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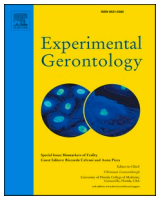

Mediterranean diet and mitochondria: New findings

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ABSTRACT

Mitochondria are subcellular organelles known for their central role in several energetic processes. Accumulating evidence supports a key role for mitochondria in the physiological response to both acute and chronic stress exposure, and, ultimately, the biological embedding of adversity in health and psychological functioning that increases the interest of these organelles in several medical conditions typical of older people. At the same time, Mediterranean diet (MedDiet) seems to affect the function of mitochondria further justifying the role of this diet in lowering the risk of negative health outcomes. In this review, we have elucidated the role of mitochondria in human diseases including the fundamental role in stress, aging, and neuropsychiatric and metabolic disorders. Overall, MedDiet can limit the production of free radicals, being rich in polyphenols. Moreover, MedDiet reduced mitochondrial reactive oxygen species (mtROS) production and ameliorated mitochondrial damage and apoptosis. Similarly, whole grains can maintain the mitochondrial respiration and membrane potential, finally improving mitochondrial function. Other components of MedDiet can have anti-inflammatory effects, again modulating mitochondrial function. For example, delphinidin (a flavonoid present in red wine and berries) restored the elevated level of mitochondrial respiration, mtDNA content, and complex IV activity; similarly, resveratrol and lycopene, present in grapefruits and tomatoes, exerted an anti-inflammatory effect modulating mitochondrial enzymes. Altogether, these findings support the notion that several positive effects of MedDiet can be mediated by a modulation in mitochondrial function indicating the necessity of further studies in human beings for finally confirming these findings.

1. Introduction

Mitochondria are subcellular organelles best known for their central role in energetics, producing adenosine triphosphate (ATP) to power most cellular processes (Daniels et al., 2020). The biogenesis of mitochondria refers to the process through which mitochondria grow in number and/or size and this is mediated by physiological stimuli, including physical exercise, dietary restrictions and temperature (Jornayvaz and Shulman, 2010). It is now widely accepted that the ability to deliver and utilize oxygen by the cardiorespiratory system and skeletal muscles, respectively (e.g., maximal aerobic capacity; maximal oxygen consumption [VO2max]), is a strong determinant of health and longevity in modern humans, so they hold a central position in cellular homeostasis and drive many aspects of the biological aging process (Kodama et al., 2009; Pimentel et al., 2003). Accumulating evidence supports a key role for mitochondria in the physiological response to both acute and chronic stress exposure, and, ultimately, the biological embedding of adversity in health and psychological functioning. In the setting of acute stress exposure, mitochondria respond dynamically to cues from stress-associated neuroendocrine, metabolic, and inflammatory pathways (Picard et al., 2014; Picard and BS, 2018). Furthermore, considering the critical role of mitochondrial functions for cellular health, a better knowledge of the main molecular players in mitochondria dysfunction could became a therapeutical target for degenerative diseases and cancer (Daniels et al., 2020; Picard and BS, 2018).

However, the current lack of knowledge of the role of mitochondria as main driver of comorbidities typical of older people is an important shortcoming. Therefore, the purpose of this review is to summarize the current literature regarding Mediterranean diet (MedDiet) and mitochondrial function in terms of health outcomes.

2. Methods

For this narrative, non-systematic review, potential eligible papers

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were screened in Pubmed and Scopus using the following search strategy, from databases inception to the 20th December 2022: "(Mediterranean Diet) AND (Mitochondrion OR Mitochondria)". We included all the works dealing with Mediterranean diet and mitochondria and the final role of modulation of Mediterranean diet on human health outcomes. We included systematic reviews, observational and intervention studies in human beings as well as in vitro and animal research. We excluded previously published narrative reviews, case reports and works written in languages other than English.

3. The role of mitochondria in human diseases

3.1. Mitochondria: general concepts

Mitochondria are termed the powerhouses of the cell as they produce most of the energy or ATP required by the cell. The mitochondria have their own genome (mtDNA) which is replicated independently of the host genome (Annesley and Fisher, 2019). The major role of mitochondria is to generate ATP for the cell. This process relies on oxidative phosphorylation (OXPHOS) and a by-product of this process is the generation of ROS. ROS are generated almost entirely by OXPHOS (about 90 %) (Kausar et al., 2018). Mitochondrial DNA is more susceptible to damage than nuclear DNA, with a 10–20 fold higher rate of mutagenesis than the nuclear genome. A cause of this higher mutation rate is the reactive oxygen species (ROS) production. An accumulation of mtDNA mutations has been associated with aging and age-related diseases such as neurological disorders and with several cancers. One of the main producers of mtDNA damage is lesions due to oxidative damage and these lesions can be repaired by DNA repair pathways, the predominant repair pathway used by the mitochondria called base excision repair (BER) and damage caused by oxidative stress. Mutations to mitochondrial repair enzymes have been associated with an increased risk of Parkinson's disease and their levels are altered in several cancers. In addition, defects in the BER pathway have been associated with diabetes and obesity. It is a particularly interesting topic as it opens up another avenue for the treatment of age-related disorders (Annesley and Fisher, 2019).

3.2. Mitochondria and aging

Mitochondria have been increasingly recognized for their importance in both the stress response and the aging process, with current research focusing on the role of mitochondria in accelerated aging and the development of age-related diseases (Han et al., 2019). Aging itself is associated with perturbations in mitochondrial structure and function, including impaired replication, alterations in mitochondrial DNA copy number (mtDNAcn) from the third decade of life onward in several postmitotic tissues (for example, muscle, heart, and brain), increased ROS production, mtDNA mutations, and organelle damage with resulting release of ccf-mtDNA (Lagouge and Larsson, 2013). In the setting of chronic stress exposure, these changes may accumulate, accelerating aging and increasing an individual risk of developing age and stress-related metabolic conditions such as cardiovascular disease (CVD) and diabetes (Picard and BS, 2018; Bratic and Larsson, 2013). Cancer, diabetes, and CVD are associated with alterations in homeostatic mechanisms governing energy usage and metabolism; it is consistent that mtDNA mutations and mitochondrial dysfunction have been documented to contribute to the onset of these diseases (Wallace, 2005).

Age-associated mitochondrial dysfunction, as assessed in vivo or at the whole tissue level, is attributable to intrinsic mitochondrial deficiency and a reduction in organellar number (Crane et al., 2010). Due to the close proximity of mtDNA to the source of ROS, lack of protection by histones, and limited capacity for DNA repair, mtDNA is more susceptible to oxidative damage than nuclear DNA (nDNA), resulting in a nearly 20-fold higher mutation rate, including deletions, tandem duplications, and single base modifications (Bua et al., 2006).

According to the mitochondrial–lysosomal axis theory of aging, mitochondrial ROS serve as an accelerant of lipofuscinogenesis, which impairs lysosomal degradative capacity and recycling of damaged mitochondria, further perpetuating redox imbalance, cytotoxicity, and debris aggregation (Nilsson and Tarnopolsky, 2019). Collectively, mitochondria and lysosomes generate the vast majority of 'accelerating agents' for oxidation, aggregation, and lipofuscinogenesis (ROS and Fe2+, respectively), play major roles in the induction of cell death, and likely contribute significantly to sarcopenia and the biological aging process. Concomitant oxidative damage, protein aggregation, lipofuscinogenesis, and inflammation are unifying features of the normal aging process, neurodegenerative disease, and lysosomal storage disorders. Activation of clearance pathways extends lifespan in multiple species, collectively suggesting that the ability to neutralize cytotoxins, recycle debris, and repair stress-induced damage is integral for survival. So the rate of aging is predominately dictated by the organelles/processes that govern the most critical needs of the cell, such as energy production (mitochondria), recycling (autophagosome, lysosome, and 26*S* proteasome), and quality control (unfolded protein response of the endoplasmic reticulum [UPRER] and mitochondrial unfolded protein response [UPTMT]). Given their importance in eukaryotic evolution, cell homeostasis, and growth, mitochondria may be considered the 'hubs of aerobic life', and are therefore assigned a central role in the Integrated Systems Hypothesis of Aging. Both major types of exercise, aerobic and resistance training, bestow multi-systemic benefits and protect against the major hallmarks of aging, including mitochondrial dysfunction, recycling deficiency, impaired quality control, and systemic inflammation, thus providing a compelling argument in support of exercise as a front-line modality to decelerate the aging process. (Terman et al., 2010)

3.3. Mitochondrial dysfunction and metabolic syndrome

Mitochondrial dysfunction is a cardinal hallmark of Metabolic Syndrome (MetS) (Di Ciaula et al., 2021). It is still unclear if mitochondrial dysfunction is the primary cause or a secondary effect of MetS (Khalil et al., 2022).

Mitochondria contribute to the pathogenesis of obesity-related metabolic disorders. Mitochondria are essential for cellular energy metabolism, as they generate ATP by oxidizing carbohydrates, lipids, and proteins (Kusminski and Scherer, 2012). The inability of mitochondria to produce and maintain sufficient levels of ATP is known as "mitochondrial dysfunction", which is the result of an imbalance in nutrient signal input, energy production, and oxidative respiration (Brand and Nicholls, 2011). Several studies suggest that an excessive intake of nutrients influences mitochondrial function (Liesa and Shirihai, 2013), and that obesity predisposes to mitochondrial dysfunction (Heinonen et al., 2015). In MetS, mitochondrial dysfunction has been identified in various target organs such as the liver, heart, and skeletal muscle, as well as in tissues and cells such as adipocytes and pancreatic islets beta cells (Bugger and Abel, 2008). The pathological expansion of body fat is associated with a chronic status of low- to-medium grade inflammation, oxidative stress, and insulin resistance (Catalán et al., 2022). An excessive intake of nutrients, especially lipids and carbohydrates, can promote mitochondrial dysfunction. Due to high-calorie intakes, the metabolism is shifted towards the lipid reservoir, reduced mitochondrial function, and biogenesis, with subsequent production of ROS and the progression of insulin resistance in the liver, muscle, and adipose tissue (Kusminski and Scherer, 2012).

Adipocytes collected from omental and/or abdominal subcutaneous adipose samples of obese patients showed a reduction in mitochondrial oxygen-consumption rates and citrate synthase activity, compared to non-obese subjects. Mitochondrial biogenesis, mitochondrial oxidative phosphorylation, and oxidative metabolic pathways in subcutaneous adipose tissue were downregulated in obese subjects, when compared to lean subjects (Heinonen et al., 2015). These effects were accompanied by a reduction in the amount of mtDNA and the mtDNA-dependent

translation system. At the molecular level, obese subjects showed reduced peroxisome proliferator–activated receptor-α (PGC1-α) expression, as a marker of altered mitochondrial biogenesis (Semple et al., 2004).

In the liver, mitochondria are involved in the metabolic pathways of lipids, proteins, carbohydrates, and xenobiotics (Grattagliano et al., 2011).

Mitochondrial dysfunction is documented in non-alcoholic fatty liver disease/metabolic dysfunction-associated fatty liver disease (NAFLD/MAFLD), the most common chronic liver disease (Caldwell et al., 1999). In the early stages of NAFLD/MAFLD the increased intrahepatic influx of circulating free fatty acids (FFAs) causes early mitochondrial biogenesis mediated by the activation of PGC1-α and increased β-oxidation rates (Szczepaniak et al., 2005). The high rate of FFAs oxidation and ATP synthesis cause the uncontrolled increase in ROS levels and changes in mitochondrial structure/function such as swelling, alteration in the mitochondrial electron transporter chain, mtDNA damage, and sirtuin (SIRT) alterations. Despite the endogenous mitochondrial antioxidant system works to counteract the oxidative stress, the mitochondrial dysfunction occurs with imbalance between ROS production and mitochondrial defense mechanisms (Wei et al., 2008).

As NAFLD/MAFLD progresses, the increased level of ROS severely impairs mtDNA function and mitochondrial ATP synthesis promoting further hepatic dysfunction, and inflammation. At the structural level, the mitochondrial electron transfer chain seems to be altered as consequence of the excessive accumulation of toxic lipids and mtROS with a direct impact on the permeability of the inner mitochondrial membrane and increased oxidative damage (Longo et al., 2021). At the molecular level, mitochondrial cytochrome P450 2E1 (CYP2E1), which is responsible for long-chain fatty acid metabolism, is directly involved in mitochondrial ROS production, and is considered a fundamental player in NAFLD/MAFLD pathophysiology (Aubert et al., 2011). Besides, mitochondrial enzymatic oxidative defense mechanisms resulted also impaired in NAFLD and non-alcoholic steatohepatitis (NASH) with progressive mitochondrial dysfunction. Furthermore, alterations of the expression of PGC-1α are associated with NAFLD pathogenesis and to NASH-hepatocellular carcinoma progression (Piccinin et al., 2019).

The relationship between insulin resistance and mitochondrial dysfunction is not fully understood. Increased production of mtROS has been associated with a high glucose intake and FFAs accumulation, the two principal factors of insulin resistance. Despite the established role of genetic and environmental factors associated with type 2 diabetes (T2DM) pathophysiology, different metabolic abnormalities are directly implicated in the etiology of T2DM. With ongoing insulin resistance and pancreatic β-cells dysfunction, mitochondrial dysfunction has been indicated as a principal contributor. The reduction in insulin sensitivity in adipocytes, hepatocytes, and skeletal muscles is related to other complications such as the increased production of ROS and an accumulation of FFAs, both of which are associated with mitochondrial dysfunction and impaired mitochondrial biogenesis in diabetic patients (Kelley et al., 2002).

In overweight/obesity and MetS, high fat and carbohydrate intake leads to lipid deposition resulting in the expansion of visceral adipocytes and an excessive influx of circulating FFAs (Vecchié et al., 2018). The involvement of metabolic abnormalities (e.g., visceral fat accumulation, insulin resistance, and inflammation) in obesity is closely related to mitochondrial dysfunction and vice versa (Lahera et al., 2017). Mitochondrial ATP production occurred with molecular (peroxisome proliferator–activated receptor-1α/β (PGC-1α/β), estrogen-related receptor alpha, and peroxisome proliferator-activated receptor alpha (PPAR-α)) and structural (outer and inner membrane translocases and mitochondrial ribosomal proteins) alteration in adipose tissue (Rong et al., 2007).

3.4. Mitochondria and stress

In response to exposure to acute stress, neuroendocrine pathways stimulate mechanisms and behaviours that modulate the use of energy stores, such as changes in eating behaviours (shifting preference towards calorically dense macronutrients) and rapid mobilization of free fatty acids from central fat stores. Mitochondria are sensitive to these changes in metabolic, endocrine stressors and stress mediators. For example, under stressful conditions, due to high levels of glucocorticoids (stress hormone) exposure, mitochondria have a reduced calcium buffering capacity, an important mitochondrial function for maintaining the internal environment of the cell. Rapid calcium flux or calcium overload into the cell promotes sensitization to cell death (Picard and BS, 2018; Du et al., 2009). In acute stress, circulating levels of important substrates, such as glucose or lipids, increase to provide the energy needed to respond to a stressor. In the context of hyperglycemia, mitochondria "join", undergoing fusion to promote survival. Under conditions of severe or prolonged exposure to stress, these substrates are chronically elevated and mitochondria fragment, increasing the risk of cell death (Hoffmann and Spengler, 2018; Shutt and McBride, 2013). Prolonged fragmentation is associated with further oxidative stress and damage to mitochondrial DNA (mtDNA) (Ridout et al., 2016). Exposure to stress-mediators precipitates mitochondrial release of signaling molecules, which are collectively referred to as mitokines. Mitokines serve as signals that indicate mitochondrial fitness, which is of particular importance in the context of environmental stressors. Mitokines include various mitochondrial metabolites, calcium, reactive oxygen species (ROS), circulating cell-free mitochondrial DNA (ccf-mtDNA), which is present in low levels in healthy individuals, abundant in inflammatory disease, and significantly increased in critically ill hospital patients. The immune system recognizes ccf-mtDNA as foreign, stemming from its evolutionary origin as bacteria, which consequently induces systemic inflammation (Picard and BS, 2018; Chandel, 2015; Zhang et al., 2010).

3.5. Mitochondria and neuropsychiatric disorders

Oxidative stress has been postulated to play a role in the pathogenesis of neuropsychiatric disorders, particularly depression and dementia. In such disease processes, it is suggested that the accumulation of ROS and mtDNA mutations, among other abnormalities, causes impaired cell functioning and replication, leading to apoptosis and neuronal atrophy (Forlenza and Miller, 2006). These findings indicate that mitochondria may play a critical role in neuronal integrity and synaptic transmission, thus, contributing to the development of stress-related disease. For example, individuals with primary mitochondrial disorders have appreciable hyperintensities within the basal ganglia, cerebellum, and brainstem along with atrophy in the cerebellum and cerebrum and white matter leukoencephalopathy (Bricout et al., 2014; Friedman et al., 2010). Mitochondrial dysfunctions are often associated with psychiatric disorders, including schizophrenia, bipolar disorder, and depression (Rosebush et al., 2017). Deficits in the components of the mitochondrial electron transport complexes (ETC) have been associated with the pathogenesis of neuropsychiatric diseases, including Alzheimer's and Parkinson's diseases, major depressive disorder (MDD), schizophrenia, and bipolar disorder, with the strongest evidence for neurodegenerative disorders (Holper et al., 2019). Mitochondrial involvement in neuropsychiatric diseases can also be evaluated using peripheral molecular biomarkers, namely mtDNAcn, a marker of mitochondrial biogenesis, and ccf-mtDNA, a potential indicator of mitochondrial stress. Additional research has also appreciated a similar relationship between elevated mtDNAcn in peripheral blood cells and autism spectrum disorders (Chen et al., 2015). In another study, ccf-mtDNA was also elevated in individuals following a suicide attempt when compared to non-suicidal controls (Lindqvist et al., 2016).

4. Mediterranean diet: general concepts

Fig. 1 graphically summarizes some of the components of MedDiet that may help explain its multiple clinical benefits. Reduced physical

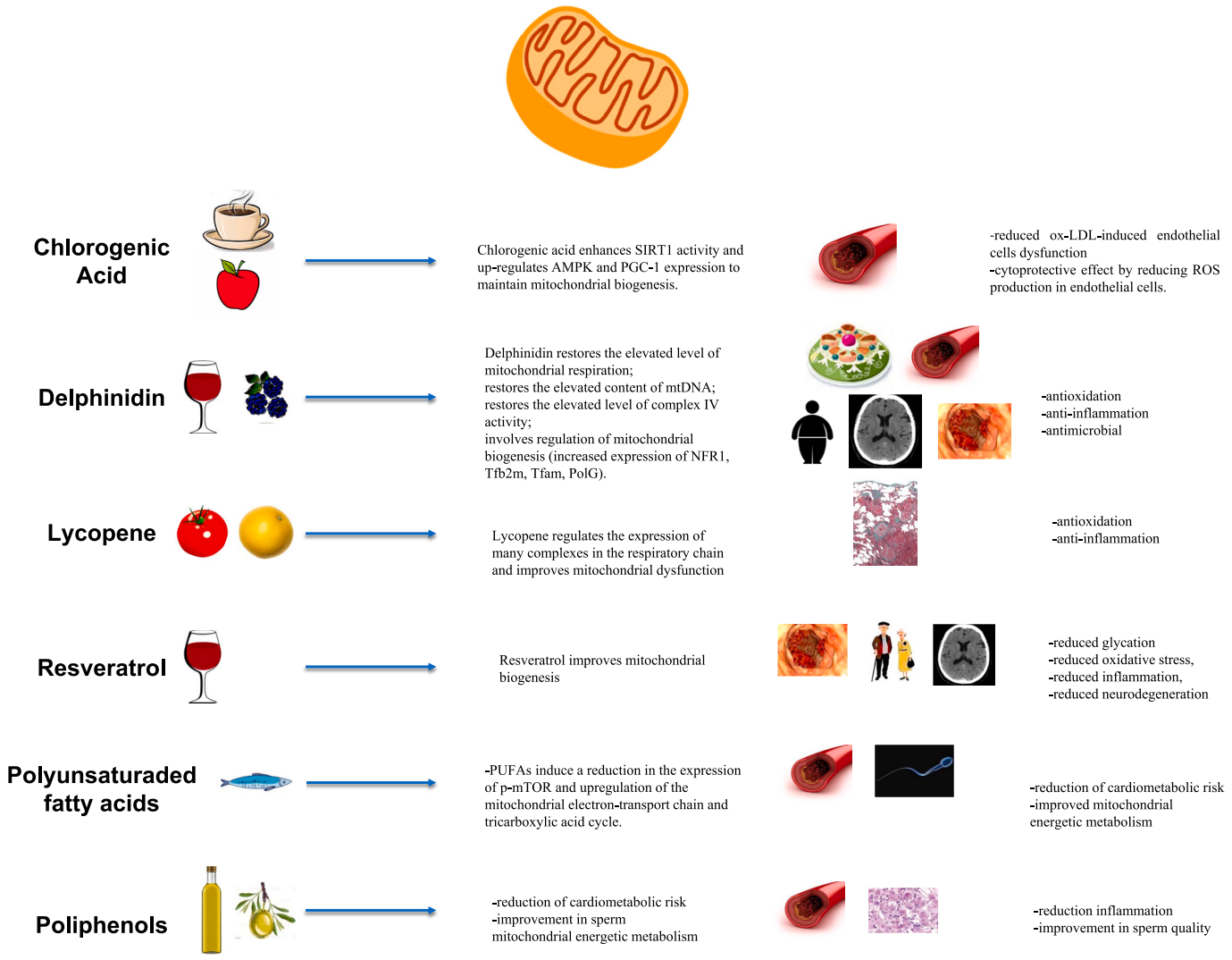

Fig. 1. Beneficial effects of Mediterranean diet on mitochondrial function and health outcomes.

activity and sedentary lifestyle, unhealthy diet, excess eating, and smoking are crucial determinants of the rise of obesity, T2DM, hypertension, and lipid profile alterations, all strong risk factors for CVD, dementia, and some forms of cancer (GBD 2017 Diet Collaborators, 2019). Various dietary patterns have been associated with health benefits (De Filippis et al., 2016a). For example, MedDiet may help preventing chronic diseases and premature mortality. This dietary pattern, mostly based on plant-derived foods (but also admitting animal-derived food in small quantities), preferring seasonal and local food consumption and production, constitutes an eating pattern that considers both health and environmental issues, is a cultural archetype that comprises the manner in which foods are selected, processed, and dispensed, together with other foundations of lifestyle. These characteristics led United Nations Educational, Scientific and Cultural Organization (UNESCO) in 2010 to include MedDiet on the list of the intangible cultural heritage of humanity (Dernini and Berry, 2015). A hallmark of MedDiet is the inclusion of unprocessed foods, which are full of healthy nutrients, as opposed to Western dietary patterns, which are rich in processed and ultra-processed foods, full of calories but very poor in nutrients ("empty calories"), linked to a high risk of developing overweight/obesity (Dominguez et al., 2019). Evidence suggests that the MedDiet possesses antioxidant and anti-inflammatory properties (Medina-Remón et al., 2017). A higher adherence to MedDiet was related to improved inflammatory markers when compared to an emblematic diet rich in carbohydrates and saturated fatty acids (Fitó et al., 2007). The protective effects of the MedDiet are the result of the diet as a whole, rather than individual components, reinforcing the idea that the interaction of various dietary components can have a beneficial synergistic effect; in fact, scientific-based evidence suggests that many components of the MedDiet display anti-inflammatory effects by reducing the activation of nuclear factor k chain transcription in B cells (NF-κB) signaling pathway and the expression of chemokine and proinflammatory cytokines such as Tumor necrosis factor alfa (TNF-α), interleuchin -1β (IL-1β), and interleuchin 6 (IL-6) (Dominguez et al., 2021) and all these factors are usually associated with mitochondria dysfunction. The decreased expression of cytokines reduces oxidative stress, low-grade inflammation, and apoptotic cell death in brain and visceral tissues. Another biomarker for inflammation is C-reactive protein (CRP), and prolonged intake of the MedDiet diminishes CRP and unusual quantity of cytokines and adipokines irrespective of weight loss increase (Richard et al., 2013).

However, several scientific-based evidences about the beneficial effects of individual components of the MedDiet have been documented. For example, olive oil exerts antidiabetic, cardioprotective, neuroprotective, and nephroprotective effects due to the presence of tyrosol, oleocanthal, and hydroxytyrosol (Freeman et al., 2008). The long-term consumption of olive oil counteracts inflammation, promotes blood vessels' relaxation, protects against T2DM, reduces blood pressure, and

increases insulin circulation (Farooqui, 2012). The MedDiet contains sea foods and fish rich in polyunsaturaded fatty acids (PUFAs) such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are metabolized producing 5-series leukotrienes and resolvins (RvE1 and RvE2). These metabolites possess anti-inflammatory effects in vivo (Calder, 2009). Red grapes and wine found in the MedDiet contain the polyphenol resveratrol (3,40,5-trihydroxystilbene), which not only has been shown in experimental research to have cardioprotective, anti-aging, and anticarcinogenic effects but to promote neuroprotective activities leading to anti-inflammatory, antioxidant, and gene-modulating effects. Resveratrol in healthy offsprings of patients with T2DM modulates the genes that influence mitochondrial function, such as PGC-1α, which is a key regulator of mitochondrial biogenesis and leads to elevation of mitochondrial content (Lagouge et al., 2006). Furthermore, resveratrol indirectly activates adenosine monophosphate (AMP) activated protein kinase (AMPK), leading to increased mitochondrial biogenesis, improved glucose tolerance, insulin sensitivity, physical endurance, and a reduction in fat accumulation (Hardie et al., 2012). A systematic review of observational and experimental research assessing the effects of polyphenols found in a MedDiet on depression symptoms found an association between polyphenol consumption and depression risk, as well as evidence suggesting that polyphenols can effectively alleviate depressive symptoms (Bayes et al., 2020).

Another key mechanism that can help explain the benefits of MedDiet is the gut microbiota, which in recent decades has emerged as a crucial player in the relationship between diet and health by means of metabolites derived from the microbial fermentation of nutrients, particularly short chain fatty acids (SCFAs). In fact, diet is a major regulator of gut microbiota composition and metabolite production, which has been related to the incidence and progression of several intestinal and extra-intestinal diseases (Gentile and Weir, 2018). A high adherence to the MedDiet was associated with an enrichment of Firmicutes and Bacteroidetes and an increase in fecal SCFAs. Conversely, poor adherence to MedDiet was associated with increased l-Ruminococcus and Streptococcus bacteria, and higher urinary trimethylamine N-oxide concentrations, a marker of increased risk of CVD (De Filippis et al., 2016b).

Flavonoids and their metabolites have been shown to exhibit positive gut-modulating properties, specifically on SCFA production and lipopolysaccharide (LPS) reduction. (Beam et al., 2021). Among the flavonoids, the proanthocyanins significantly increased Bifidobacterium spp., while decreasing Enterobacteriaceae (Yamakoshi et al., 2001). This is also consistent with another study that found that flavonoids increase Bifidobacterium and Lactobacillus (Molan et al., 2009). Hidalgo et al., found that flavanol-3-ol monomers promoted the growth of *Clostridium coccoides–eubacterium rectale*, which has the potential to produce large amounts of the SCFA butyrate and the monomer (+) − catechin increases the growth of Lactobacillus–enterococcus spp., Bifidobacterium spp., and *Escherichia coli* (Hidalgo et al., 2012). Interestingly, a study that was conducted to examine the effects of flavonoids on insulin resistance, found that the subjects who consumed a flavonoid-rich cranberry extract had a reduction in inflammation, by modulating the specific bacteria *Akkermansia muciniphila* (Anhê et al., 2017). A study that was conducted on human subjects, who were given polyphenol-rich mango, found a reduction in endotoxin LPS, and an increased production of SCFA (Venancio et al., 2018). Polyphenols have positive effects on the gut microbiome. The consumption of the red wine was associated with an increase in Bifidobacteria and the beneficial bacteria Bacteroides and Prevotella (Queipo-Ortuño et al., 2012). On the other side, western diets and ultra-processed foods, characterized by low levels of dietary fibre or micronutrients, present a plethora of nutritional components, including refined carbohydrates (sugar and refined grains), low-quality fats (trans fatty acids and an excessive omega 6 (ω-6)/omega 3 (ω-3) ratio due to the refined oils), salt and unhealthy additives (mainly sweeteners), and finally excessive red and processed meat consumption. Moreover, they comprise a poor food matrix that will have detrimental effects at the intestinal barrier, leading to leaky gut, gut dysbiosis and altered metabolites, further leading to a local inflammation and the presence of LPS in the bloodstream that will contribute to systemic endotoxemia and chronic inflammation (García-Montero et al., 2021). The role of ω-3 on the gut microbiota would seem to modulate the inflammatory response which lies at the base of several chronic non-communicable degenerative diseases (CNCDDs), such as atherosclerosis, cancer, neurodegenerative diseases, chronic renal failure, diabetes mellitus, male obesity secondary hypogonadism etc. (Merra et al., 2020)

A randomized controlled trial, the NU-age project, investigated if a 1-year MedDiet intervention could alter the gut microbiota and reduce frailty. The results of this trial showed that MedDiet was associated with modulation of the microbiome in a relatively consistent manner (across the countries) and, in turn, associated with reduced frailty (Ghosh et al., 2020).

In addition, there are some proposed mechanisms that are disease-specific (e.g., cancer, CVD) such as changes in hormones and growth factors linked to cancer pathogenesis. Women following a MedDiet had a significant elevation of the plasma concentration of several binding proteins, such as insulin-like growth factor binding protein (IGFBP)-1, IGFBP-2, and sex hormone binding globulin, resulting in a reduction of the biological activity of insulin-like growth factor-1 (IGF-1), testosterone, and oestradiol. Insulin, estrogens, androgens, and IGF-1 are powerful cellular mitogens, linked to the development and growth of several tumors, including breast, colon, prostate, pancreatic, and endometrial cancer (Longo and Fontana, 2010).

Other proposed pathways to explain the impact of dietary factors on aging and on incident Noncommunicable diseases (NCDs) are epigenetic mechanisms, such as DNA and histone methylation, histone acetylation, as well as non-coding RNA (Zhang and Kutateladze, 2018). As opposed to what happens to DNA that cannot change, epigenetic modifications can occur in response to various stimuli, such as the exposure to nutrients, toxins, pesticides, and pollutants. Interestingly, various MedDiet components comprise bioactive elements that have been lately studied, particularly for their antitumor actions (Divella et al., 2020).

The MedDiet includes a high consumption of green vegetables rich in magnesium, which is a main constituent of chlorophyll. The magnesium present in chlorophyll plays a crucial role in the metabolism of insulin and glucose by translocating the phosphate from ATP to protein through its influence on tyrosine kinase activity of the insulin receptor. Magnesium is one of the cofactors of more than 600 enzymatic reactions and it is important for ATP metabolism. It is also necessary for the regulation of blood pressure, insulin metabolism, muscle contraction, cardiac excitability, neuromuscular conduction, and vasomotor tone. The deficiency of magnesium is known to be associated with the onset of T2DM, while its consumption reduces the intensity of diabetes by sensitizing insulin (Lu et al., 2016).

There is strong evidence for the association of adherence to MedDiet with reduced risk of all-cause mortality, as well as incident coronary heart disease, CVD, myocardial infarction, and diabetes (Dinu et al., 2018). The MedDiet also has significant protective effects in MetS (Kastorini et al., 2011).

Tobore showed that the MedDiet is counted among the principles necessary for the treatment of multiple sclerosis, together with “disease-modifying” drugs, cessation of smoking and alcohol consumption, stress relieving activities and peer support programs (Tobore, 2021).

There is some evidence of the association between MedDiet adherence, or between nutrient intake with antioxidant properties and the prevention of frailty. Most authors agree that the MedDiet is the best diet model that we can propose to maintain health, or to get old with a lower incidence of frailty syndrome and disability due to chronic diseases and physical and cognitive impairment more frequently observed in old age (Bonnefoy et al., 2015).

Results from a longitudinal study on a cohort of 690 non-institutionalized old people, from the InCHIANTI Study, confirmed that subjects following the traditional MedDiet developed a significantly

lower risk of frailty (OR = 0.30; 95 % CI: 0.14–0.66). Authors also confirmed that a high adherence to a MedDiet pattern was associated with a lower risk of low physical activity (OR = 0.62; 95 % CI: 0.40–0.96) and low walking speed (Talegawkar et al., 2012).

5. Mediterranean diet and mitochondria

Table 1 summarizes the importance of MedDiet in mitochondrial function. It is important to note that the MedDiet is rich in polyphenols and other naturally derived compounds that have substantial antioxidant properties, the capacity to scavenge free radicals, and the ability to modulate endogenous antioxidant defense mechanisms. These effects may involve mitochondrial antioxidant enzymes. Due to their antioxidant properties, polyphenols can reduce the inflammation and mitochondrial dysfunction characteristic of MetS. In addition, the antioxidant properties of the polyphenols present in the MedDiet reduced mtROS production and ameliorated mitochondrial damage and apoptosis in different experimental studies. Several studies reported the health-promoting effects of the MedDiet due to its high fibre content. (Rudrapal et al., 2022)

Table 1
Role of nutrients in Mediterranean diet in mitochondrial function and consequent clinical effects.

Nutrients	Mitochondrial effects	Clinical effects	References
Polyphenols	- involve mitochondrial antioxidant enzymes	- reduced inflammation characteristic of the Metabolic Syndrome	Rudrapal et al. (2022)
Chlorogenic acid (coffee beans and apples)	- enhancing SIRT1 activity and up-regulating AMPK and PGC-1 expression to maintain mitochondrial biogenesis	- reduced ox-LDL-induced endothelial cells dysfunction - cytoprotective effect by reducing ROS production in endothelial cells	Tsai et al. (2018)
Delphinidin (red wine and berries)	- restored the elevated level of mitochondrial respiration - restored the elevated content of mtDNA - restored the elevated level of complex IV activity - involves regulation of mitochondrial biogenesis (increase the expression of NFR1, Tfb2m, Tfam, PolG)	- antioxidation - anti-inflammation - antimicroorganism - antidiabetes - antiobesity - cardiovascular protection - neuroprotection - anticancer	Duluc et al. (2014)
Lycopene (tomatoes and grapefruits)	- regulating the expression of many complexes in the respiratory chain - improving mitochondrial dysfunction	- anti-inflammation	Wang et al. (2019); Feng et al. (2016)
Resveratrol (red wine)	- improve mitochondrial biogenesis	- glycation - oxidative stress - inflammation - neurodegeneration - several types of cancer protection - anti-aging	Gueguen et al. (2015); Baur et al. (2006); Galiniak et al. (2019)
PUFA	- reduction in the expression of p-mTOR - upregulation of the mitochondrial electron-transport chain and tricarboxylic acid cycle	- reduce cardiometabolic risk - sperm mitochondrial energetic metabolism	Nadtochiy and Redman (2011); Ferramosca and Zara (2022)

Various in vitro studies evaluated the beneficial effects of polyphenol-rich foods on MetS mediating mitochondrial modulation. In detail, the protective role of chlorogenic acid (CGA) found in coffee beans and apples against ox-LDL-induced endothelial cells dysfunction as cellular model of atherosclerosis was evaluated using human endothelial cells. CGA displayed mitochondria-mediated effects by enhancing SIRT1 activity and up-regulating AMPK and PGC-1 expression to maintain mitochondrial biogenesis. In addition, CGA treatment exhibited a cytoprotective effect by reducing ROS production in endothelial cells (Tsai et al., 2018).

In mice fed high-fat diets, CGA significantly changed the composition of the gut microbiota and increased the abundance of short chain fatty acid (SCFA)-producers (e.g., Dubosiella, Romboutsia, Mucispirillum, and Faecalibaculum and Akkermansia), which can protect the intestinal barrier. In addition, mice with the CGA-altered microbiota had decreased body weight and fat content and inhibited metabolic endotoxemia. Therefore, CGA-induced changes in the gut microbiota played an important role in the inhibition of metabolic endotoxemia in mice fed a high-fat diet (Ye et al., 2021).

Similarly, in endothelial cells with VEGF-induced mitochondrial dysfunction, delphinidin (a flavonoid present in red wine and berries) restored the elevated levels of mitochondrial respiration, mtDNA content, and complex IV activity. In addition, delphinidin increased the expression of nuclear related factor 1 (NRF1), transcription factor B2 of the mitochondria (TFB2m), transcription factor A of the mitochondria (TFAm), and DNA polymerase gamma (PolG), all of which are involved in the regulation of mitochondrial biogenesis (Duluc et al., 2014). Lycopene (LYC), a member of the carotene phytochemical family, present in tomatoes and grapefruits, exerted an anti-inflammatory effect on mice exposed to lipopolysaccharide through improving mitochondrial dysfunction. In detail, LYC upregulated the expression of silent mating-type information regulation 2 homolog-1 (SIRT1), PGC1α, cyclooxygenase 5b (Cox5b), cyclooxygenase 7a1 (Cox7al), cyclooxygenase 8b (Cox8b), and cytochrome *c* somatic (Cycs). In addition, a partial effect of LYC was proved in regulating the expression of many complexes in the respiratory chain (Wang et al., 2019). Another in vitro study using human neuroblastoma cells SH-SY5Y showed a protective effect of lycopene against Hydrogen Peroxide (H2O2)-induced depolarization of the mitochondrial membrane. LYC also increased the expression of B-cell-leukemia/lymphoma 2 (Bcl2) and decreased Bcl2 associated x protein (Bax) expression (Feng et al., 2016).

Whole grains also represent an important category in the MedDiet, with a beneficial impact on metabolic diseases. Especially, 5-heptadecylresorcinol, a biomarker of whole grain rye consumption, protects against H2O2-induced oxidative stress in rat pheochromocytoma (PC-12) by activating the Sirtuin 3-Forkhead box O3a (SIRT3-FOXO3a) signaling pathway. In addition, it reduced mitochondrial ROS levels and maintained the mitochondrial respiration and membrane potential, which leads to an increase in ATP production and cell respiration (Liu et al., 2020).

Another study found that the antioxidant effect of resveratrol found in grapes, berries, and cacao is dose- and age-dependent. This polyphenol competes with nicotinamide in a solubilized complex of mitochondria to improve their activity (Gueguen et al., 2015). These results have also been confirmed by Baur et al. using a high-calorie-diet mice model which demonstrated a SIRT-1-dependent effect of resveratrol on the activation of PGC-1α resulting in the improvement of mitochondrial biogenesis (Baur et al., 2006). It has many properties including activity against glycation, oxidative stress, inflammation, neurodegeneration, several types of cancer, and aging (Galiniak et al., 2019).

The properties of the prebiotic resveratrol, which modifies the variability and composition of the intestinal microbiota, are also manifested in the decreased Firmicutes/Bacteroidetes ratio, which instead is increased in obese patients and in patients with systemic diseases (Cueva et al., 2017). The metabolite dihydroresveratrol comes from the resveratrol fermentation in the cecum, colon, and rectum by the microbiota, which acts as a drug in the human large intestine. Therefore, the beneficial effects are not only due to resveratrol but also due to the products of its metabolism (Ozdal et al., 2016). The administration of resveratrol results in a reduced formation of trimethylamine-N-oxide (TMAO), a metabolite of carnitine and choline, resulting from the digestion of red meat, egg yolk, and fatty cheeses and liver (Roberts et al., 2018). A high concentration of TMAO is considered a riskfactor for heart attack and stroke because it activates platelet activity predisposing to thrombosis (Roberts et al., 2018).

Short-chain fatty acids (SCFAs) are the end products of the fermentation of insoluble fibre by the gut microbiota. Evidence suggests that SCFAs can modulate several metabolic disorders such as obesity, insulin resistance, and T2DM (Portincasa et al., 2022). Butyrate, an SCFA present in the MedDiet, promotes fatty acid oxidation and improves mitochondrial function. The vegetables, nuts, and fish characteristics of the MedDiet contain significant amounts of PUFAs. The correlation between PUFA intake (especially ω-3) and decreased cardiometabolic risk has been well- documented (Nadtochiy and Redman, 2011). Additionally, dietary ω-3 PUFAs have shown substantial positive effects on mitochondrial function and structure. These effects seem to be mediated by a reduction in the expression of phospho-Mammalian target of rapamycin (p-mTOR), accompanied by the upregulation of the mitochondrial electron-transport chain and tricarboxylic acid cycle. Several studies in humans have demonstrated the beneficial effect of the bioactive compounds present in the MedDiet on MetS, suggesting advanced health-promoting effects through the targeting of mitochondria. This could be used to promote additional pharmacological and nutraceutical effects, especially on the gastrointestinal system and muscle strength (Vecchié et al., 2018 Feb). The administration of PUFA, especially ω-3 PUFA is a key element for sperm quality, determines an increase in sperm mitochondrial energetic metabolism and a reduction in oxidative damage. This may be of interest for the treatment of male infertility (Ferramosca and Zara, 2022).

6. Conclusions

Mitochondria are essential organelles for energy production. They are sensitive to inflammation-induced oxidative stress. Mitochondria can perceive inflammatory signals, and they are among the first organelles affected by systemic inflammation (Magnani et al., 2020). Unregulated inflammation may damage the mitochondrial structure, reduce mitochondrial biogenesis, interrupt mitochondrial function, and lead to tissue dysfunction. Further, in the process of synthesizing ATP via oxidative phosphorylation, ROS will be generated by mitochondria (Bhatti et al., 2017). Excessive generation of ROS due to systemic inflammation triggers oxidative stress, which reinforces chronic inflammation (Magnani et al., 2020). Diet has been associated with oxidative stress (Vetrani et al., 2013). Several studies have demonstrated that a high-quality diets, such as MedDiet, were associated with lower oxidative stress levels (Aleksandrova et al., 2021) and so a lower incidence of diseases. By means of substances contained in foods constituting the MedDiet, it may improve mitochondrial function and reduce cardiovascular, metabolic and neoplastic risks, promoting a healthy longevity. Future intervention studies are needed for better exploring the real impact of the Mediterranean diet on mitochondrial function, in order to better indicate the role of these organelles in the pathophysiology of conditions typical of older people.

CRediT authorship contribution statement

Pollicino and Veronese wrote the first draft of the manuscript; Dominguez and Barbagallo critically revised the manuscript. All the authors approved the final version, submitted to the journal.

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