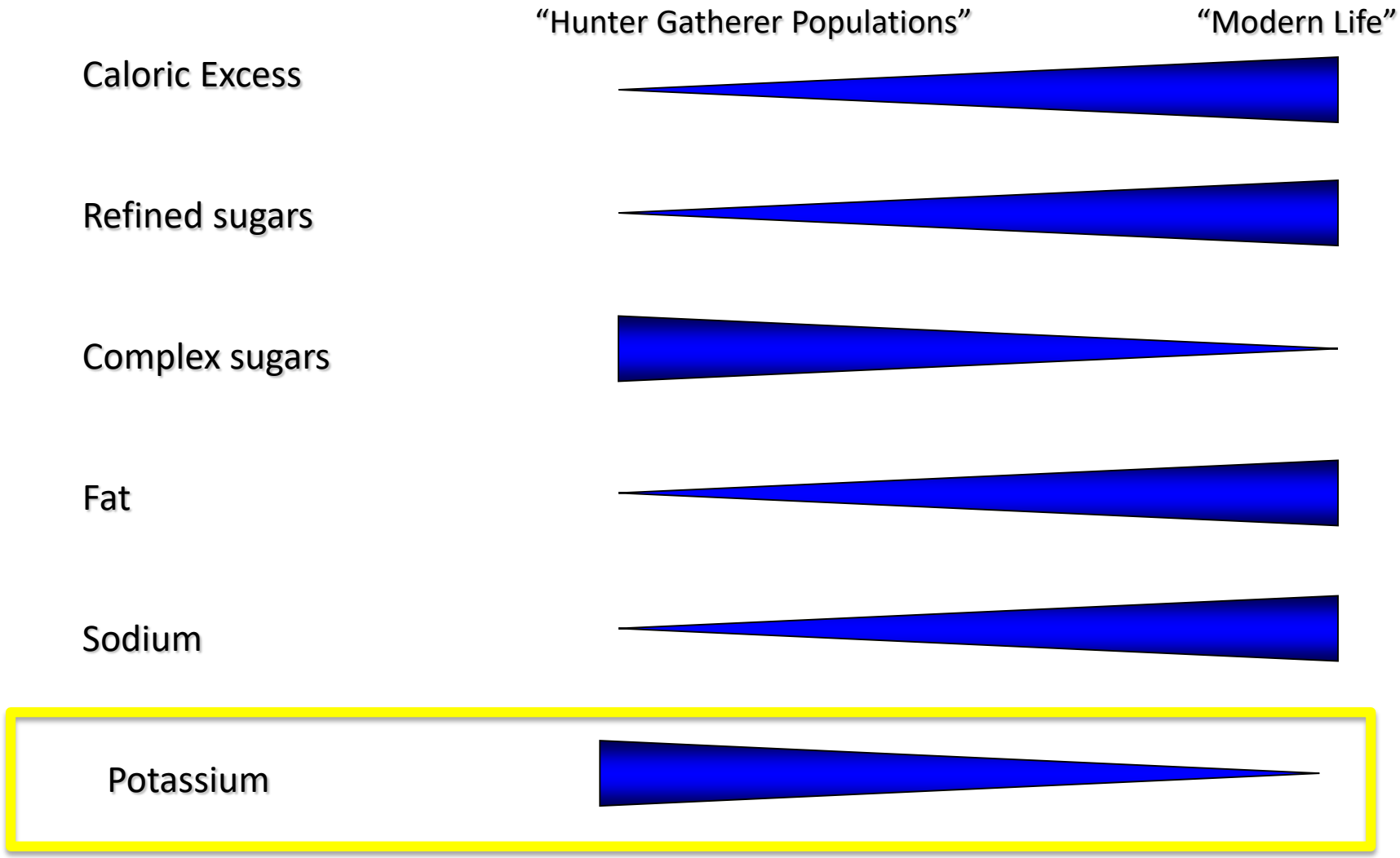
- **Fewer than 1 in 5 people with hypertension have the problem under control.**

- **Hypertension is a major cause of premature death worldwide.**

- **One of the global targets for noncommunicable diseases is to reduce the prevalence of hypertension by 25% by 2025 (baseline 2010).**

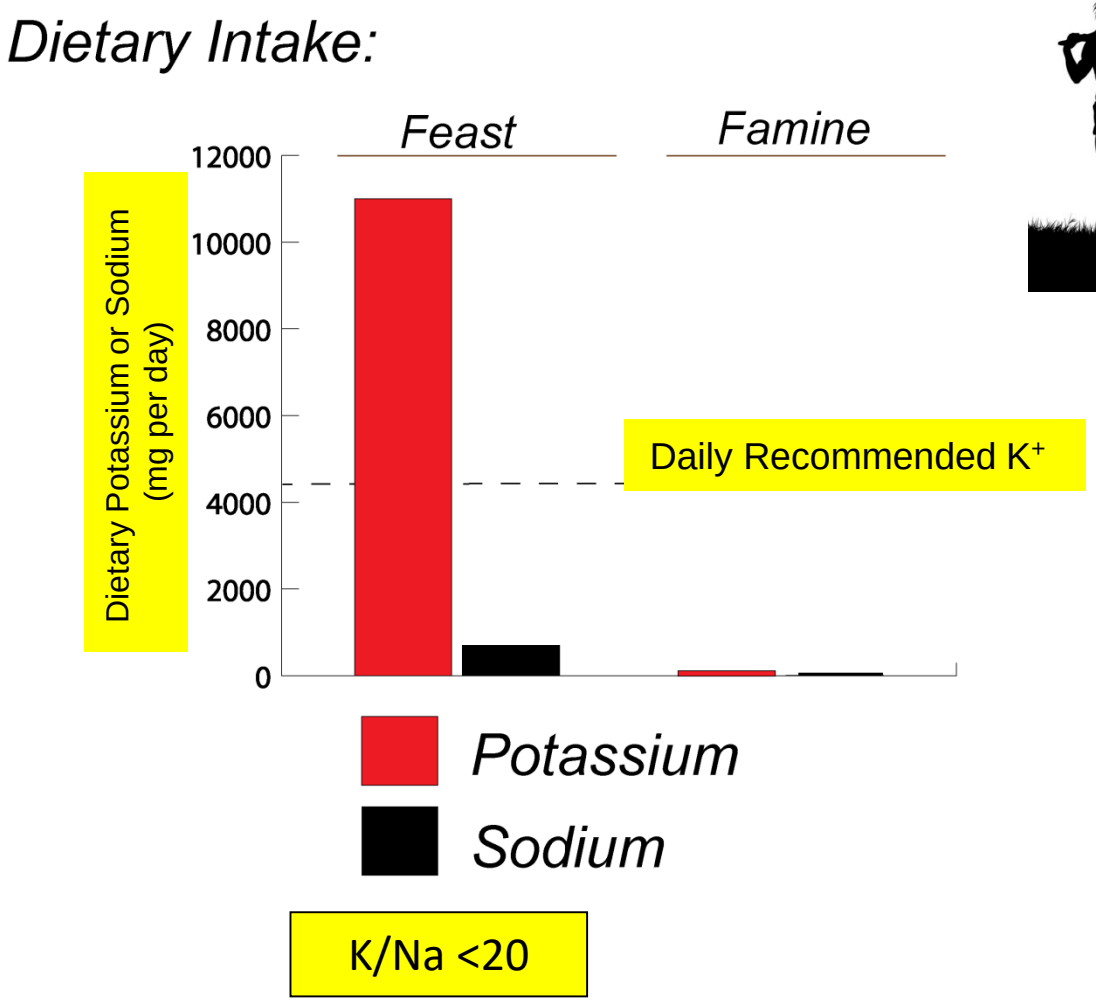
Source WHO
https://www.who.int/news-room/fact-sheets/detail/hypertension

Dietary Changes in human populations



Slide kindly provided by JP Montani

Dietary Potassium Intake in paleolithic ancestors: feast vs fast



- Potassium Switch Best equipped for the "Paleolithic" Diet
- Dietary Potassium Restriction turns the Switch, Causing Urinary Sodium Retention
- Appropriate for a long lasting fast or famine

Slide kindly provided by Paul A Welling

Practical Implications
Potassium Deficiency of The Modern Diet

Paleolithic Vs. Modern Diet

K/Na >20

K/Na <0.8

- Potassium Switch Best equipped for the "Caveman" Diet
- "Feeds the Fire" in Western Sodium Rich Diet: a typical gene-culture-environment mismatch

High dietary sodium in the face of a signal for avid sodium reabsorption feeds the fire of hypertension

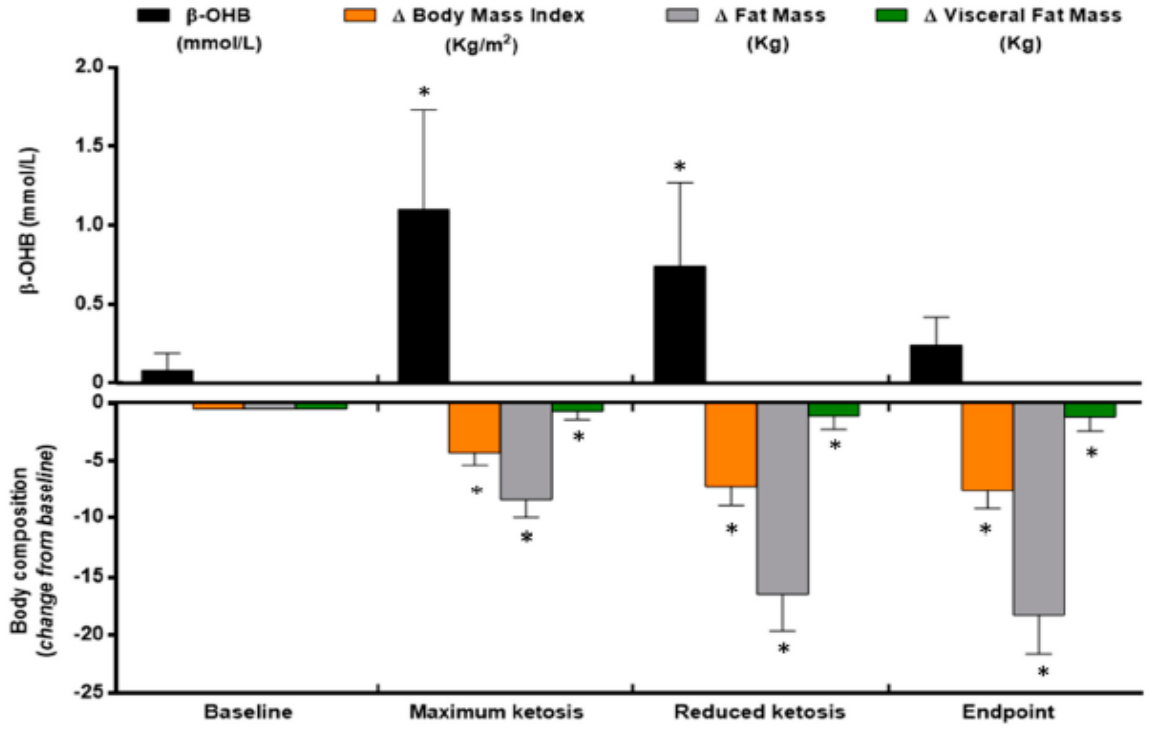
Illustration from From:
Conquering Salt Habit to Reduce Hypertension,
Harvard Medical School Patient Education

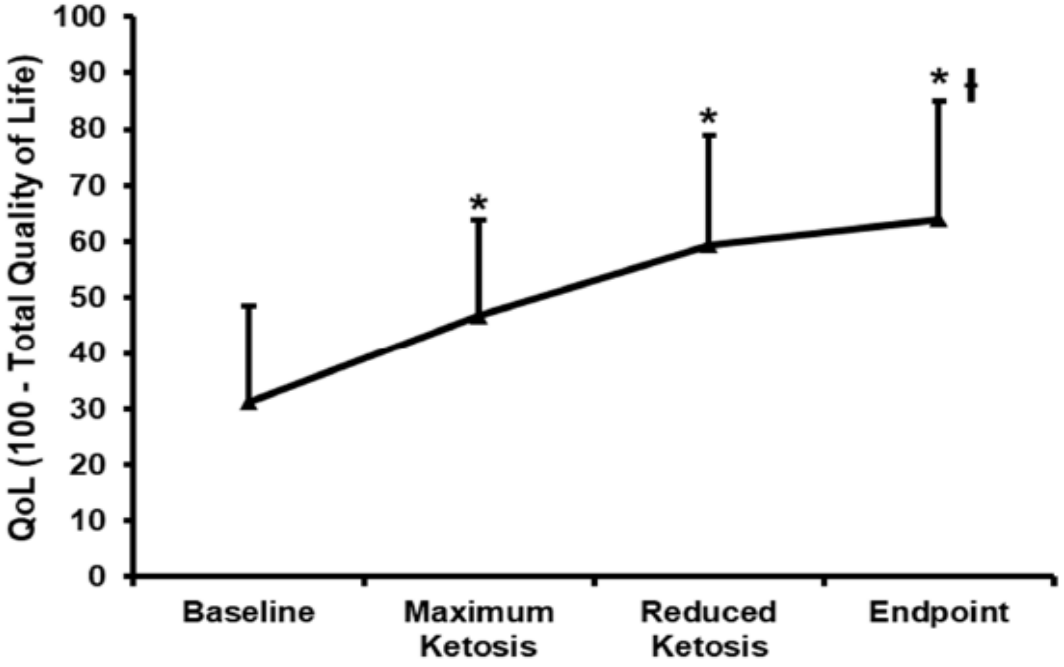
Slide kindly provided by Paul A Welling

Article

Effect of A Very Low-Calorie Ketogenic Diet on Food and Alcohol Cravings, Physical and Sexual Activity, Sleep Disturbances, and Quality of Life in Obese Patients

Ana I. Castro [1,2,†], Diego Gomez-Arbelaez [1,3,†], Ana B. Crujeiras [1,2,†], Roser Granero [2,4], Zaida Aguera [2,5], Susana Jimenez-Murcia [2,5], Ignacio Sajoux [6], Patricio Lopez-Jaramillo [7], Fernando Fernandez-Aranda [2,5,‡] and Felipe F. Casanueva [1,2,*,‡]





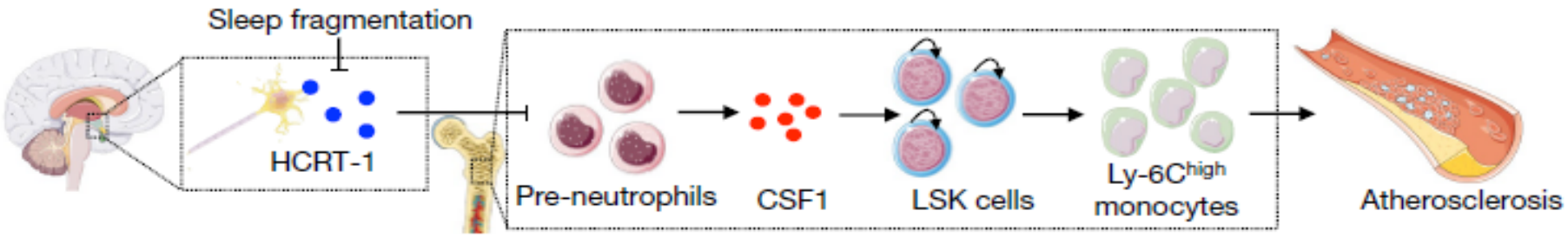
Castro AI, Nutrients 2018

LETTER

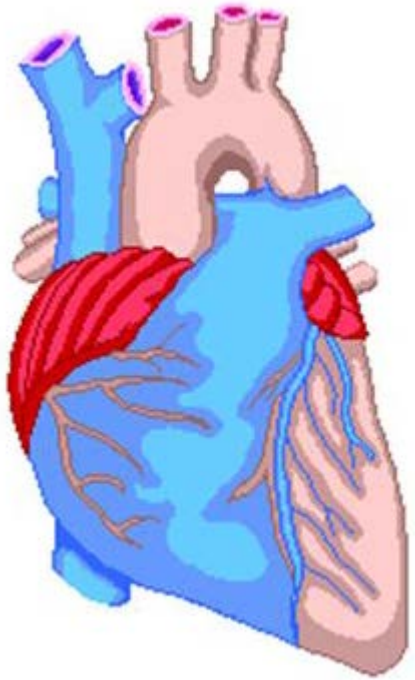
https://doi.org/10.1038/s41586-019-0948-2

Sleep modulates haematopoiesis and protects against atherosclerosis

Cameron S. McAlpine[1], Máté G. Kiss[1,2,3], Sara Rattik[1], Shun He[1], Anne Vassalli[4], Colin Valet[1], Atsushi Anzai[1], Christopher T. Chan[1], John E. Mindur[1], Florian Kahles[1], Wolfram C. Poller[1], Vanessa Frodermann[1], Ashley M. Fenn[1], Annemijn F. Gregory[1], Lennard Halle[1], Yoshiko Iwamoto[1], Friedrich F. Hoyer[1], Christoph J. Binder[2,3], Peter Libby[5], Mehdi Tafti[4], Thomas E. Scammell[6], Matthias Nahrendorf[1,7] & Filip K. Swirski[1,7]*



Cuore e metabolismo energetico



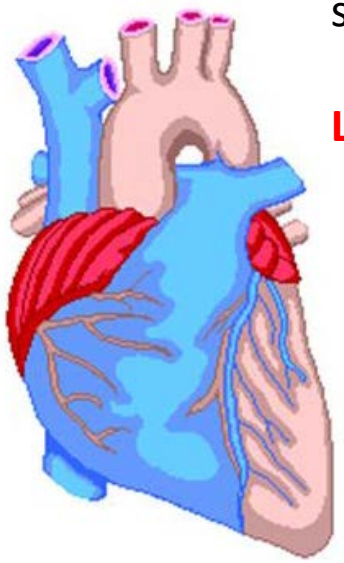
Il cuore è l'organo con il più alto consumo energetico e la più alta richiesta ossidativa dell organismo

Consumo metabolico giornaliero > 400 Kcal/kg; turnover di 6-35 kg ATP/giorno. Il 70% del suo rifornimento energetico deriva dall'ossidazione degli acidi grassi

Elevata flessibilità metabolica in condizioni fisiologiche!
In condizioni patologiche (cardiomiopatia diabetica, scompenso cardiaco, ipertensione) tale flessibilità metabolica viene persa!

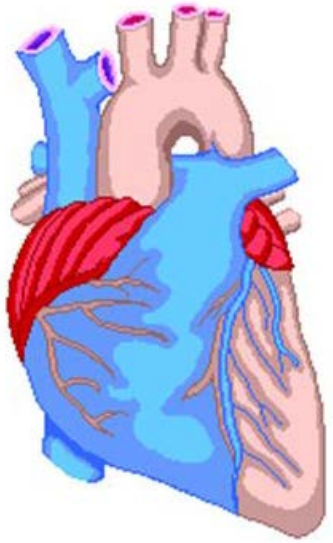
Cuore e metabolismo energetico

In condizioni fisiologiche, il cuore ossida I corpi chetonici in modo proporzionale alla loro produzione, a discapito dell'ossidazione degli acidi grassi e del glucosio.
I corpi chetonici sono più efficienti dal punto di vista energetico, producendo più energia disponibile per la sintesi di ATP a parità di molecole di ossigeno utilizzate.



L'ossidazione dei corpi chetonici limita la produzione di ROS e lo stress ossidativo

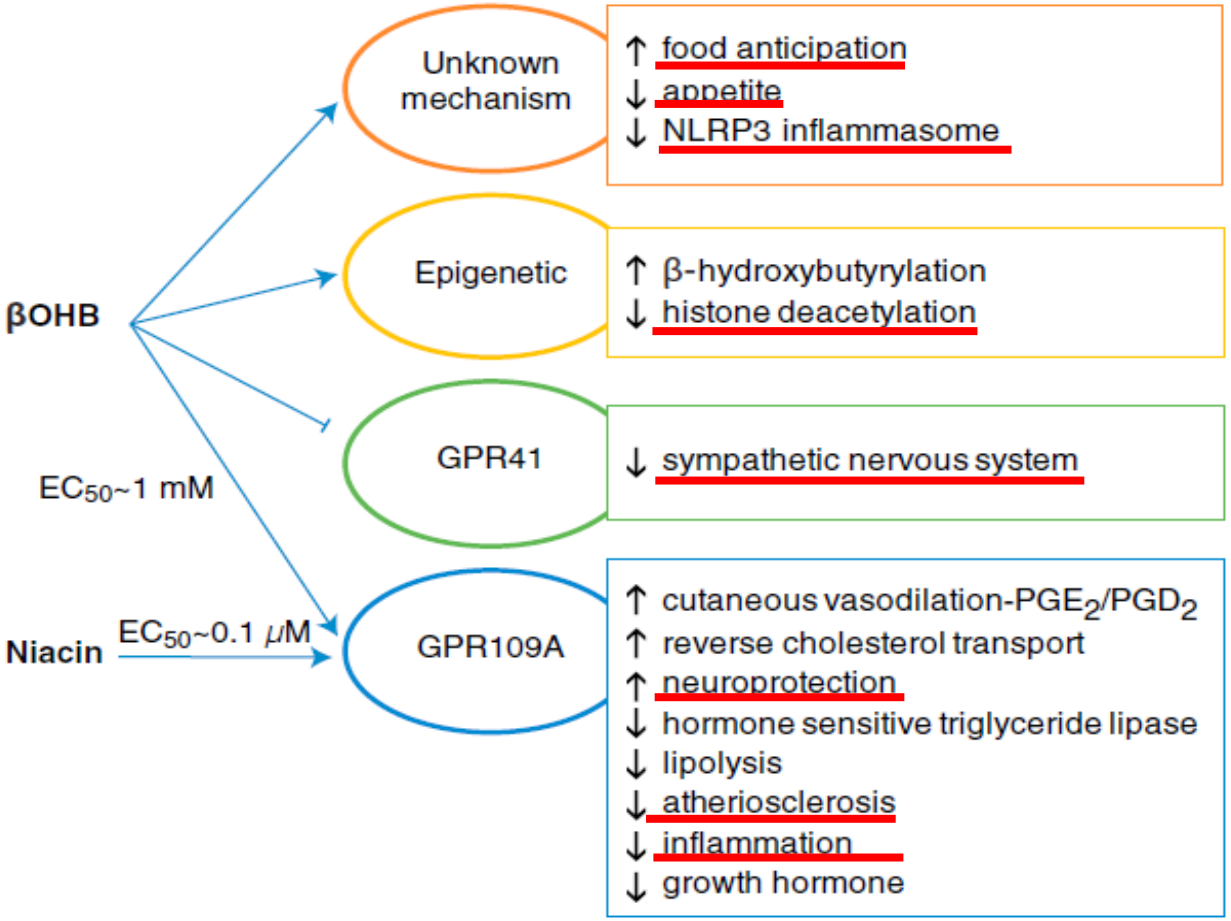
Cuore e metabolismo energetico



Studi preliminari di intervento e studi osservazionali suggeriscono un ruolo favorevole dei corpi chetonici sulla funzione cardiaca. In modelli sperimentali di ischemia e riperfusione, i corpi chetonici hanno mostrato un effetto protettivo, probabilmente legato all'incremento dei mitocondri nel cardiomiocita, o all'upregulation di mediatori cruciali della fosforilazione ossidativa. **Veech (2003) ha dimostrato che 5 mM di corpi chetonici aggiunti ad una soluzione glucosata aumentavano del 25% la contrattilità di un cuore isolato e perfuso con una riduzione del consumo di ossigeno**

Copyright 2001, Hypothesis Paper-Ketone Bodies, Potential Therapeutic Uses by Veech et al. (8) Reproduced by permission of Taylor & Francis, Inc, http:/ /routledge-ny.com.

Azioni biologiche dei corpi chetonici



- Riduzione dell'infiammazione (GPR109A è abbondantemente espresso da monociti e macrofagi)
- Riduzione dell stress ossidativo
- Aumento delle proteine antiossidanti
- Riduzione dell'appetito/aumento della sazietà
- Miglioramento delle proteine mitocondriali

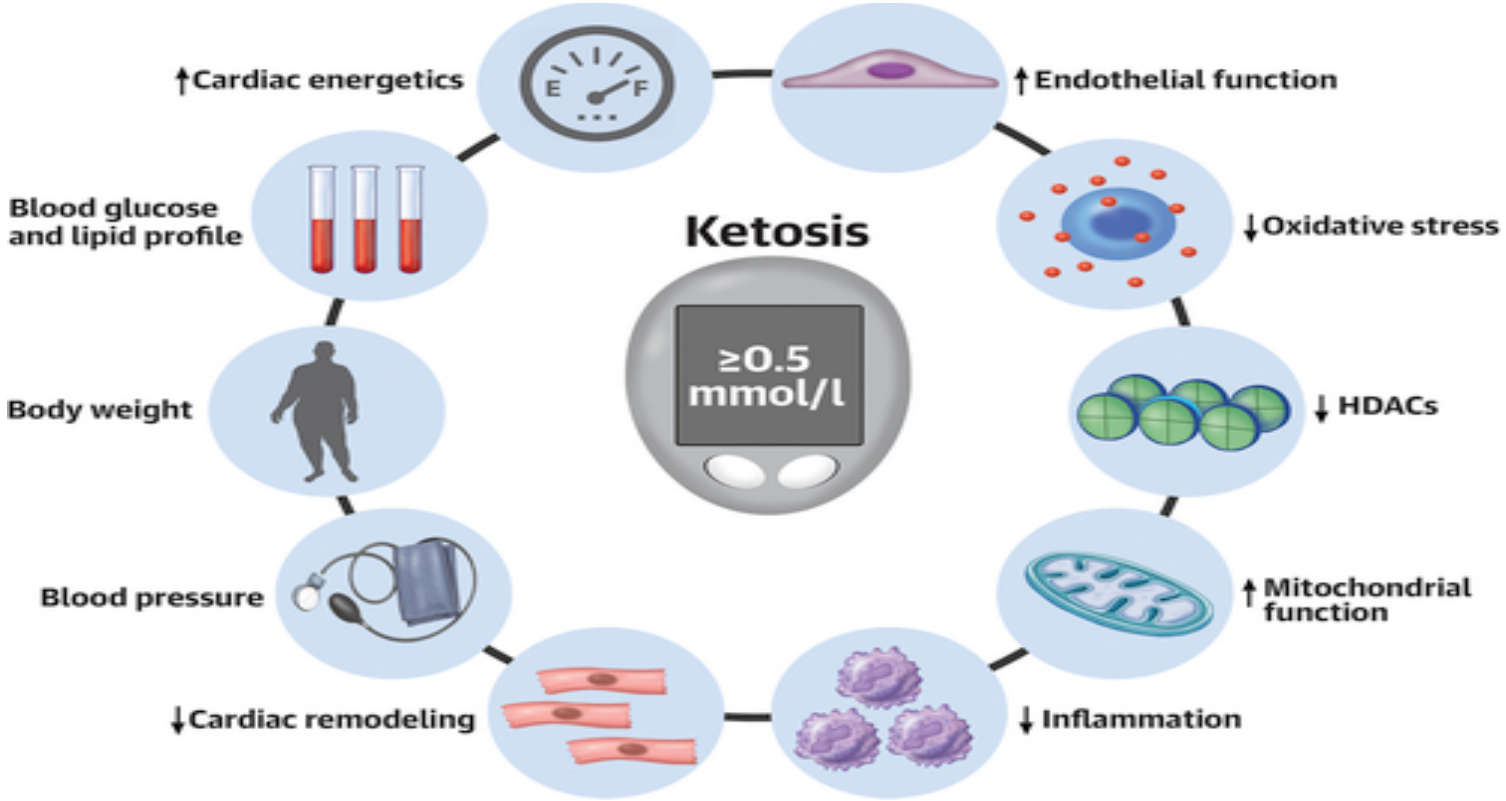
Metodo che può essere applicato in diversi contesti clinici!

Puchalska P and Crawford PA, Cell Metabolism 2017

Therapeutic Potential of Ketone Bodies for Patients With Cardiovascular Disease

JACC Focus Seminar

Salva R. Yurista, MD, PhD,[a] Cher-Rin Chong, PhD,[b,c] Juan J. Badimon, PhD,[d] Daniel P. Kelly, MD,[e] Rudolf A. de Boer, MD, PhD,[a] B. Daan Westenbrink, MD, PhD[a]



Salva R. Yurista et al. *J Am Coll Cardiol* 2021

Prolonged Caloric Restriction in Obese Patients With Type 2 Diabetes Mellitus Decreases Myocardial Triglyceride Content and Improves Myocardial Function

Sebastiaan Hammer, MSc,*† Marieke Snel, MD,‡ Hildo J. Lamb, MD, PhD,†
Ingrid M. Jazet, MD, PhD,‡ Rutger W. van der Meer, MD,† Hanno Pijl, MD, PhD,*
Edo A. Meinders, MD, PhD,‡ Johannes A. Romijn, MD, PhD,* Albert de Roos, MD, PhD,†
Johannes W. A. Smit, MD, PhD*

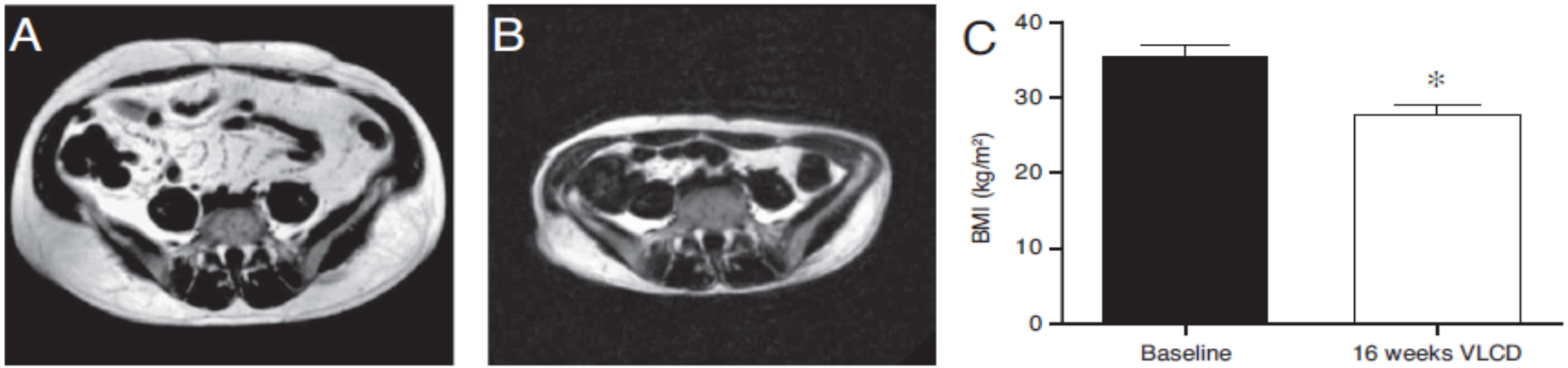


Figure 1 Fat Stores and Body Mass Index

Example of a transverse slice at the level of the 5th lumbar vertebrae showing visceral and subcutaneous fat depots, illustrating the effects of 16 weeks of caloric restriction in the same patient **(A and B)**. Body mass index (BMI) is decreased after prolonged caloric restriction **(C)**. *$p < 0.001$. VLCD = very-low-calorie diet.

Hammer S, J Am Coll Cardiol 2008

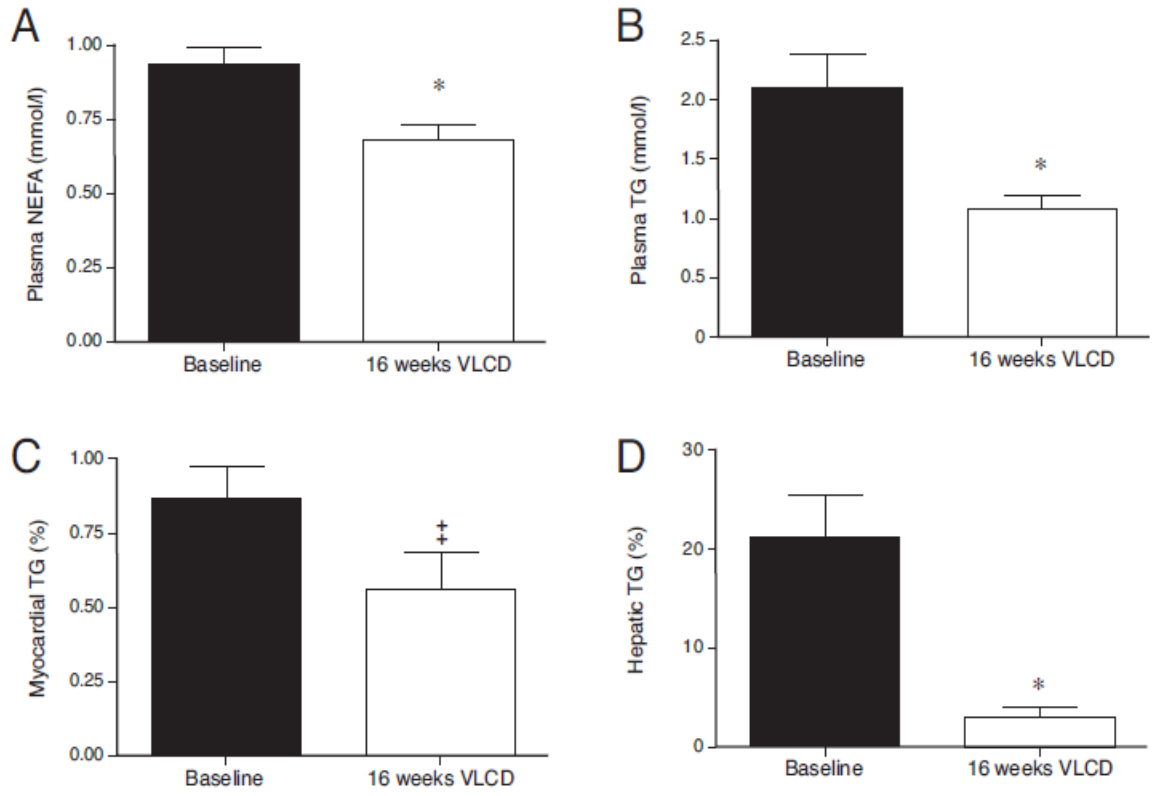


Figure 2 Metabolic Changes at Baseline and After 16 Weeks of VLCD

Changes in plasma NEFA **(A)**, plasma TG levels **(B)**, and myocardial **(C)**, and hepatic **(D)** TG content on prolonged caloric restriction. *$p < 0.001$; †$p < 0.05$. Data are mean ± SEM. NEFA = nonesterified fatty acids; TG = triglyceride; VLCD = very-low-calorie diet.

Table 2 Intraindividual Effects of 16 Weeks of Caloric Restriction on Systolic and Diastolic Function in Obese Patients With T2DM

	Baseline	After 16 Weeks of Caloric Restriction
Systolic blood pressure (mm Hg)	144 ± 8	118 ± 6*
Diastolic blood pressure (mm Hg)	81 ± 2	71 ± 2*
Heart rate (beats/min)	78 ± 3	61 ± 2*
LVEF (%)	57 ± 2	58 ± 2
Stroke volume (ml)	102 ± 6	103 ± 8
Stroke volume index (ml/m^2)	45 ± 2	51 ± 3†
Cardiac output (ml/min)	7,971 ± 601	6,508 ± 401‡
Cardiac index (l/min/m^2)	3.5 ± 0.2	3.2 ± 0.2
LV mass (g)	118 ± 7	99 ± 6*
LV mass index (g/m^2)	53 ± 3	49 ± 3†
ED volume (ml)	177 ± 8	177 ± 11
ED index (ml/m^2)	79 ± 3	88 ± 4†
ES volume (ml)	76 ± 4	74 ± 5
ES index (ml/m^2)	34 ± 2	37 ± 2
E deceleration (ml/s^2 × 10^{-3})	4.04 ± 0.50	4.30 ± 0.42
E/A peak ratio	1.02 ± 0.08	1.18 ± 0.06†
E/Ea	11.9 ± 1.2	11.4 ± 1.5

Conclusions

Prolonged caloric restriction in obese T2DM patients decreases BMI and improves glucoregulation associated with decreased myocardial TG content and improved diastolic heart function. Therefore, myocardial TG stores in obese patients with T2DM are flexible and amendable to therapeutic intervention by caloric restriction.

Hammer S, J Am Coll Cardiol 2008 *

METABOLISM CLINICAL AND EXPERIMENTAL 77 (2017) 65–72

ELSEVIER

Available online at www.sciencedirect.com

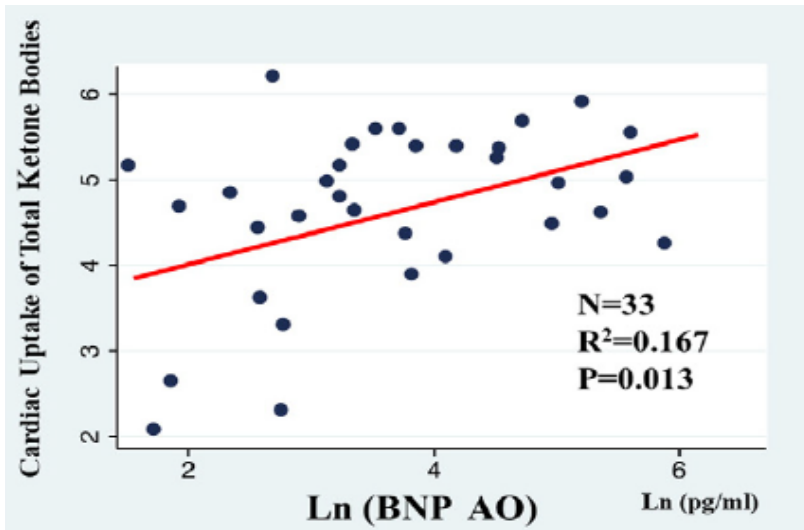
Metabolism

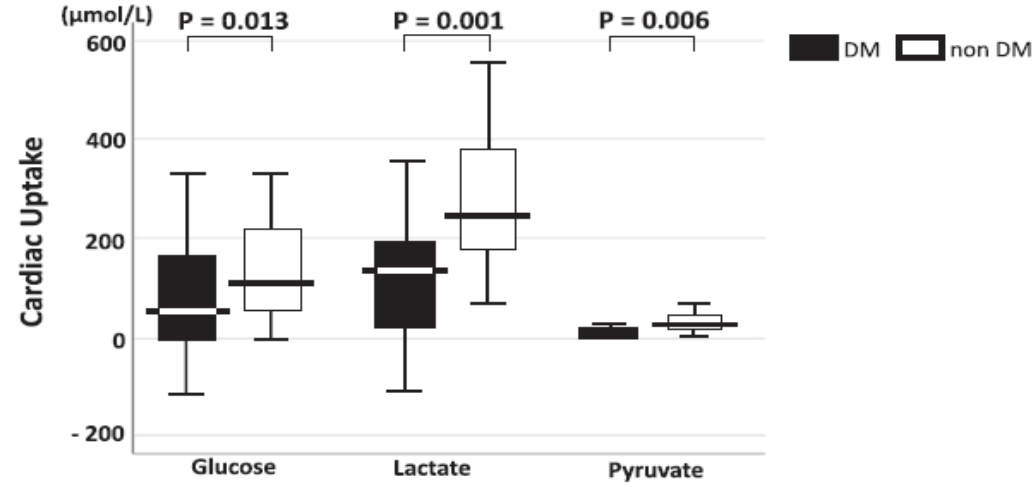
www.metabolismjournal.com

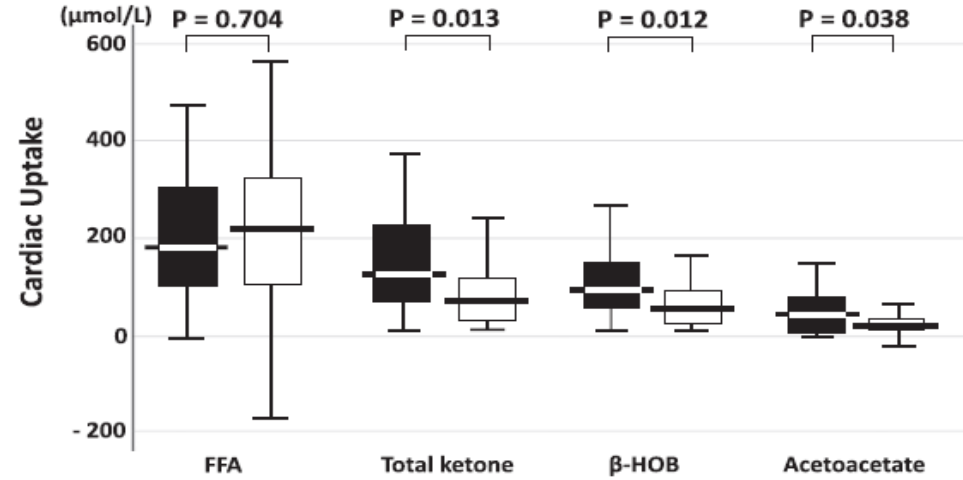
The diabetic heart utilizes ketone bodies as an energy source

Yuji Mizuno[a,*], *Eisaku Harada*[a], *Hitoshi Nakagawa*[b], *Yoshinobu Morikawa*[c], *Makoto Shono*[a], *Fumihito Kugimiya*[a], *Michihiro Yoshimura*[d], *Hirofumi Yasue*[a]

[a] *Division of Cardiovascular Medicine, Kumamoto Aging Research Institute, Kumamoto, Japan*
[b] *First Department of Internal Medicine, Nara Medical University, Nara, Japan*
[c] *Division of Cardiovascular Medicine, Minami-nara General Medical Center, Japan*
[d] *Division of Cardiology, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan*





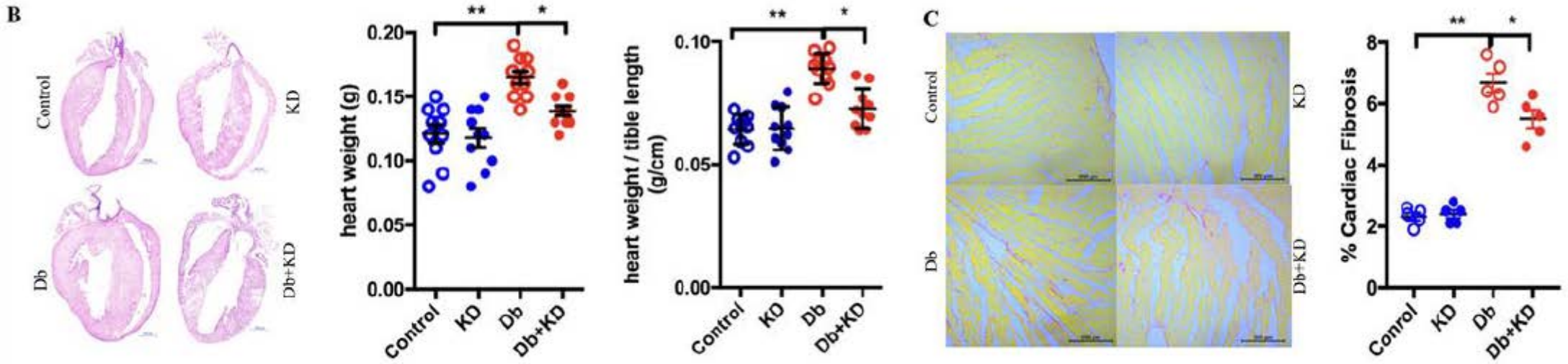


Aging and Disease
www.aginganddisease.org
Volume 11, Number 2; 229-240, April 2020
http://dx.doi.org/10.14336/AD.2019.0510

Original Article

Ketogenic Diet Ameliorates Cardiac Dysfunction via Balancing Mitochondrial Dynamics and Inhibiting Apoptosis in Type 2 Diabetic Mice

Yongzheng Guo[1,#], Cheng Zhang[2,#], Fei-Fei Shang[3], Minghao Luo[1], Yuehua You[1], Qiming Zhai[4], Yong Xia[1,3,5], Suxin Luo[1,*]



Original article

MOLECULAR METABOLISM

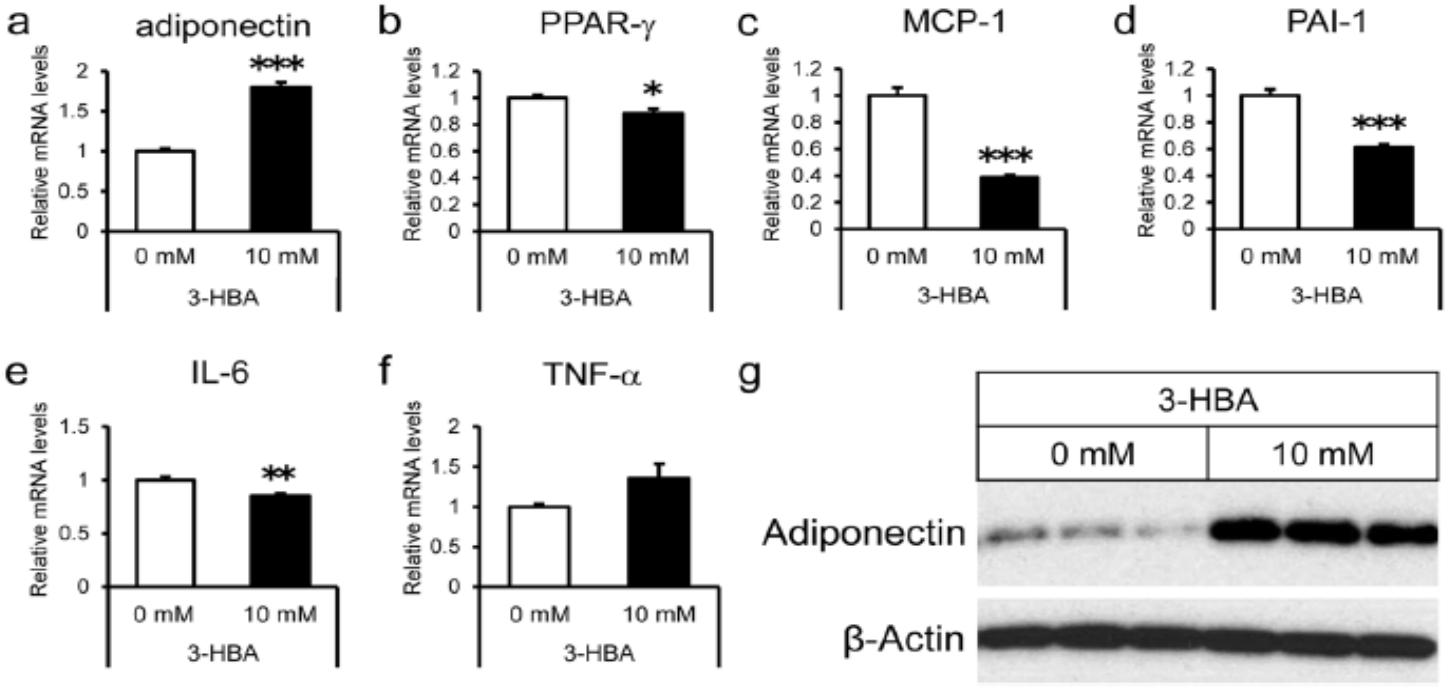
Cardiomyocyte-specific deficiency of ketone body metabolism promotes accelerated pathological remodeling

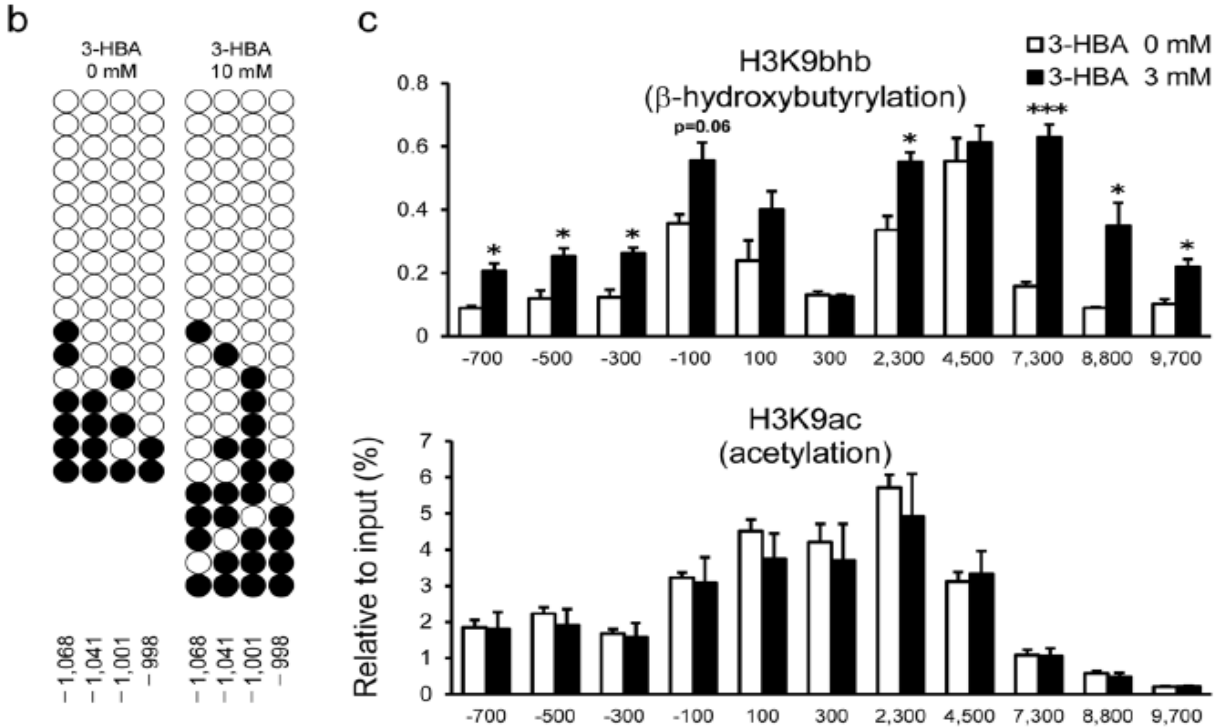
Rebecca C. Schugar [1], Ashley R. Moll [1], D. André d'Avignon [2], Carla J. Weinheimer [1], Attila Kovacs [1], Peter A. Crawford [1,3,*]

Topi con difetto genetico nel metabolismo dei corpi chetonici (succinyl-CoA:3-oxoacid CoA transferase (SCOT) selettivamente nel cardiomiocita mostrano accelerato rimodellamento cardiaco patologico in risposta a danno sperimentale indotto da sovraccarico pressorio

Schugar RC et al. MOLECULAR METABOLISM 3 (2014) 754e769

Azione del 3-HBA sull'espressione di adiponectina di adipociti in coltura



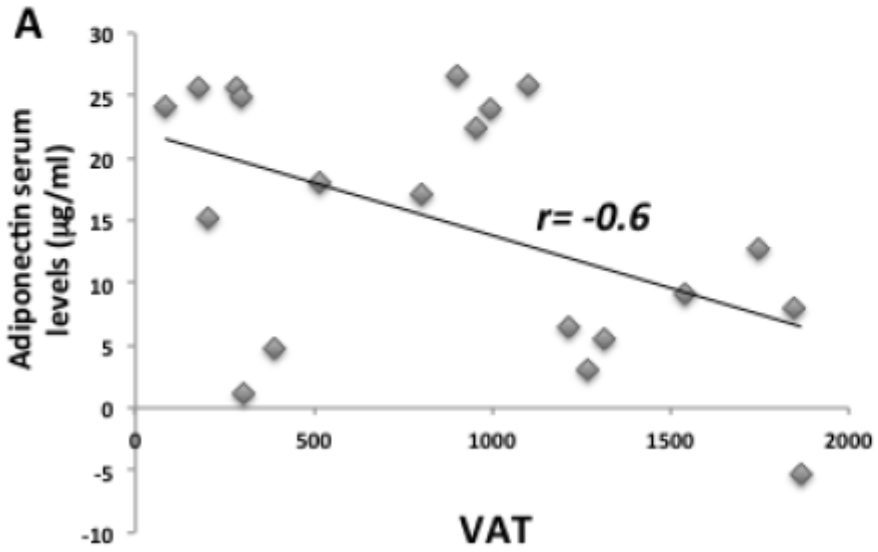


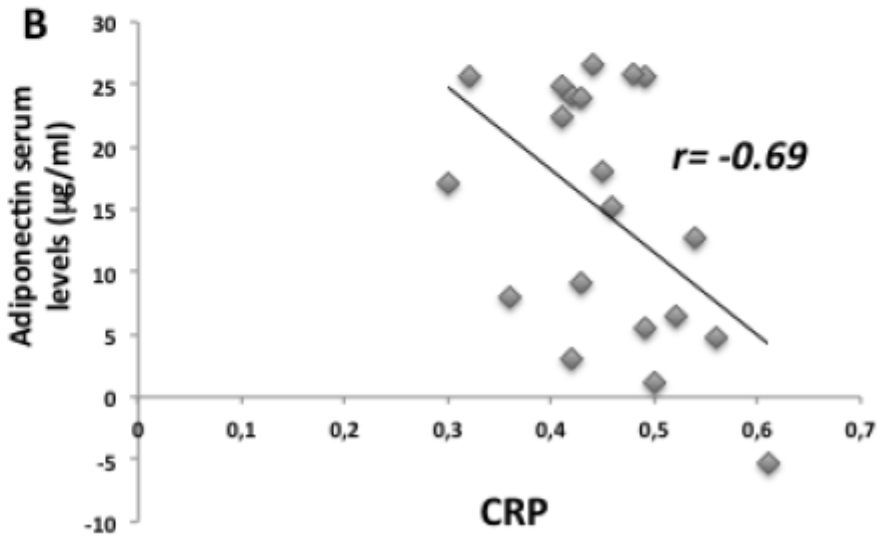
Nishitani S et al. Scientific reports, 2018 – 8:880

Short-Term Physiological Effects of a Very Low-Calorie Ketogenic Diet: Effects on Adiponectin Levels and Inflammatory States

Vincenzo Monda [1,†], Rita Polito [2,3,†], Annarita Lovino [3], Antonio Finaldi [3], Anna Valenzano [3], Ersilia Nigro [2], Gaetano Corso [3], Francesco Sessa [3], Alessio Asmundo [4], Nunzio Di Nunno [5], Giuseppe Cibelli [3] and Giovanni Messina [3,*]

	Adiponectin Levels (μg/mL)		*p*-Value
	Male	Female	
VLCKD obese participants T0	9.23 ± 0.7	12.44 ± 1.07	<0.05
VLCKD obese participants T1	23.67 ± 1.6	27.3 ± 1.33	<0.05





Short-Term Physiological Effects of a Very Low-Calorie Ketogenic Diet: Effects on Adiponectin Levels and Inflammatory States

	VLCKD Obese Participants		*p*-Value
	T0	T1	
Sex male/female	10/10	10/10	
Age	48 ± 8.2	-	ns
Height (m)	1.67 ± 0.1		ns
Weight (kg)	91.33 ± 17.1	78.73 ± 13.3	<0.001
BMI (kg/m^2)	32.19 ± 4.78	27.76 ± 3.6	<0.001
VAT (g)	1541.55 ± 141.6	927.79 ± 104.9	<0.001
FM (g)	39,208.77 ± 1432.5	27,377.03 ± 1217.4	<0.001
FFM (g)	48,789.57 ± 1712.3	48,093.68 ± 1670.6	ns
BMD	1225.57 ± 21.2	1229.31 ± 21.4	ns
Total cholesterol (mg/dL)	220.13 ± 50.7	173.91 ± 32.9	<0.05
HDL (mg/dL)	55.13 ± 11.1	47.76 ± 9.1	ns
LDL (mg/dL)	141.83 ± 36.4	107.57 ± 27.7	<0.05
Triglycerides (mg/dL)	135.54 ± 125.2	83.25 ± 26.1	<0.05
Glycemia (mg/dL)	96.68 ± 4.6	93.09 ± 3.3	<0.05
HGB (g/dL)	14.13 ± 1,3	13.83 ± 0.9	ns
Hba1c (%)	5.65 ± 0.3	5.38 ± 0.3	ns
Insulinemia (µU/mL)	10.53 ± 7.1	5.37 ± 3.7	<0.05
Uric acid (mg/dL)	4.86 ± 1.0	5.27 ± 1.1	ns
Total protein (g/dL)	7.30 ± 0.4	7.13 ± 0.4	ns
AST-GOT (U/L)	21.27 ± 5.9	23.31 ± 11.4	<0.05
ALT-GPT (U/L)	26.51 ± 14.8	26.06 ± 16.2	<0.05
Gamma GT (U/L)	31.19 ± 19.8	15.31 ± 5.4	<0.05
CRP (mg/mL)	0.89 ± 0.1	0.48 ± 0.1	<0.05
Adiponectin (µg/mL)	10.8 ± 1.2	25.55 ± 1.3	<0.001
TNF-α (pg/mL)	345 ± 6.5	278 ± 9.2	<0.05
IL-10 (pg/mL)	117 ± 7	168 ± 8.8	<0.001
IL-6 (pg/mL)	236 ± 4.4	232 ± 5	ns

antioxidants

MDPI

Article

Effects of Very Low Calorie Ketogenic Diet on the Orexinergic System, Visceral Adipose Tissue, and ROS Production

Anna Valenzano [1,†], Rita Polito [1,†], Valentina Trimigno [1], Antonella Di Palma [1], Fiorenzo Moscatelli [1], Gaetano Corso [1], Francesco Sessa [1], Monica Salerno [2], Angelo Montana [2], Nunzio Di Nunno [3], Marinella Astuto [4], Aurora Daniele [5], Marco Carotenuto [6], Giovanni Messina [1], Giuseppe Cibelli [1,*] and Vincenzo Monda [7]

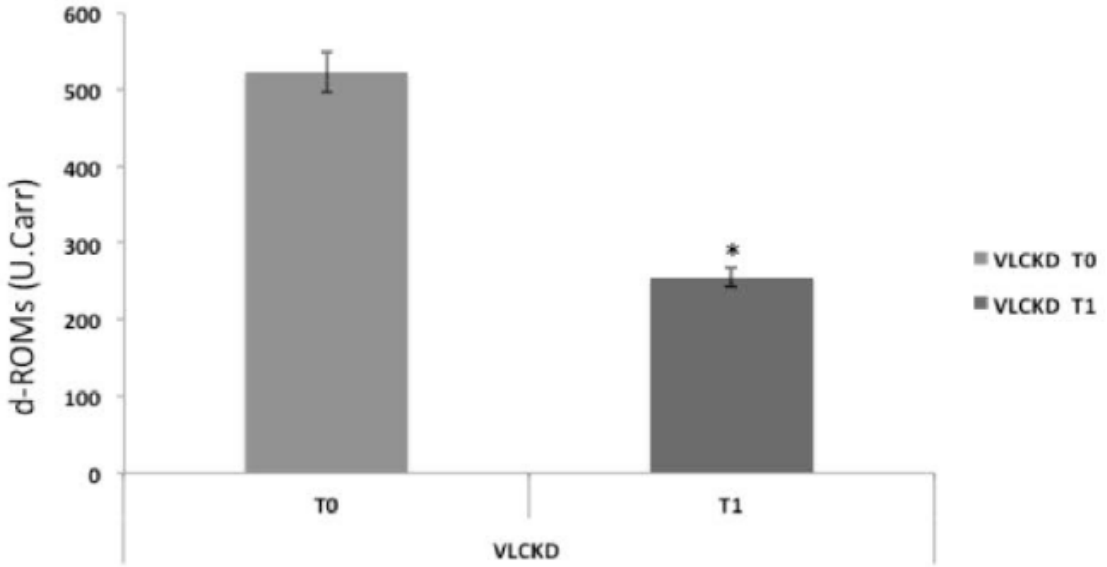


Figure 4. Reactive oxygen metabolite (d-ROM) plasma levels were strongly modified in VLCKD subjects. Reactive oxygen metabolites in the plasma of VLCKD obese subjects before diet were higher than those of VLCKD obese subjects after diet therapy. *: statistically significant difference.

Archives of Biochemistry and Biophysics 662 (2019) 143–150

Contents lists available at ScienceDirect

Archives of Biochemistry and Biophysics

journal homepage: www.elsevier.com/locate/yabbi

The effects of the ketone body β-hydroxybutyrate on isolated rat ventricular myocyte excitation-contraction coupling

Matthew Klos[a,b], Sherry Morgenstern[a], Kayla Hicks[b], Shreyas Suresh[c], Eric J. Devaney[a,b,*]

[a] Department of Pediatric Cardiac Surgery, UH Hospitals Cleveland, Cleveland, OH, 44106, USA
[b] Case Western Reserve University School of Medicine, Cleveland, OH, 44106, USA
[c] Case Western Reserve University School of Graduate Studies, Cleveland, OH, 44106, USA

- βOHB improves single cell excitation-contraction coupling and is protective against hypoxia
- βOHB may be a beneficial adaptation for the heart during periods of nutrient scarcity and or metabolic dysregulation

*

ESC
European Society of Cardiology

European Journal of Heart Failure (2021)
doi:10.1002/ejhf.2278

RESEARCH ARTICLE

Dietary interventions and nutritional supplements for heart failure: a systematic appraisal and evidence map

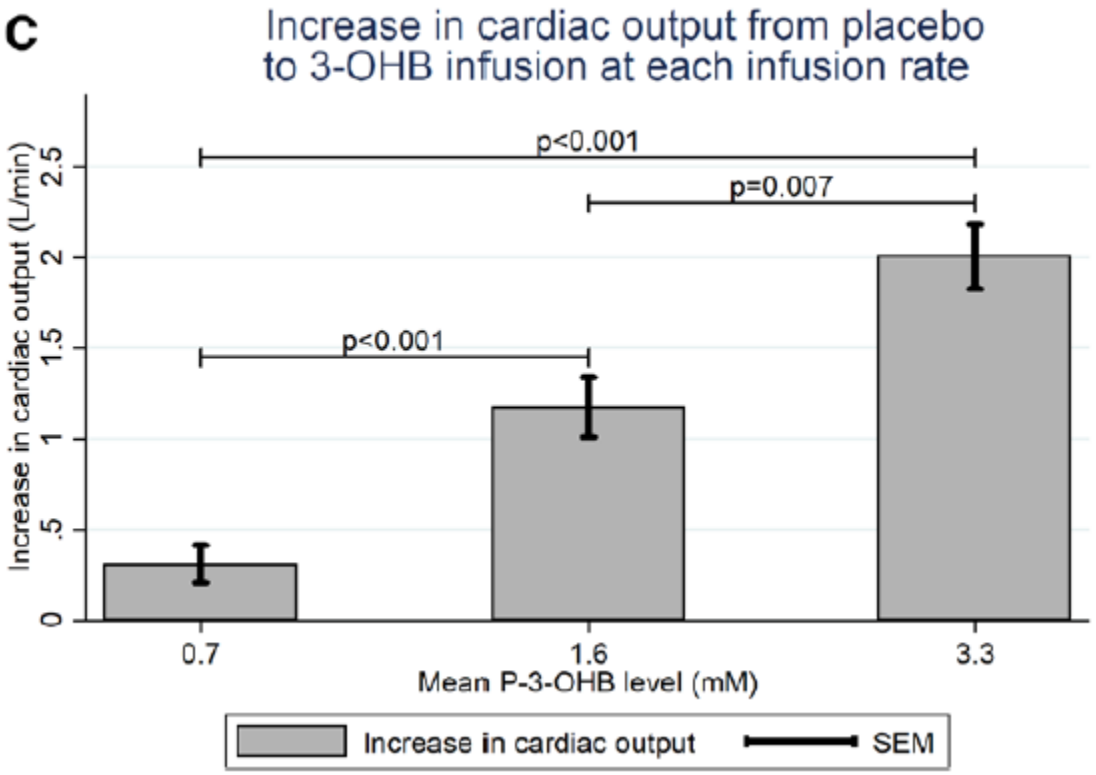
Muhammad Shahzeb Khan[1], Fiza Khan[2], Gregg C. Fonarow[3], Jayakumar Sreenivasan[4], Stephen J. Greene[5], Safi U. Khan[6], Muhammad Shariq Usman[7], Muthiah Vaduganathan[8], Marat Fudim[5], Stefan D. Anker[9], and Javed Butler[1]*

no RCT data exists regarding the impact of other dietary interventions in HF, such as intermittent fasting, ketogenic diet, and the DASH diet.

Circulation

ORIGINAL RESEARCH ARTICLE

Cardiovascular Effects of Treatment With the Ketone Body 3-Hydroxybutyrate in Chronic Heart Failure Patients



Clinical Perspective

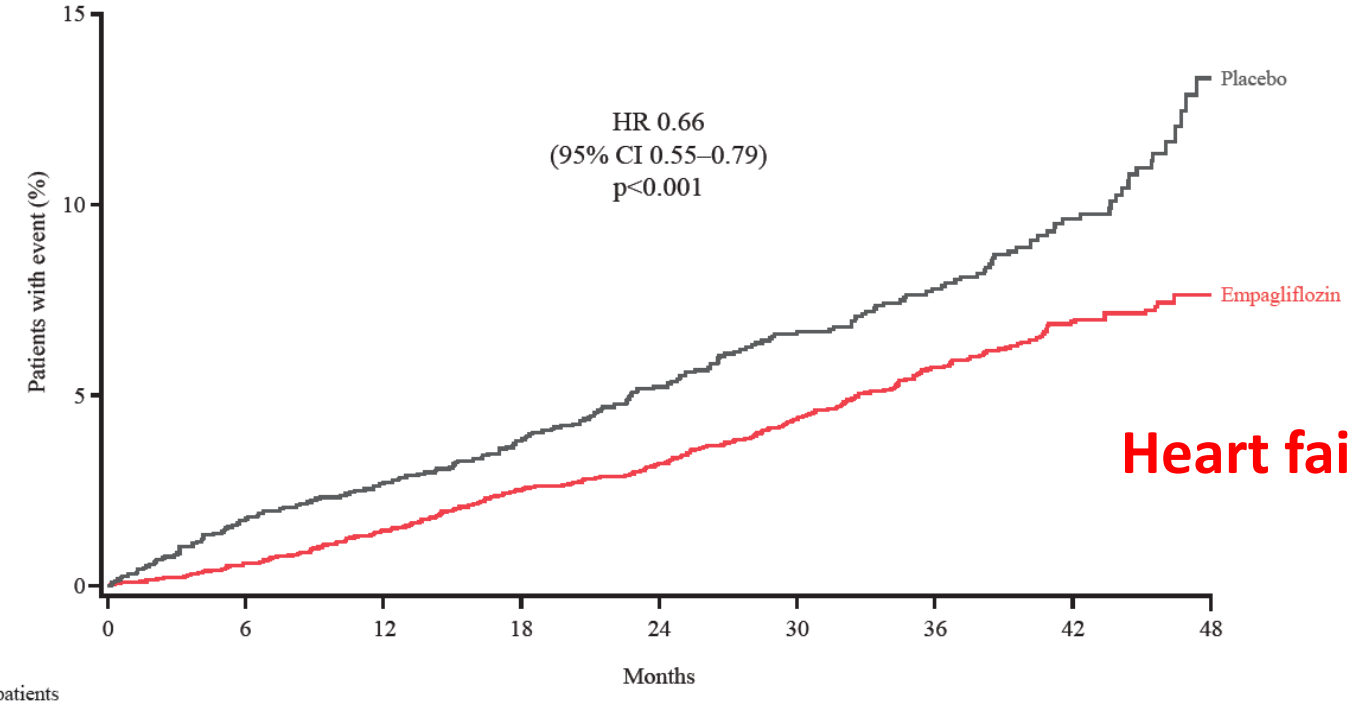
What Is New?

- In patients with heart failure and reduced ejection fraction, infusion of the ketone body 3-hydroxybutyrate increased cardiac output by 2 L/min (40%) with an absolute improvement in left ventricular ejection fraction (8%). The observed effects were accompanied by vasodilation with a resultant stable systemic and pulmonary blood pressure.
- The hemodynamic effects of ketones were dose-dependent and detectable in the physiological concentration range.
- The coupling between myocardial oxygen consumption and cardiac work did not deteriorate despite increased cardiac output.
- The hemodynamic effects of 3-hydroxybutyrate were observed in both heart failure and reduced ejection fraction patients and age-matched volunteers.

What Are the Clinical Implications?

- The current study is the first in man to demonstrate that modulation of circulating ketone levels may represent a novel treatment principle in patients with heart failure.

Heart Failure Outcomes with Empagliflozin in Patients with Type 2 Diabetes at High Cardiovascular Risk: Results of the EMPA-REG OUTCOME® Trial



No. of patients									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Heart failure hospitalisation or CV death

David Fitchett et al. *Eur Heart J* 2016

The NEW ENGLAND JOURNAL of MEDICINE

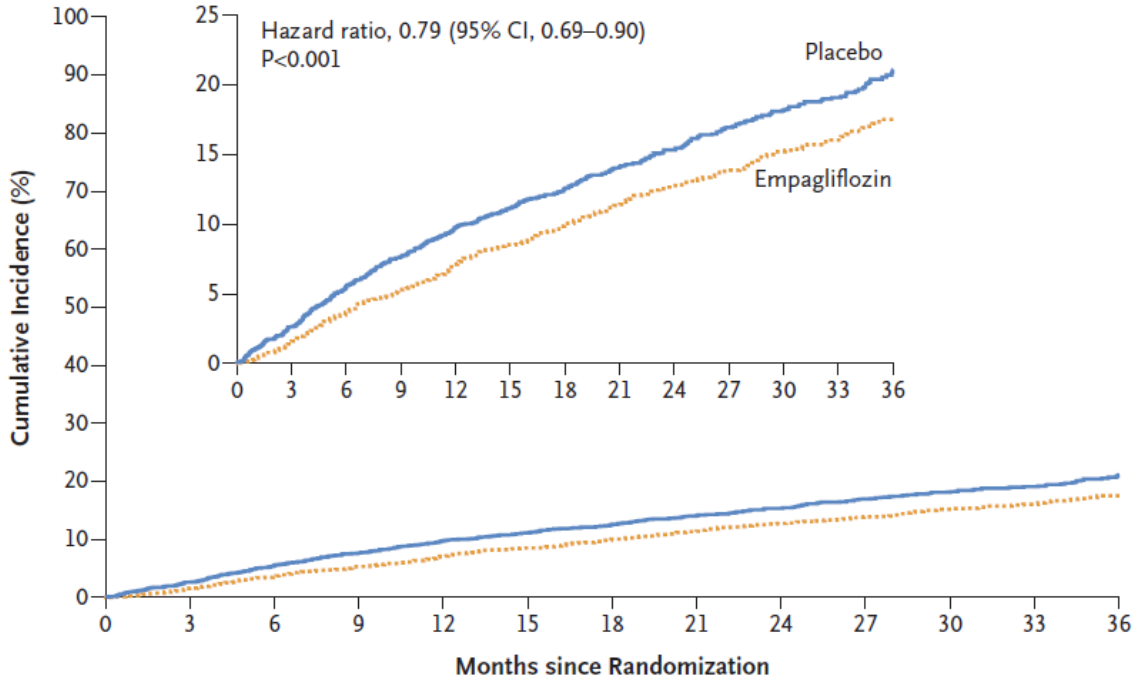
ORIGINAL ARTICLE

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

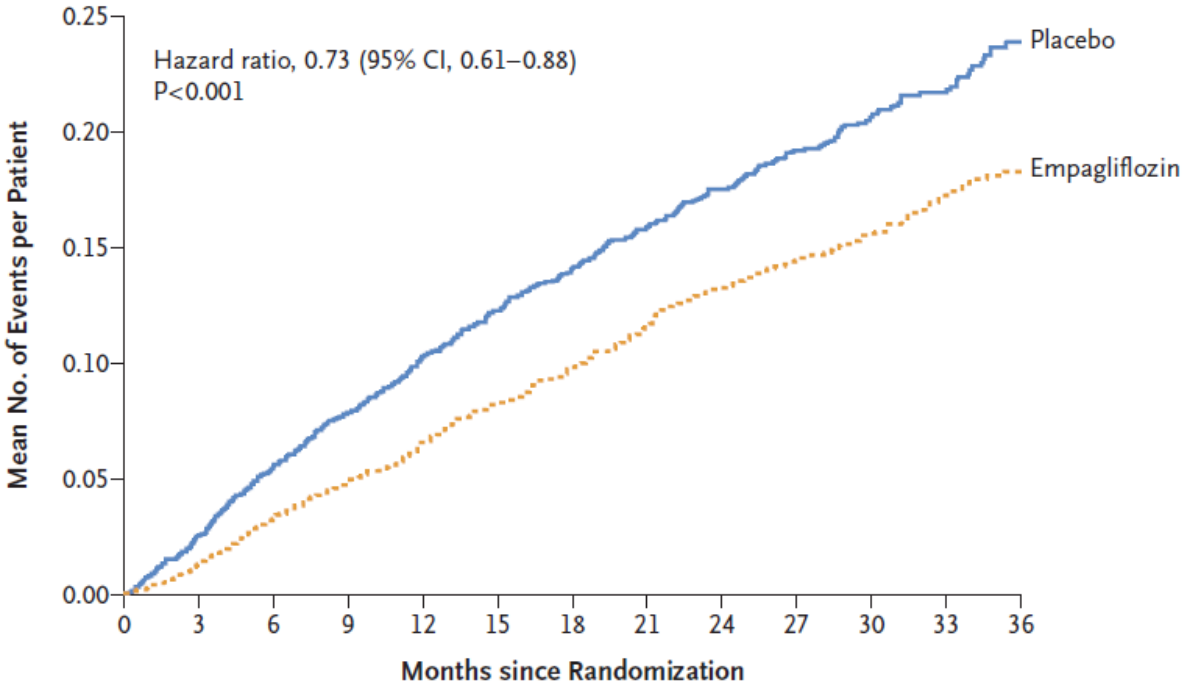
BREAKING NEWS!!!

In patients with heart failure and a preserved ejection fraction, SGLT2 inhibition with empagliflozin led to a 21% lower relative risk in the composite of cardiovascular death or hospitalization for heart failure, which was mainly related to a 29% lower risk of hospitalization for heart failure with empagliflozin

Primary Outcome: a Composite of Cardiovascular Death or Hospitalization for Heart Failure



Secondary Outcome: Hospitalizations for Heart Failure.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

BREAKING NEWS!
Is it because of ketone bodies??

Since SGLT2 receptors are not located in cardiomyocytes, indirect mechanisms, including ketosis, are likely to account for the benefit. SGLT2 inhibitors decrease the insulin to glucagon ratio and increase lipolysis, both of which favor formation of ketones.
In fact, empagliflozin treatment mildly increases BHB levels (0.56 mmol/L in patients with diabetes, 0.27 mmol/L in patient without diabetes) with chronic dosing (28 days). Because SGLT2 inhibitor therapy increases ketone metabolism in animal models of HF, increased circulating levels of ketones may plausibly increase myocardial utilization of ketones. Indeed, the systemic ketosis achieved with SGLT2 inhibitors that decrease HF hospitalization is similar to levels shown to be beneficial in HF

Circulation

NO ACCESS | ARTICLE

Effect of Dapagliflozin on Atrial Fibrillation in Patients with Type 2 Diabetes Mellitus: Insights from the DECLARE-TIMI 58 Trial

Originally published 27 Jan 2020 https://doi.org/10.1161/CIRCULATIONAHA.119.044183

Results: Dapagliflozin reduced the risk of AF/AFL events by 19% (264 versus 325 events, 7.8 versus 9.6 events per 1000 patient-years, hazard ratio 0.81, 95% CI 0.68 to 0.95, P=0.009). The reduction in AF/AFL events was consistent regardless of presence or absence of a history of AF/AFL at baseline

Conclusions: Dapagliflozin decreased the incidence of reported episodes of AF/AFL adverse events in high-risk patients with T2DM. This effect was consistent regardless of the patients' prior history of AF, ASCVD, or HF

HHS Public Access
Author manuscript
Circ Res. Author manuscript; available in PMC 2018 April 28.

Published in final edited form as:
Circ Res. 2017 April 28; 120(9): 1501–1517. doi:10.1161/CIRCRESAHA.117.309732.

Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes

Laila Staerk, MD[1,2,3], **Jason A. Sherer, MD, MPH**[4], **Darae Ko, MD**[2,5,6], **Emelia J. Benjamin, MD, ScM**[2,3,5,6,7], and **Robert H. Helm, MD**[6]

…….Other modifiable risk factors, including sedentary lifestyle, oxidative stress, smoking, obesity, diabetes mellitus, obstructive sleep apnea, and elevated blood pressure predispose to AF and each factor has been shown to induce structural and electrical remodeling of the atria.

Circulation. 2020 June 02; 141(22): 1800–1812. doi:10.1161/CIRCULATIONAHA.119.045033.

Implications of Altered Ketone Metabolism and Therapeutic Ketosis in Heart Failure

Senthil Selvaraj, MD, MA[1], **Daniel P. Kelly, MD**[2], **Kenneth B. Margulies, MD**[1,2,3]

[1]Division of Cardiovascular Medicine, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA

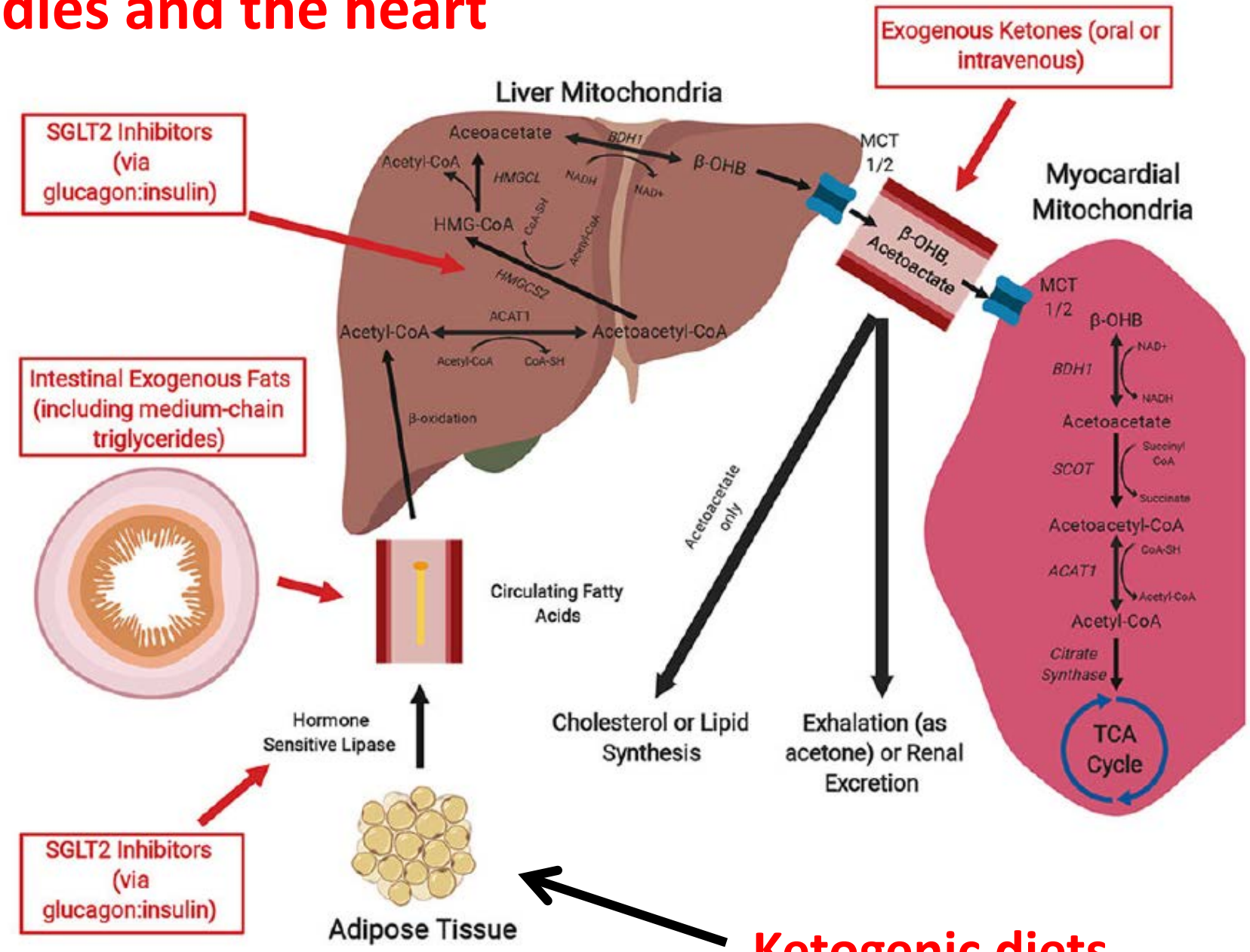
[2]Cardiovascular Institute and Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

[3]Heart Failure and Transplant Program, Perelman School of Medicine, University of Pennsylvania, Translational Research Center, 3400 Civic Center Boulevard, Philadelphia, PA

Open questions:

- Do ketone bodies work as alternate cardiac fuels, vasodilators, and/or via other signaling pathways?
- Will they prove useful for both chronic and acute (boosting short-term activity tolerance or in decompensated heart failure) indications?
- Could peripheral effects of ketosis contribute to improved outcomes in cardiomyopathies?
- How does ketone body supplementation interact with myocardial branched-chain amino acid metabolism (a recently discovered pathway in HF genesis)?

Ketone Bodies and the heart



Ketogenic diets

Adapted from Selveraj S et al. Circulation 2020

Take home messages

- VLCKD rapidly reduce all cardiovascular risks in obese patients, potentially preventing cardiovascular events and improving quality of life in the long term.
- Ketone bodies are a precious source of energy for the heart
- Ketone bodies have promise as a novel therapeutic tool for heart failure and arrhythmias

Thank you!!