International Journal of Biochemistry and Cell Biology 138 (2021) 106050

Contents lists available at ScienceDirect

International Journal of Biochemistry and Cell Biology

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

The ketogenic diet as a therapeutic intervention strategy in mitochondrial disease

Changbo Qu [a,b,c], Jaap Keijer [d], Merel J.W. Adjobo-Hermans [b,c], Melissa van de Wal [b,c], Tom Schirris [c,e], Clara van Karnebeek [c,f], Yihang Pan [a,**], Werner J.H. Koopman [b,c,*]

[a] Tomas Lindahl Nobel Laureate Laboratory, Precision Medicine Research Center, The Seventh Affiliated Hospital of Sun Yat-sen University (SAHSYSU), Shenzhen, 518107, China
[b] Department of Biochemistry (286), Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, the Netherlands
[c] Radboud Center for Mitochondrial Medicine, Radboud University Medical Center, Nijmegen, the Netherlands
[d] Human and Animal Physiology, Wageningen University & Research, Wageningen, the Netherlands
[e] Department of Pharmacology and Toxicology, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, the Netherlands
[f] Department of Pediatrics, Radboud University Medical Center, Nijmegen, the Netherlands

ARTICLE INFO

Keywords:
Mitochondria
Mitochondrial disease
Ketone bodies
Bioenergetics

ABSTRACT

Classical mitochondrial disease (MD) represents a group of complex metabolic syndromes primarily linked to dysfunction of the mitochondrial ATP-generating oxidative phosphorylation (OXPHOS) system. To date, effective therapies for these diseases are lacking. Here we discuss the ketogenic diet (KD), being a high-fat, moderate protein, and low carbohydrate diet, as a potential intervention strategy. We concisely review the impact of the KD on bioenergetics, ROS/redox metabolism, mitochondrial dynamics and mitophagy. Next, the consequences of the KD in (models of) MD, as well as KD adverse effects, are described. It is concluded that the current experimental evidence suggests that the KD can positively impact on mitochondrial bioenergetics, mitochondrial ROS/redox metabolism and mitochondrial dynamics. However, more information is required on the bioenergetic consequences and mechanistic mode-of-action aspects of the KD at the cellular level and in MD patients.

1. Introduction

Mitochondria are double-membrane organelles residing in the cytosol of virtually every eukaryotic cell. Functionally, mitochondria are well-known with respect to their role in ATP generation, although they are also involved in fatty acid oxidation (FAO), reactive oxygen species

Abbreviations: ACA, acetoacetate; AcCoA, acetyl coenzyme A; AMPK, AMP-activated protein kinase; β-HAD, β-hydroxyacyl-CoA dehydrogenase; BHB, β-hydroxybutyrate; C10, decanoic acid; CI-CV, complex I to complex V; CS, citrate synthase; CAT, catalase; ETC, electron transport chain; ETF, electron-transferring flavoprotein; FA, fatty acid; $FADH_2$, flavin adenine dinucleotide; FAO, fatty acid oxidation; FATP, fatty acid transfer protein; FGF21, Fibroblast growth factor 21; GCL, glutamate cysteine ligase; GLUTs, glucose transporters; GPX, glutathione peroxidase; GR, glutathione reductase; GSH, reduced glutathione; GS, glutathione synthase; GSSG, oxidized glutathione; HDACs, histone deacetylases; KD, ketogenic diet; LCAD, long-chain acyl-CoA dehydrogenase; LS, Leigh syndrome; LHON, Leber's hereditary optic neuropathy; LKB1, liver kinase B1; mAD, modified Atkins Diet; MCAD, medium-chain acyl-CoA dehydrogenase; MCT-KD, medium-chain triglyceride ketogenic diet; Mfn2, mitofusin 2; MD, mitochondrial disease; MELAS, Mitochondrial encephalopathy lactic acidosis, and stroke-like episodes; MIM, mitochondrial inner membrane; mPT, mitochondrial permeability transition; mPTP, mitochondrial permeability transition pore; mTORC1, mammalian target of rapamycin complex 1; mtDNA, mitochondrial DNA; NAD^+, oxidized nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyltransferase; nDNA, nuclear DNA; NNT, nicotinamide nucleotide transhydrogenase; NRF2, nuclear factor erythroid-derived 2-related factor 2; OXPHOS, oxidative phosphorylation; PARP, polyADP ribose polymerase; PEO, Progressive external ophthalmoplegia; PI3K, Phosphatidylinositol 3-kinase; PPP, pentose phosphate pathway; PRDX3, peroxiredoxin 3; ROS, reactive oxygen species; SCFAs, short chain fatty acids; SOD, superoxide dismutase; TCA, tricarboxylic acid; TRXR2, thioredoxin reductase 2; $TRXS_2$, oxidized thioredoxin; $TRX(SH)_2$, reduced thioredoxin; UCPs, uncoupling proteins; VLCAD, very-long-chain acyl-CoA dehydrogenase.

* Corresponding author at: Department of Biochemistry (286), Radboud Institute for Molecular Life Sciences (RIMLS), Radboud University Medical Center (Radboudumc), P.O. Box 9101, NL-6500 HB, Nijmegen, the Netherlands.
** Corresponding author at: The Seventh Affiliated Hospital of SunYat-senUniversity, Shenzhen, 518107, China.
E-mail addresses: panyih@mail.sysu.edu.cn (Y. Pan), Werner.Koopman@radboudumc.nl (W.J.H. Koopman).

https://doi.org/10.1016/j.biocel.2021.106050
Received 1 June 2021; Received in revised form 2 July 2021; Accepted 16 July 2021
Available online 21 July 2021

(ROS) generation, calcium (Ca^{2+}) homeostasis and the induction of apoptosis and inflammatory responses (Weinberg et al., 2015; Bulthuis et al., 2019) Glucose often represents the initial substrate for mitochondrial ATP generation (Fig. 1A,B). Following entry into the cell via glucose transporters (GLUTs), glucose enters the glycolysis pathway to generate ATP, reduced nicotinamide adenine dinucleotide (NADH) and pyruvate. Also, other monosaccharides like galactose can enter the glycolysis pathway to form pyruvate, albeit at a much slower rate (Iannetti et al., 2018). Importantly, glycolysis is also interfaced with other key pathways including amino acid metabolism and redox homeostasis (via the pentose phosphate pathway; PPP). When glycolysis is highly active, for instance during mitochondrial dysfunction, excess amounts of pyruvate can be converted into lactate, which is transported out of the cell thereby acidifying the extracellular environment (Fig. 1B).

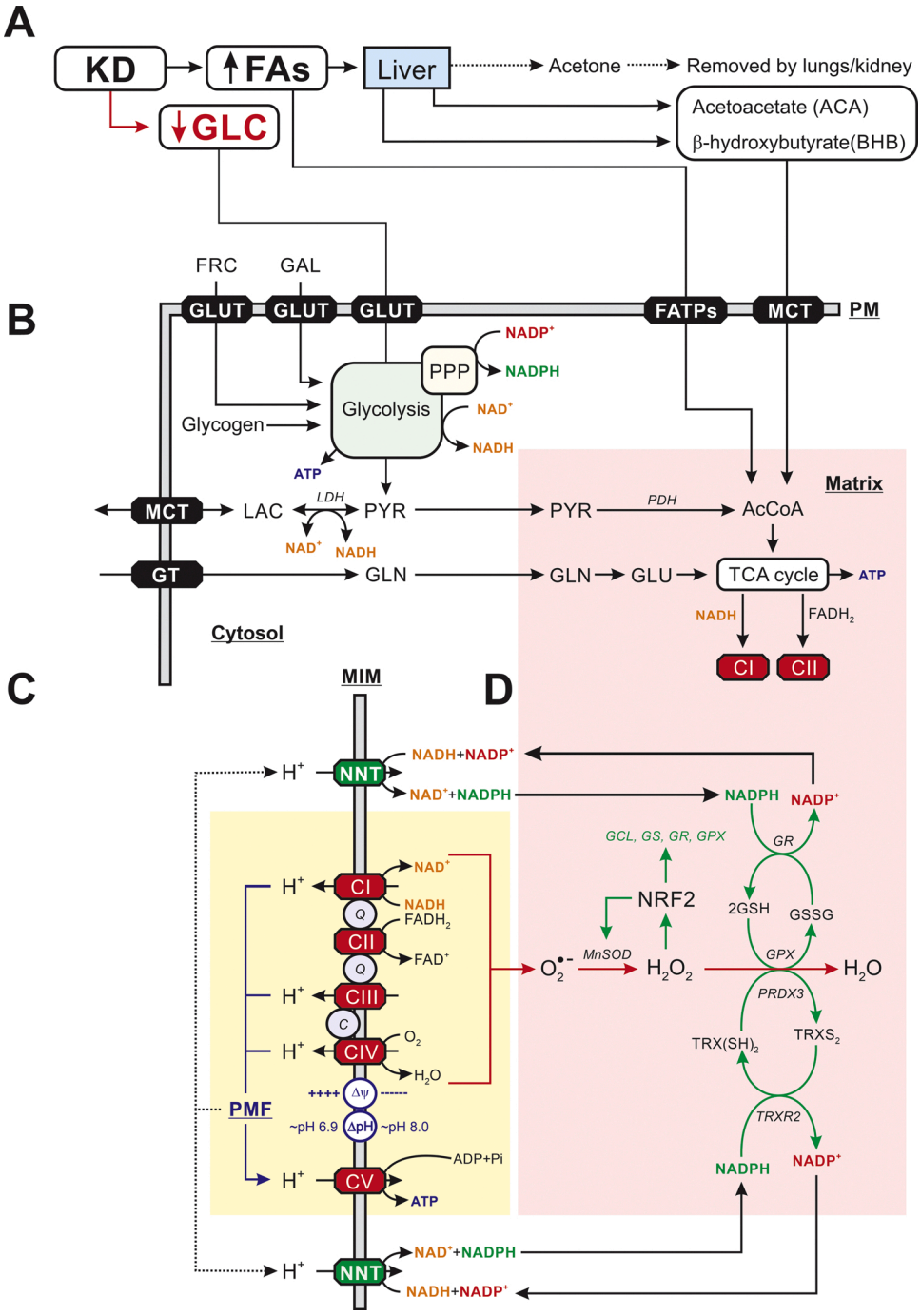

Fig. 1. Impact of the ketogenic diet on cellular energy metabolism and redox homeostasis. (A) The ketogenic diet (KD) contains high and low levels of fatty acids (FAs) and glucose (GLC), respectively. FA uptake stimulates hepatic production of acetoacetate (ACA) and β-hydroxybutyrate (BHB). Mitochondria in extrahepatic cells can take up FAs, ACA and BHB to generate acetyl coenzyme A (AcCoA) and fuel the tricarboxylic acid (TCA) cycle. The latter generates substrates for electron transport chain (ETC) complex I (CI; NADH) and complex II (CII; $FADH_2$). (B) Galactose (GLC) and fructose (FRC) enter the cell via glucose transporters (GLUTs) after which they are converted by the glycolysis pathway into pyruvate (PYR), ATP, NAD^+ and NADH. Glycogen also can reversibly be converted into GLC. Glycolysis is linked to redox metabolism (NADPH, $NADP^+$) via the pentose phosphate pathway (PPP). PYR is either reversibly converted into lactate (LAC), which is released from the cell, or enter mitochondria to be converted into AcCoA. Alternatively, glutamine (GLN) can be taken up by the cell, converted into glutamate (GLU) and enter the TCA cycle. (C) CI and CII accept electrons from NADH and $FADH_2$, respectively, and donate them to Coenzyme Q_{10} ("Q''). The latter molecule transports electrons to CIII, from where they are conveyed to CIV by cytochrome-c ("C''). At CIV, the electrons are donated to molecular oxygen (O_2) to form water. During electron transport, energy is gradually released and used (at CI, CIII, and CIV) to expel protons (H^+) from the mitochondrial matrix across the MIM. As a consequence, an inward-directed trans-MIM proton-motive force (PMF) is generated, consisting of an electrical ($\Delta\psi$) and chemical (ΔpH) component. The PMF is utilized by CV to catalyze the formation of ATP from adenosine diphosphate (ADP) and inorganic phosphate (Pi) by allowing the controlled re-entry of protons into the matrix. (D) Electrons escaping from the ETC complexes can form superoxide ($O_2^{\bullet-}$), which is subsequently converted into hydrogen peroxide (H_2O_2) and water (H_2O). This involves the action of various ROS-detoxifying systems. ROS levels can stimulate gene expression of Nuclear factor erythroid 2-related factor 2 (NRF2), which increases expression of superoxide dismutase 2 (SOD2 or MnSOD), glutamate cysteine ligase (GCL), glutathione synthase (GS), glutathione reductase (GR) and glutathione peroxidase (GPX). This allows a more efficient removal of $O_2^{\bullet-}$ and H_2O_2. Nicotinamide nucleotide transhydrogenase (NNT), provides a functional link between OXPHOS (yellow) and mitochondrial redox homeostasis (pink) by converting NADH + $NADP^+$ into NAD^++NADPH. See main text for details. This figure was compiled using information from: Branco et al., 2016; Koopman et al., 2013; Bulthuis et al., 2019; Morris et al., 2020; Teixeira et al., 2021; Huang et al., 2006.

Normally, the majority of pyruvate enters mitochondria, where it is converted into acetyl coenzyme A (AcCoA) to fuel ATP production by the integrated action of the tricarboxylic acid (TCA) cycle and the oxidative phosphorylation (OXPHOS) system (see below). ATP can also be produced from other substrates like glutamine and FAs entering the TCA cycle (Goodpaster and Sparks, 2017). Importantly, the conversion of pyruvate into AcCoA by pyruvate dehydrogenase (PDH) is irreversible and therefore carbohydrates can be converted into fats but not *vice versa* (Frayn and Evans, 2019). Action of the electron transport chain (ETC) is central to mitochondrial ATP generation (Fig. 1C). The ETC consists of five multi-subunit complexes (CI–CV) and two electron transport molecules, Coenzyme Q_{10} and cytochrome-*c*, which are embedded in the mitochondrial inner membrane (MIM). Collectively, the ETC catalyzes electron transfer from NADH (at CI) and reduced flavin adenine dinucleotide ($FADH_2$; at CII) via Coenzyme Q10 to CIII (Fig. 1C). From thereon, cytochrome-*c* transports electrons to CIV where they are donated to molecular oxygen (O_2). ETC action is linked to ATP production by the F_oF_1-ATPase (CV) by a chemiosmotic coupling mechanism (Mitchell and Moyle, 1967). This involves the ETC-mediated creation of an inward-directed trans-MIM proton motive force. The latter consists of a chemical (ΔpH) and electrical component (Δψ), which drive CV-mediated proton reentry into the mitochondrial matrix and thereby ATP generation. Importantly, electrons can also enter the ETC via alternative pathways that are often tissue-specific. These pathways include electron donation to Coenzyme Q_{10} by glycerol-3-phosphate dehydrogenase, dihydroorotate dehydrogenase and the electron-transferring flavoprotein (ETF)-ubiquinone oxidoreductase (Koopman et al., 2010). Cellular ATP generation is highly flexible and can rapidly switch from mitochondrial OXPHOS- to glycolysis-mediated ATP production when the former pathway is impaired (Liemburg-Apers et al., 2015, 2016). In addition to ATP generation, ETC action also sustains virtually all other mitochondrial functions including metabolite/ion exchange and protein import (Bulthuis et al., 2019). Moreover, mitochondria can produce reactive oxygen species (ROS) as "by-products" of ETC action, in particular during pathological conditions (Murphy, 2009). These ROS can act as messenger molecules in physiological cell control and induce antioxidant signaling (Fig. 1D), but, when reaching too high levels, can induce oxidative stress (Halliwell and Gutteridge, 2015). Under non-pathological conditions too high ROS levels are prevented by the action of various interlocked antioxidant pathways including the nicotinamide nucleotide transhydrogenase (NNT), glutathione (GSH), glutathione peroxidase (GPX) and superoxide dismutase (SOD) enzymes (Fig. 1D).

2. The KD impacts on mitochondrial energy metabolism

The ketogenic diet (KD) is a high-fat, moderate protein, and low-carbohydrate diet that exists in various formulations including: (**1**) the "classical" KD, (**2**) the "medium-chain triglyceride" (MCT-KD), and (**3**) the less restrictive "modified Atkins diet" (mAD). For the classical KD, the ratio of fat to carbohydrate and protein is 4:1 (4 g of fat for every 1 g of protein plus carbohydrate), which reduces carbohydrate intake (Dhamija et al., 2013). Relative to the classical KD, the MCT-KD results in a more efficient generation of ketone bodies, which provide an additional energy source for extrahepatic tissues, (Augustin et al., 2018). The mAD mimics the classical KD but is a more palatable diet with a 1:1 ratio of fat to carbohydrates and protein (Olgac et al., 2020). Functionally, the KD mimics a metabolic state of fasting and/or caloric restriction/starvation, during which the body shifts from carbohydrate metabolism (*e.g.* glucose, galactose) to fat metabolism, leading to enhanced FAO, gluconeogenesis and ketogenesis. These processes mainly occur in the liver (Fig. 1A) and lead to production of ketone bodies, which enter the blood stream (Morris et al., 2020). The generated ketone bodies consist of acetone (largely removed by lung/kidney action), acetoacetate (ACA) and β-hydroxybutyrate (BHB). The latter represents the major circulating form of ketone bodies (Jensen et al., 2020). In extrahepatic cells, FAs, ACA and BHB enter the mitochondrial matrix, where they are converted into AcCoA that fuels the TCA cycle (Yang et al., 2019). The KD alters gut microbiome composition (Paoli et al., 2019) by increasing the amount of "good bacteria" (*Akkermansia, Bacteroidetes, Firmicutes, Muciniphila, Lactobacillus*), which generate short-chain FAs (SCFAs) like acetate, propionate and butyrate. In parallel, the KD decreases pro-inflammatory "bad bacteria" (*Desulfovibrio, Turicibacter*). With respect to mitochondrial energy metabolism, gut microbiota can release metabolites that directly affect ETC function and mitochondrial ATP production. For instance, hydrogen sulfide produced by intestinal bacteria can inhibit mitochondrial CIV or serve as an alternative ETC electron donor (Szabo et al., 2014). In addition, microbiota-produced butyrate significantly increased mitochondrial oxygen consumption during oxidative stress conditions (Clark and Mach, 2017). The KD and low-carbohydrate diet also functionally upregulate bioenergetic pathways (Miller et al., 2018): (**1**) the OXPHOS system (CI, CII, CIII, CIV, CV and cytochrome-*c*), (**2**) the TCA cycle (citrate synthase, isocitrate dehydrogenase, malate dehydrogenase), (**3**) FAO (carnitine palmitoyltransferase, medium-chain acyl-CoA dehydrogenase/MCAD, long-chain acyl-CoA dehydrogenase/LCAD, very-long-chain acyl-CoA dehydrogenase/VLCAD, β-hydroxyacyl-CoA dehydrogenase/β-HAD), and (**4**) ketolysis (β-hydroxybutyrate dehydrogenase). In a neuronal context, the MCT-KD (*i.e.* decanoic acid or C10) stimulated the astrocyte-neuron lactate shuttle (Augustin et al., 2018). The latter mediates neuronal lactate import (produced in astrocytes), to drive the formation of pyruvate for mitochondrial ATP generation (Magistretti and Allaman, 2018). In addition, BHB has been shown to suppress microglial activation, which is a hallmark of brain pathology (Dheen et al., 2007; Ghosh et al., 2018).

3. The KD impacts on mitochondrial redox metabolism

Evidence was provided that the KD reduces oxidative stress, potentially mediated by activation of nuclear factor erythroid-derived 2-related factor 2 (NRF2; Yarar-Fisher et al., 2021). The latter acts as a key controlling factor in antioxidant responses (Fig. 1D) and mitohormesis (Wallace et al., 2010; Achanta and Rae, 2017; Teixeira et al., 2021). Alternatively, KD-fed mice displayed lower ROS levels in brain relative to standard diet-fed controls. Mechanistically, it is suggested that KD may diminish ROS production by increasing the expression and activity of mitochondrial uncoupling proteins (UCPs; Sullivan et al., 2004). In a mouse model of ischemic stroke, combined ACA/BHB injection increased the NAD^+/NADH ratio relative to vehicle-treated control animals (Yin et al., 2015). Relevant in the context of this review, NAD^+ is generated by CI and the NNT and functionally links mitochondrial bioenergetics with ROS/redox homeostasis (Fig. 1C,D). NAD^+ is a substrate of various other enzymes including polyADP ribose polymerase (PARP), cyclic ADP ribose synthetases, and Sirtuin (SIRT) deacetylases, involved in mitochondrial redox metabolism (Cantó et al., 2015; Katsyuba and Auwerx, 2017). Moreover, BHB treatment activates AMP-activated protein kinase (AMPK), which is a major regulator of cellular bioenergetics and the activity/abundance of nicotinamide phosphoribosyltransferase (NAMPT), a key enzyme in the NAD^+ salvage pathway (Bae et al., 2016; Han et al., 2016).

4. The KD impacts on mitochondrial dynamics and mitophagy

To maintain a healthy mitochondrial population and network structure, mitochondria are motile and undergo continuous cycles of fission and fusion (Archer, 2013). Aberrations in mitochondrial structure were observed in a large variety of human diseases including MD (Bulthuis et al., 2019). It was found that expression of the mitochondrial fusion protein Mitofusin 2 (Mfn2) is required for adaption to a high-fat diet (Liesa and Shirihai, 2013). Moreover, *in vivo* evidence suggests that the KD reduces mitochondrial fission and thereby improves

mitochondrial function in the heart of Type 2 diabetic mice (Guo et al., 2020). It was also demonstrated that BHB stimulates mitochondrial elongation in cultured cells (Santra et al., 2004) and ameliorates mitochondrial morphology aberrations in mouse brain and muscle (Li et al., 2018; Ahn et al., 2020). Mitochondrial dynamics is crucial for the selective removal of damaged mitochondria by mitochondria-specific autophagy "mitophagy" (Kluge et al., 2013). With respect to MD, evidence was provided that defective mitochondria with high levels of mutated mtDNA can be selectively removed by mitophagy (Suen et al., 2010), and that the expression level of the mitophagy regulator gene BNIP3 is significantly increased in the liver of KD-fed mice, suggesting potential mitophagy activation (Newell et al., 2016).

5. Application of the KD in MD patients, animal models and MD patient-derived cells

Current evidence suggests that 1136 human gene products are mitochondrially localized (Rath et al., 2021). A previous inventory demonstrated that mutations in 265 of these genes were linked to human disease (Koopman et al., 2012), which was increased to more than 340 during the last decade (Gusic and Prokisch, 2021). For the sake of brevity, we here will primarily focus on mutations in genes encoding mitochondrial OXPHOS subunits. Genetically, 92 different genes encoding these subunits have been described (Koopman et al., 2013). Mutations in 81 of these genes have been linked to primary OXPHOS disorder (Frazier et al., 2019). In case of CI, CIII, CIV and CV, these mutations can be either nuclear DNA (nDNA)- or mitochondrial DNA (mtDNA)-encoded, whereas for CII these mutations all originate from the nDNA. Dietary intervention is frequently used for symptomatic management of MD patients, as these diets are readily available and their (patient-specific) application diminishes the requirement for pharmaceutical prescription (Gorman et al., 2016). The KD was originally developed in the 1920s for treating epilepsy (Kang et al., 2006). Although limited experimental data is available, the effect of the KD has been evaluated in various MD and MD-related (OXPHOS deficiency) models (Table 1). Using diverse readouts, positive effects of the KD were described in case reports of human patients with Björnstad syndrome, MD, PDH deficiency, Alpers-Huttenlocher syndrome, progressive ophthalmoplegia, Ohtahara syndrome and mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). In addition, (transient) positive effects were reported in patients with epilepsy and ETC defects. The latter included, children with glucose transporter type 1 deficiency syndrome, children with myoclonic-astatic epilepsy and adults with mitochondrial myophathy and progressive external ophthalmoplegia (PEO). In animal models, phenotypic improvement by the KD was demonstrated in mice with mitochondrial myopathry, CI deficiency, CIII deficiency and mitochondrial pyruvate carrier deficiency, as well as in flies with mitochondrial encephalomyopathy. Finally, studies with cell models of MELAS, Leigh syndrome (LS), Kearns-Sayre syndrome (KSS) and Leber's hereditary optic neuropathy (LHON), revealed positive effects of the KD on mtDNA copy number (MELAS), CI stability (MELAS), citrate synthase activity (LS), FA metabolism (LS), catalase (CAT) activity, oxidative stress (LS), and mtDNA mutational load (LHON).

6. Adverse effects of the KD

In addition to the potentially positive effects described in the previous sections the KD can also display detrimental effects. For instance, the effect of ketone bodies appears to be concentration dependent, as exemplified by the observation in mice that high BHB levels can induce minor damage to blood-brain barrier integrity (Orhan et al., 2016). A recent study showed that feeding KD exacerbated spongiosis and gliosis in a mouse model of mitochondrial spongiotic brain disease (Ignatenko et al., 2020). Furthermore, due to the chemical properties of ketone bodies, the KD induced blood acidosis in rats after 60 days (Arsyad et al.,

Table 1
Effect of the ketogenic diet in selected models of mitochondrial dysfunction.

Model	Treatment and effects	Reference
Patients		
CASE REPORT: 7-year-old female with Björnstad syndrome and BCS1L-related mitochondrial disease (BCS1L is implicated in CIII biogenesis).	mAD with 30−40 g/day carbohydrates [1500 kcal/day], 10% of energy from carbohydrates, 25% from protein and 65% from fat. Blood ketone levels of 2−4 mM were achieved. mAD improved hair growth. After 4 months no improvement of hearing. Hair was lost again 6 months after cessation of the diet.	Della Marina et al., 2020
CASE REPORT: 3-year-old female with MD (mutation m.5559A > G in the mt-tRNA^{Trp} gene)	High-fat KD in combination with antioxidant supplementation improved neurologic status and heart parameters.	Deberles et al., 2020
CASE REPORT: 3-year-old boy with pyruvate dehydrogenase deficiency	Seizure frequency was reduced and psychomotor development improved.	Di Pisa et al., 2012
CASE REPORT: 31-month-old female with Alpers-Huttenlocher syndrome	KD containing 4 parts fat:1 part each of carbohydrate and protein. Clinical improvement, dramatic electroencephalogram improvement	Joshi et al., 2009
CASE REPORT: 7-year-old male who presented at the age of 7 months with progressive ophthalmoplegia and later developed cerebellar ataxia, spasticity, and dystonia (*NDUFV1* mutation).	Seemingly improved the oculomotor palsy but did not correct other neurologic symptoms.	Laugel et al., 2007
CASE REPORT: 3-month-old female with Ohtahara syndrome and CI deficiency.	Partial control of seizures after consuming classic KD with mitochondrial cocktail (coenzyme Q_{10} 5 mg/kg/day, thiamine 5 mg/kg/day, L-carnitine 100 mg/kg/day, rivoflavin 5 mg/kg/day, vitamin C 50 mg/kg/day, vitamin E 200 IU/day, and vitamin B complex) supplementation.	Seo et al., 2010
CASE REPORT: 22-year-old female with MELAS (m.3260A > G)	A modified KD and magnesium were introduced, leading to seizure freedom despite development of a new stroke-like lesion. A decrease in frequency of stroke-like episodes was observed.	Steriade et al., 2014
Fourteen children with epilepsy and ETC defects	KD with 4:1 lipid to nonlipid ratio (% by weight), but without nitial fasting and fluid restriction. Seven patients became seizure-free after commencing the classic KD, 3 of whom successfully completed the diet without relapse.	Kang et al., 2007
Five adults with MM/PEO	mAD induced progressive muscle pain, leakage of muscle enzymes leading to premature discontinuation of the diet. Follow-up after 2 years suggests activation of muscle regeneration.	Ahola et al., 2016
Eleven children with myoclonic-astatic epilepsy	KD induced a > 50 % reduction in seizures in over half of the children.	Caraballo et al., 2006
Six Japanese males (7–16 years old) with glucose	mAD markedly decreased epileptic seizures and other paroxysmal events in all	Ito et al., 2011

(*continued on next page*)

Table 1 (*continued*)

Model	Treatment and effects	Reference
transporter type 1 deficiency syndrome	patients. In addition, an improvement in motivation and cognitive function was observed.	
Animal models		
Mouse with MM	An *ad libitum* KD slowed down disease progression.	Ahola-Erkkilä et al., 2010
Harlequin mouse with CI deficiency	High fat diet improved neurodegenerative symptoms.	Schiff et al., 2011
Mice with CIII deficiency (*Bcs1l* mutant)	Classic KD delayed liver fibrosis and inhibits stellate cell activation and hepatic progenitor cell response.	Purhonen et al., 2017
Drosophila model of mitochondrial encephalomyopathy	KD reduced seizure recovery time and severity of seizure phenotype.	Fogle et al., 2016
Mice with mitochondrial pyruvate carrier deficiency	Progressively developing cardiac dilation and contractile dysfunction was completely reversed.	McCommis et al., 2020
Cell models		
SH-SY5Y cybrid cells modeling MELAS (m.3260A > G; 98.6 % mutant load).	DMEM medium containing: "low" glucose (0.5 g/L), 1% glutamine, 50 μg/ml uridine, 5 mM ACA and 5 mM BHB. mtDNA copy number was increased but the mutant load was not changed (no heteroplasmy shift) after treatment with ketone bodies.	Frey et al., 2017
Primary fibroblasts from six LS patients (*NDUFV1*, *NDUFV2*, *NDUFS3*, *NDUFS4* mutation). Rotenone treatment (CI inhibitor) was also used.	DMEM medium containing 25 mM glucose, 1 mM pyruvate, 4 mM glutamine and 50 mg/l uridine, to which was added: 250 μM C10, 5 mM BHB or 5 mM ACA. 6 days treatment. C10 increased CS activity in 50 % of patients in a PPAR-γ-mediated manner. C10 increased FA metabolism, CAT activity and decreased oxidative stress. Not all cell lines responded to C10.	Kanabus et al., 2016
Cybrid cell lines modeling LHON	Treatment with ketone bodies reduced the percentage of the m.13094 T > C heteroplasmic mutation. This treatment also increased the mtDNA levels of the m.11778 G > A mitochondrial genotype.	Emperador et al., 2019
A cloned heteroplasmic cell line modeling Kearns–Sayre syndrome	Treatment with KD for 5 days increased the proportion of wild-type mtDNA from 13 % to ~22 % and improved mitochondrial protein synthesis.	Santra et al., 2004

2020). In this context, too high ketone body plasma concentrations were associated with adverse outcomes, whereas lower levels were beneficial (Nasser et al., 2020). Moreover, gastrointestinal disorders, such as diarrhea, were also frequently observed (Kang et al., 2004). Although it is unclear whether application of the KD directly increases the incidence of cardiovascular disease, a 25-year follow-up study in a large cohort, suggested that a low-carbohydrate diet is associated with increased mortality (Nasser et al., 2020). The KD was also demonstrated to increase cardiac fibrosis potentially by BHB-induced effects on the Sirtuin 7 promotor (Xu et al., 2021). Moreover, KD treatment was associated with mild carnitine depletion (Berry-Kravis et al., 2001), progressive bone mineral content loss (Bergqvist et al., 2008) and kidney stone formation (Kielb et al., 2000). In case of MD, treatment of MM/PEO patients with the mAD induced progressive muscle pain and leakage of muscle enzymes. These effects lead to premature termination of the diet. However, follow-up analysis after 2 years suggested that muscle regeneration occurred in the MM/PEO patients (Ahola et al., 2016).

7. Summary and future perspectives

Evidence obtained in various cellular and organismal models, supports the conclusion that the KD affects mitochondrial bioenergetics, mitochondrial ROS/redox metabolism, and mitochondrial dynamics. Previous analysis of LS patient cells suggests that several of these parameters are disturbed in MD and therefore might constitute potential targets for intervention (Koopman et al., 2012, 2013; Koopman et al., 2016). However, the information in the previous section illustrates that our current understanding of the bioenergetic consequences and mechanistic aspects of the KD in MD patients is still insufficient. As a first step towards addressing this problem, MD patient-derived cells constitute an easily accessible model system that can be analyzed with respect to the above and additional parameters (*e.g.,* oxygen consumption, ROS/redox state, mitochondrial dynamics, cell viability). To allow proper analysis of these cell models, it is crucial to apply KD-mimicking culture media with respect to incubation time, refreshment regimen, substrate concentrations (*e.g.,* glucose, galactose, pyruvate, glutamine, lactate, FAs), and FA and/or ketone body composition (*e.g.,* C8, C10, BHB). This requires quantitative information on glucose, FA, and BHB blood levels in human subjects during KD treatment. The serum level of fibroblast growth factor 21 (FGF21) has been proposed as a biomarker of muscle-manifesting mitochondrial respiratory chain deficiency (Suomalainen et al., 2011), as well as mitochondrial translation and mtDNA maintenance disorders (Lehtonen et al., 2016). Importantly, FGF21 is a regulator of energy homeostasis (Fisher and Maratos-Flier, 2016) and promotes ketone body utilization in neurons through AMPK activation (Katsu-Jiménez and Giménez-Cassina, 2019). Though still controversial (Badakhsi and Jin, 2020), FGF21 might constitute a biomarker in MD patients to evaluate KD effects. In addition, analysis of serum acylcarnitine and amino acid profiles at different time point during KD treatment could be useful to predict the effectiveness of KD (Hung et al., 2021). We conclude that the potential benefits of the KD were observed under specific conditions in various models. This suggests that different mitochondrial diseases might require different ketogenic diets. Therefore, integrated efforts at the clinical and mechanistic level are required to better understand KD mode-of-action.

Declaration of Competing Interest

WJHK is a scientific advisor of Khondrion B.V. (Nijmegen, The Netherlands). This company was not involved in the writing of the manuscript nor in the decision to submit the manuscript for publication.

Acknowledgements

The project of Dr. Qu at the Radboud University Medical Center is supported by The International Exchange Fellowship Program of the Sun Yat-sen University, China, the "Sanming Project of Medicine" in Shenzhen to Y. Pan (No. SZSM201911003), and the Research Start-up Fund of the Seventh Affiliated Hospital of Sun Yat-sen University to C. Qu (ZSQYRSFPD0028). We apologize for not including various studies due to space limitations.

References

Achanta, L.B., Rae, C.D., 2017. β-Hydroxybutyrate in the brain: One Molecule, multiple mechanisms. Neurochem. Res. 42 (1), 35–49.

Ahn, Y., Sabouny, R., Villa, B.R., Yee, N.C., Mychasiuk, R., Uddin, G.M., et al., 2020. Aberrant mitochondrial morphology and function in the BTBR mouse model of autism is improved by two weeks of ketogenic diet. Int. J. Mol. Sci. 21 (9), 3266.

Ahola, S., Auranen, M., Isohanni, P., Niemisalo, S., Urho, N., Buzkova, J., et al., 2016. Modified Atkins diet induces subacute selective ragged-red-fiber lysis in mitochondrial myopathy patients. EMBO Mol. Med. 8 (11), 1234–1247.
Ahola-Erkkilä, S., Carroll, C.J., Peltola-Mjösund, K., Tulkki, V., Mattila, I., Seppänen-Laakso, T., Oresic, M., et al., 2010. Ketogenic diet slows down mitochondrial myopathy progression in mice. Hum. Mol. Genet. 19 (10), 1974–1984.
Archer, S.L., 2013. Mitochondrial dynamics - mitochondrial fission and fusion in human diseases. N. Engl. J. Med. 369 (23), 2236–2251.
Arsyad, A., Idris, I., Rasyid, A.A., Usman, R.A., Faradillah, K.R., Latif, W.O.U., et al., 2020. Long-term ketogenic diet induces metabolic acidosis, anemia, and oxidative stress in healthy wistar rats. J. Nutr. Metab. 2020, 3642035.
Augustin, K., Khabbush, A., Williams, S., Eaton, S., Orford, M., Cross, J.H., et al., 2018. Mechanisms of action for the medium-chain triglyceride ketogenic diet in neurological and metabolic disorders. Lancet Neurol. 17 (1), 84–93.
Badakhsi, Y., Jin, T., 2020. Current understanding and controversies on the clinical implications of fibroblast growth factor 21. Crit. Rev. Lab Sci. 31, 1–30.
Bae, H.R., Kim, D.H., Park, M.H., Lee, B., Kim, M.J., Lee, E.K., et al., 2016. β-Hydroxybutyrate suppresses inflammasome formation by ameliorating endoplasmic reticulum stress via AMPK activation. Oncotarget 7 (41), 66444–66454.
Bergqvist, A.G., Schall, J.I., Stallings, V.A., Zemel, B.S., 2008. Progressive bone mineral content loss in children with intractable epilepsy treated with the ketogenic diet. Am. J. Clin. Nutr. 88 (6), 1678–1684.
Berry-Kravis, E., Booth, G., Sanchez, A.C., Woodbury-Kolb, J., 2001. Carnitine levels and the ketogenic diet. Epilepsia 42 (11), 1445–1451.
Branco, A.F., Ferreira, A., Simões, R.F., Magalhães-Novais, S., Zehowski, C., Cope, E., Silva, et al., 2016. Ketogenic diets: from cancer to mitochondrial diseases and beyond. Eur. J. Clin. Invest. 46 (3), 285–298.
Bulthuis, E.P., Adjobo-Hermans, M.J.W., Willems, P., Koopman, W.J.H., 2019. Mitochondrial morphofunction in mammalian Cells. Antioxid. Redox Signal. 30 (18), 2066–2109.
Cantó, C., Menzies, K.J., Auwerx, J., 2015. NAD^+ Metabolism and the control of energy homeostasis: a balancing act between mitochondria and the nucleus. Cell Metab. 22 (1), 31–53.
Caraballo, R.H., Cersósimo, R.O., Sakr, D., Cresta, A., Escobal, N., Fejerman, N., 2006. Ketogenic diet in patients with myoclonic-astatic epilepsy. Epileptic Disord. 8 (2), 151–155.
Clark, A., Mach, N., 2017. The crosstalk between the gut microbiota and mitochondria during exercise. Front. Physiol. 8, 319.
Deberles, E., Maragnes, P., Penniello-Valette, M.J., Allouche, S., Joubert, M., 2020. Reversal of cardiac hypertrophy with a ketogenic diet in a child with mitochondrial disease and hypertrophic cardiomyopathy. Can. J. Cardiol. 36 (10), 1690. e1691–1690.e1693.
Della Marina, A., Leiendecker, B., Roesch, S., Wortmann, S.B., 2020. Ketogenic diet for treating alopecia in BCS1l-related mitochondrial disease (Bjornstad syndrome). JIMD Rep. 53 (1), 10–11.
Dhamija, R., Eckert, S., Wirrell, E., 2013. Ketogenic diet. Can. J. Neurol. Sci. 40 (2), 158–167.
Dheen, S.T., Kaur, C., Ling, E.A., 2007. Microglial activation and its implications in the brain diseases. Curr. Med. Chem. 14 (11), 1189–1197.
Di Pisa, V., Cecconi, I., Gentile, V., Di Pietro, E., Marchiani, V., Verrotti, A., et al., 2012. Case report of pyruvate dehydrogenase deficiency with unusual increase of fats during ketogenic diet treatment. J. Child Neurol. 27 (12), 1593–1596.
Emperador, S., López-Gallardo, E., Hernández-Ainsa, C., Habbane, M., Montoya, J., Bayona-Bafaluy, M.P., et al., 2019. Ketogenic treatment reduces the percentage of a LHON heteroplasmic mutation and increases mtDNA amount of a LHON homoplasmic mutation. Orphanet J. Rare Dis. 14 (1), 1–6.
Fisher, F.M., Maratos-Flier, E., 2016. Understanding the physiology of FGF21. Annu. Rev. Physiol. 78, 223–241.
Fogle, K.J., Herzler, J.I., Shon, J.H., Palladino, M.J., 2016. The ATP-sensitive K channel is seizure protective and required for effective dietary therapy in a model of mitochondrial encephalomyopathy. J. Neurogenet. 30 (3), 247–258.
Frayn, K.N., Evans, R., 2019. Human Metabolism: a Regulatory Perspective, 4th ed. Wiley-Blackwell, USA.
Frazier, A.E., Thorburn, D.R., Compton, A.G., 2019. Mitochondrial energy generation disorders: genes, mechanisms, and clues to pathology. J. Biol. Chem. 294 (14), 5386–5395.
Frey, S., Geffroy, G., Desquiret-Dumas, V., Gueguen, N., Bris, C., Belal, S., et al., 2017. The addition of ketone bodies alleviates mitochondrial dysfunction by restoring complex I assembly in a MELAS cellular model. Biochim. Biophys. Acta. Mol. Bas. Dis. 1863 (1), 284–291.
Ghosh, S., Castillo, E., Frias, E.S., Swanson, R.A., 2018. Bioenergetic regulation of microglia. Glia 66 (6), 1200–1212.
Goodpaster, B.H., Sparks, L.M., 2017. Metabolic flexibility in health and disease. Cell Metab. 25 (5), 1027–1036.
Gorman, G.S., Chinnery, P.F., DiMauro, S., Hirano, M., Koga, Y., McFarland, R., et al., 2016. Mitochondrial diseases. Nat. Rev. Dis. Prim. 2, 16080.
Guo, Y., Zhang, C., Shang, F.F., Luo, M., You, Y., Zhai, Q., et al., 2020. Ketogenic diet ameliorates cardiac dysfunction via balancing mitochondrial dynamics and inhibiting apoptosis in Type 2 diabetic mice. Aging Dis. 11 (2), 229–240.
Gusic, M., Prokisch, H., 2021. Genetic basis of mitochondrial diseases. FEBS Lett. 595 (8), 1132–1158.
Halliwell, B., Gutteridge, J.M., 2015. Free Radicals in Biology and Medicine. Oxford University Press, USA.
Han, X., Tai, H., Wang, X., Wang, Z., Zhou, J., Wei, X., et al., 2016. AMPK activation protects cells from oxidative stress-induced senescence via autophagic flux restoration and intracellular NAD^+ elevation. Aging Cell 15 (3), 416–427.
Huang, T.-T., Naeemuddin, M., Elchuri, S., Yamaguchi, M., Kozy, H.M., Carlson, E.J., et al., 2006. Genetic modifiers of the phenotype of mice deficient in mitochondrial superoxide dismutase. Hum. Mol. Genet. 15 (7), 1187–1194.
Hung, P.L., Lin, J.L., Chen, C., Hung, K.Y., Hsieh, T.Y., Hsu, M.H., et al., 2021. An examination of serum acylcarnitine and amino acid profiles at different time point of ketogenic diet therapy and their association of ketogenic diet effectiveness. Nutrients 13 (1), 21.
Iannetti, E.F., Smeitink, J.A.M., Willems, P., Beyrath, J., Koopman, W.J.H., 2018. Rescue from galactose-induced death of Leigh Syndrome patient cells by pyruvate and NAD^+. Cell Death Dis. 9 (11), 1135.
Ignatenko, O., Nikkanen, J., Kononov, A., Zamboni, N., Ince-Dunn, G., Suomalainen, A., 2020. Mitochondrial spongiotic brain disease: astrocytic stress and harmful rapamycin and ketosis effect. Life Sci. Alliance 3 (9) e202000797.
Ito, Y., Oguni, H., Ito, S., Oguni, M., Osawa, M., 2011. A modified Atkins diet is promising as a treatment for glucose transporter type 1 deficiency syndrome. Dev. Med. Child Neurol. 53 (7), 658–663.
Jensen, N.J., Wodschow, H.Z., Nilsson, M., Rungby, J., 2020. Effects of ketone bodies on brain metabolism and function in neurodegenerative diseases. Int. J. Mol. Sci. 21 (22), 8767.
Joshi, C.N., Greenberg, C.R., Mhanni, A.A., Salman, M.S., 2009. Ketogenic diet in Alpers-Huttenlocher syndrome. Pediatr. Neurol. 40 (4), 314–316.
Kanabus, M., Fassone, E., Hughes, S.D., Bilooei, S.F., Rutherford, T., Donnell, M.O., et al., 2016. The pleiotropic effects of decanoic acid treatment on mitochondrial function in fibroblasts from patients with complex I deficient Leigh syndrome. J. Inherit. Metab. Dis. 39 (3), 415–426.
Kang, H.C., Chung, D.E., Kim, D.W., Kim, H.D., 2004. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. Epilepsia 45 (9), 1116–1123.
Kang, H.C., Kim, H.D., Lee, Y.M., Han, S.H., 2006. Landau-Kleffner syndrome with mitochondrial respiratory chain-complex I deficiency. Pediatr. Neurol. 35 (2), 158–161.
Kang, H.C., Lee, Y.M., Kim, H.D., Lee, J.S., Slama, A., 2007. Safe and effective use of the ketogenic diet in children with epilepsy and mitochondrial respiratory chain complex defects. Epilepsia 48 (1), 82–88.
Katsu-Jiménez, Y., Giménez-Cassina, A., 2019. Fibroblast growth Factor-21 promotes ketone body utilization in neurons through activation of AMP-dependent kinase. Mol. Cell. Neurosci. 101, 103415.
Katsyuba, E., Auwerx, J., 2017. Modulating NAD^+ metabolism, from bench to bedside. EMBO J. 36 (18), 2670–2683.
Kielb, S., Koo, H.P., Bloom, D.A., Faerber, G.J., 2000. Nephrolithiasis associated with the ketogenic diet. J. Urol. 164 (2), 464–466.
Kluge, M.A., Fetterman, J.L., Vita, J.A., 2013. Mitochondria and endothelial function. Circ. Res. 112 (8), 1171–1188.
Koopman, W.J.H., Nijtmans, L.G., Dieteren, C.E., Roestenberg, P., Valsecchi, F., Smeitink, J.A., et al., 2010. Mammalian mitochondrial complex I: biogenesis, regulation, and reactive oxygen species generation. Antioxid. Redox Signal. 12 (12), 1431–1470.
Koopman, W.J.H., Willems, P.H.G.M., Smeitink, J.A.M., 2012. Monogenic mitochondiral disorders. N. Engl. J. Med. 366 (12), 1132–1141.
Koopman, W.J.H., Distelmaier, F., Smeitink, J.A., Willems, P.H., 2013. OXPHOS mutations and neurodegeneration. EMBO J. 32 (1), 9–29.
Koopman, W.J.H., Beyrath, J., Fung, C.W., Koene, S., Rodenburg, R.J., Willems, P.H., et al., 2016. Mitochondrial disorders in children: toward development of small-molecule treatment strategies. EMBO Mol. Med. 8 (4), 311–327.
Laugel, V., This-Bernd, V., Cormier-Daire, V., Speeg-Schatz, C., de Saint-Martin, A., Fischbach, M., 2007. Early-onset ophthalmoplegia in Leigh-like syndrome due to *NDUFV1* mutations. Pediatr. Neurol. 36 (1), 54–57.
Lehtonen, J.M., Forsström, S., Bottani, E., Viscomi, C., Baris, O.R., Isoniemi, H., et al., 2016. FGF21 is a biomarker for mitochondrial translation and mtDNA maintenance disorders. Neurology 87 (22), 2290–2299.
Li, J., Kanasaki, M., Xu, L., Kitada, M., Nagao, K., Adachi, Y., et al., 2018. A ketogenic amino acid rich diet benefits mitochondrial homeostasis by altering the AKT/4EBP1 and autophagy signaling pathways in the gastrocnemius and soleus. Biochim. Biophys. Acta Gen. Subj. 1862 (7), 1547–1555.
Liemburg-Apers, D.C., Schirris, T.J., Russel, F.G., Willems, P.H., Koopman, W.J., 2015. Mitoenergetic dysfunction triggers a rapid compensatory increase in steady-state glucose flux. Biophys. J. 109 (7), 1372–1386.
Liemburg-Apers, D.C., Wagenaars, J.A., Smeitink, J.A., Willems, P.H., Koopman, W.J., 2016. Acute stimulation of glucose influx upon mitoenergetic dysfunction requires LKB1, AMPK, Sirt2 and mTOR-RAPTOR. J. Cell. Sci. 129 (23), 4411–4423.
Liesa, M., Shirihai, O.S., 2013. Mitochondrial dynamics in the regulation of nutrient utilization and energy expenditure. Cell Metab. 17 (4), 491–506.
Magistretti, P.J., Allaman, I., 2018. Lactate in the brain: from metabolic end-product to signalling molecule. Nat. Rev. Neurosci. 19 (4), 235–249.
McCommis, K.S., Kovacs, A., Weinheimer, C.J., Shew, T.M., Koves, T.R., Ilkayeva, O.R., et al., 2020. Nutritional modulation of heart failure in mitochondrial pyruvate carrier-deficient mice. Nat. Metab. 2 (11), 1232–1247.
Miller, V.J., Villamena, F.A., Volek, J.S., 2018. Nutritional ketosis and mitohormesis: potential implications for mitochondrial function and human health. J. Nutr. Metab. 2018, 5157645.
Mitchell, P., Moyle, J., 1967. Chemiosmotic hypothesis of oxidative phosphorylation. Nature 213 (5072), 137–139.
Morris, G., Maes, M., Berk, M., Carvalho, A.F., Puri, B.K., 2020. Nutritional ketosis as an intervention to relieve astrogliosis: possible therapeutic applications in the treatment of neurodegenerative and neuroprogressive disorders. Eur. Psych. 63 (1), e8.
Murphy, M.P., 2009. How mitochondria produce reactive oxygen species. Biochem. J. 417 (1), 1–13.

Nasser, S., Vialichka, V., Biesiekierska, M., Balcerczyk, A., Pirola, L., 2020. Effects of ketogenic diet and ketone bodies on the cardiovascular system: concentration matters. World J. Diabet. 11 (12), 584–595.
Newell, C., Shutt, T.E., Ahn, Y., Hittel, D., Khan, A., Rho, J.M., et al., 2016. Tissue specific impacts of a ketogenic diet on mitochondrial dynamics in the BTBRT+tf/j mouse. Front. Physiol. 7, 654.
Olgac, A., İnci, A., Okur, İ., Biberoğlu, G., Oğuz, D., Ezgü, F.S., et al., 2020. Beneficial effects of modified Atkins diet in glycogen storage disease type IIIa. Ann. Nutr. Metab. 76 (4), 233–241.
Orhan, N., Ugur Yilmaz, C., Ekizoglu, O., Ahishali, B., Kucuk, M., Arican, N., et al., 2016. Effects of beta-hydroxybutyrate on brain vascular permeability in rats with traumatic brain injury. Brain Res. 1631, 113–126.
Paoli, A., Mancin, L., Bianco, A., Thomas, E., Mota, J.F., Piccini, F., 2019. Ketogenic diet and microbiota: Friends or enemies? Genes (Basel) 10 (7), 534.
Purhonen, J., Rajendran, J., Mörgelin, M., Uusi-Rauva, K., Katayama, S., Krjutskov, K., et al., 2017. Ketogenic diet attenuates hepatopathy in mouse model of respiratory chain complex III deficiency caused by a Bcs1l mutation. Sci. Rep. 7 (1), 957.
Rath, S., Sharma, R., Gupta, R., Ast, T., Chan, C., Durham, T.J., et al., 2021. MitoCarta3.0: an updated mitochondrial proteome now with sub-organelle localization and pathway annotations. Nucl. Acids Res. 49 (D1), D1541–d1547.
Santra, S., Gilkerson, R.W., Davidson, M., Schon, E.A., 2004. Ketogenic treatment reduces deleted mitochondrial DNAs in cultured human cells. Ann. Neurol. 56 (5), 662–669.
Schiff, M., Bénit, P., El-Khoury, R., Schlemmer, D., Benoist, J.F., Rustin, P., 2011. Mouse studies to shape clinical trials for mitochondrial diseases: high fat diet in Harlequin mice. PLoS One 6 (12), e28823.
Seo, J.H., Lee, Y.M., Lee, J.S., Kim, S.H., Kim, H.D., 2010. A case of Ohtahara syndrome with mitochondrial respiratory chain complex I deficiency. Brain Dev. 32 (3), 253–257.
Steriade, C., Andrade, D.M., Faghfoury, H., Tarnopolsky, M.A., Tai, P., 2014. Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) may respond to adjunctive ketogenic diet. Pediatr. Neurol. 50 (5), 498–502.
Suen, D.F., Narendra, D.P., Tanaka, A., Manfredi, G., Youle, R.J., 2010. Parkin overexpression selects against a deleterious mtDNA mutation in heteroplasmic cybrid cells. Proc. Natl. Acad. Sci. U.S.A. 107 (26), 11835–11840.
Sullivan, P.G., Rippy, N.A., Dorenbos, K., Concepcion, R.C., Agarwal, A.K., Rho, J.M., 2004. The ketogenic diet increases mitochondrial uncoupling protein levels and activity. Ann. Neurol. 55 (4), 576–580.
Suomalainen, A., Elo, J.M., Pietiläinen, K.H., Hakonen, A.H., Sevastianova, K., Korpela, M., et al., 2011. FGF-21 as a biomarker for muscle-manifesting mitochondrial respiratory chain deficiencies: a diagnostic study. Lancet Neurol. 10 (9), 806–818.
Szabo, C., Ransy, C., Módis, K., Andriamihaja, M., Murghes, B., Coletta, C., et al., 2014. Regulation of mitochondrial bioenergetic function by hydrogen sulfide. Part I. Biochemical and physiological mechanisms. Br. J. Pharmacol. 171 (8), 2099–2122.
Teixeira, J., Basit, F., Willems, P., Wagenaars, J.A., van de Westerlo, E., Amorim, R., et al., 2021. Mitochondria-targeted phenolic antioxidants induce ROS-protective pathways in primary human skin fibroblasts. Free Rad. Biol. Med. 163, 314–324.
Wallace, D.C., Fan, W., Procaccio, V., 2010. Mitochondrial energetics and therapeutics. Annu. Rev. Pathol. Mech. Dis. 5, 297–348.
Weinberg, S.E., Sena, L.A., Chandel, N.S., 2015. Mitochondria in the regulation of innate and adaptive immunity. Immunity 42 (3), 406–417.
Xu, S., Tao, H., Cao, W., Cao, L., Lin, Y., Zhao, S.M., et al., 2021. Ketogenic diets inhibit mitochondrial biogenesis and induce cardiac fibrosis. Signal Trans. Targ. Therap. 6 (1), 54.
Yang, H., Shan, W., Zhu, F., Wu, J., Wang, Q., 2019. Ketone bodies in neurological diseases: focus on neuroprotection and underlying mechanisms. Front. Neurol. 10, 585.
Yarar-Fisher, C., Li, J., Womack, E.D., Alharbi, A., Seira, O., Kolehmainen, K.L., et al., 2021. Ketogenic regimens for acute neurotraumatic events. Curr. Opin. Biotechnol. 70, 68–74.
Yin, J., Han, P., Tang, Z., Liu, Q., Shi, J., 2015. Sirtuin 3 mediates neuroprotection of ketones against ischemic stroke. J. Cereb. Blood Flow Metab. 35 (11), 1783–1789.