What Is the Routine Mitochondrial Health Check-Up Good For? A Holistic Approach in the Framework of 3P Medicine

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Abbreviations

3PM	Predictive, preventive and personalised medicine
AD	Atopic dermatitis
AF	Atrial fibrillation
ATP	Adenosine triphosphate
BHI	Bioenergetics health index
BRB	Blood–retinal barrier
CFS	Chronic fatigue syndrome
cGAS/STING	Cyclic GMP-AMP Synthase/Stimulator of Interferon Genes
COVID	Corona virus disease
CTD	Connective tissue dysregulation
DAKD	Diabetes associated kidney disease
DM	Diabetes mellitus
DR	Diabetic retinopathy
ECM	Extracellular matrix
ESRD	End stage renal disease
FSP	Flammer syndrome phenotype
HIF1-alpha	Hypoxia inducible factor 1 alpha subunit
IL-18	Interleukin 18

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IL-1β	Interleukin 1β
IS	Ischemic stroke
MAVS	Mitochondria-associated adaptor molecule
MHI	Mitochondrial health index
MHQC	Mitochondrial health quality control
MIA	Maternal immune activation
MRI	Magnetic resonance imaging
mtDNA	Mitochondrial Deoxyribonucleic acid
mtDNA-CN	Mitochondrial deoxyribonucleic acid- copy number
NLRP3	Nucleotide-binding domain, Leucine-Rich–containing family, Pyrin domain-containing-3 protein
NRF2	Nuclear factor erythroid 2–related factor 2
OSAS	Obstructive sleep apnoea syndrome
PDR	Proliferative diabetic retinopathy
PPPM	Predictive, preventive and personalised medicine
RMEC	Retinal microvascular endothelial cells
ROS	Reactive oxygen species
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TLR9	Toll-like receptor 9
ZBP1	Z-DNA binding protein 1

1 By Regulating Whole-Body Physiological Functions, Mitochondria Are at the "Forefront" of Holistic PPPM Approach

As the "powerhouse" of eukaryotic cells, mitochondria regulate whole-body physiological functions. The super-ordinated position mitochondria have secured for themselves via two pillars, namely as the main energy producer and genotoxic stress sentinel in the human body. Depending on the tissue type, with 2000 to 8000 per cell mitochondria are the most abundant subcellular organelle. For example, in heart, up to 70% of mass is created by mitochondria as the dominant organelle and powerful tissue remodelling modulator. Mitochondrial DNA (mtDNA) is lean on repair mechanisms and, therefore, very damage prone—the features which favour mtDNA for carrying out the role of a potent genotoxic stress sentinel in affected cells, tissues and organs. The proposed mechanisms consider mtDNA as the systemic second messenger of the cellular stress and a direct activator of the nuclear DNA repair machinery towards genotoxic conditions traced that, however, under progressing pathophysiological conditions, such as malignant transformation, may result in chemoresistance of cancer tissue [1]. Contextually, inhibiting mitochondrial metabolism is a new strategy in cancer therapeutic treatment [2].

Mitochondria evolve to sense any kind of stressors (environmental, metabolic, neuro/endocrine) and stress mediators (e.g., glucocorticoids and sex hormones, etc.). Responding to stress conditions, mitochondria undergo dynamic morphological and functional changes and generate signals of adaptation. Being situated in close proximity to the nucleus, mitochondria are capable to regulate human genome and cellular fate (health and death) via epigenetic mechanisms [3].

Mitochondrial disorders are described amongst the most frequent inborn defects in metabolism causing mainly dysfunction of the oxidative phosphorylation system composed of the electron transport chain and ATP-synthase [4]. The genetic defects underlie about a half of all registered mitochondrial diseases.

Mitochondrial health and bioenergetics health are tightly linked together (Fig. 1). Their indexation has been proposed for quantifying mitochondrial functionality and energetic efficacy [5].

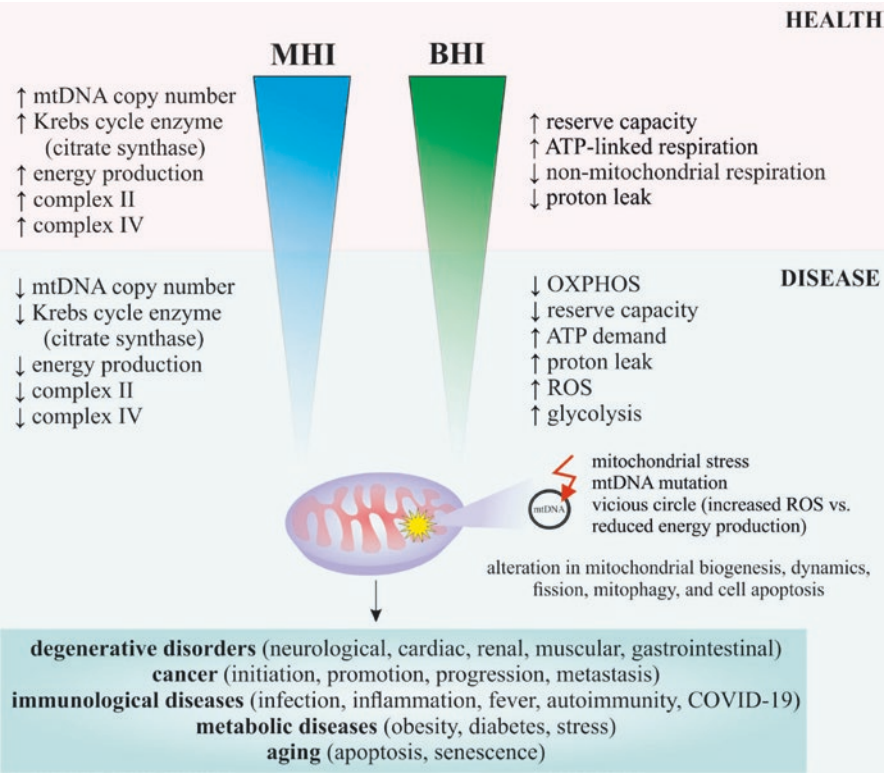

Fig. 1 MHI and BHI in health and disease. *mtDNA* mitochondrial DNA, *MHI* mitochondrial health index, *BHI* bioenergetic health index, *OXPHOS* oxidative phosphorylation, *ATP* adenosine triphosphate [5]

1.1 Mitochondrial Dynamics and Circadian Rhythmicity

Mitochondria are responsive to environmental stimuli such as high and low temperature, genotoxic environment, tobacco smoking, etc. To adapt to the ever-changing environment, mitochondria are highly dynamic in their shape and functionality. Loss of this flexibility known as "imbalanced mitochondrial dynamics" is associated with severe systemic disorders and represent as attractive therapeutic target in broad spectrum of human pathologies [6].

Accumulating research data demonstrate that mitochondrial morphology, generation of mitochondrial mass as well as mitochondrial respiration and ROS (reactive oxygen species) production—all directly depend on a circadian clock aligned to the light-darkness cycles [7]. Preclinical studies suggested that molecular clock disturbances lead to changed mitochondrial respiration. This knowledge is essential for better understanding abrogated mitochondrial rhythmicity and associated health risks in subpopulations exposed to changing daytime rhythms, e.g., typical for shift workers.

1.2 Shift Work

Shift work, light at night and ageing lead to altered circadian rhythmicity in mitochondria and may cause severe pathologies. A study by R. Bescos et al. reported on significant metabolic alterations in healthy adults exposed to only four nights of stimulated shift work, including reduced insulin sensitivity and mitochondrial function [8]. Disturbed physiologic circadian mechanisms are associated with systemic effects linked to abrogated mitochondrial rhythmicity including myocardial ischemia-reperfusion injury [9]. In cardiac tissue, intact mitochondrial rhythmicity plays a crucial role. Circadian dysfunction exacerbates cardiac injury. Concomitant myocardial infarction is further characterised by excessive cardiac cell death, autophagy and clearance of damaged mitochondria associated with ventricular dysfunction.

Chrono-therapeutic approach is recommended to prevent systemic mitochondrial dysfunction-associated damage in shift work as the circadian misalignment. Melatonin is the primary circadian output signal from the brain targeting mitochondria and modulating diverse molecular pathways depending on the light-darkness cycles [10]. Restoring nocturnal melatonin production is an effective therapeutic approach in maintaining mitochondrial health and bioenergetics. To this end, in preclinical studies, melatonin treatment significantly ameliorated ageing-related impairments in mitochondrial function [11].

1.3 Chronic Stress, Fatigue and Mitochondrial Burnout

As described above, mitochondria are adaptive to environmental stressors. However, chronic stress overload may cause imbalanced mitochondrial dynamics leading to

mitochondrial burnout with systemic effects and downstream pathologies. For example, toxicological studies demonstrated clear associations between chronic exposure to pesticides, severe mitochondrial injury and chronic diseases including cancers, diabetes mellitus, Parkinson's and Alzheimer's diseases, amyotrophic lateral sclerosis as well as reproductive dysfunction and inborn defects [12]. Experiments with the site-specific irradiation exposure revealed genotoxic insult to nuclear and mitochondrial DNA with downstream regulation events stabilising genome to costs of mitochondrial autophagy. Mitochondrial autophagy eliminates damaged mtDNA to prevent endonuclease G-mediated genome instability [13].

Four pillars are considered to functionally link stress reactions with mitochondria [14], namely

- Energy resources provided by functional mitochondria are decisive for an adequate stress response at molecular, cellular, organ and systemic levels.
- Adequate hormonal regulation is governed by healthy mitochondria.
- Mitochondrial, neuroendocrine and metabolic stress regulation is physiologically performed in a reciprocal manner.
- Behavioural patterns in psychologic distress response strongly depend on the mitochondrial health.

Under chronic psychologic distress conditions, metabolic and neuroendocrine stress mediators cause imbalanced mitochondrial dynamics and burnout followed by sustainable functional recalibration and allostatic load of mitochondria affecting brain tissue and cognitive functions, endocrine and immune systems synergistically involved into development of psychosomatic deficits and inadequate reactions towards non-compensated stress overload. Corresponding molecular and cellular mechanisms (epigenetic control of signalling and metabolic pathways) play the key role in the mitochondrial burnout promoted systemic dysfunction and cascading associated pathologies. Contextually, individual psychosocial experiences and resulting emotion response directly reflects the level of mitochondrial health which is an attractive target in behavioural medicine and well-being PPPM approach in the entire population.

Mitochondrial burnout is further linked to the mitochondrial mass variability, intra-mitochondrial calcium homeostasis, mitochondrial membrane potential, the level of oxidation and apoptosis/mitophagy under a non-compensated stress overload [15].

As the key stress-modulator, mitochondria influence all aspects of the stress response including systemic cortisol and catecholamine levels [14] differentiating between adequate (healthy controls) and abnormal (chronic fatigue, amongst others) stress response.

Metabolic shifts detected in the chronic fatigue syndrome (CFS) are extremely complex including irregularities in the energetic profiles, amino acids/nucleotides/nitrogens/hormones patterns and oxidative stress response associated metabolites—all directly related to compromised mitochondrial functionality [16]. In turn, over 60% of patients with mitochondrial disease report excessive symptomatic fatigue

and over 30%—severe, functionally limiting fatigue symptoms [17]. CFS is frequently diagnosed in relation to clinically established comorbidities which are many of associated with CFS that additionally complicate CFS treatment. Biological underpinning of CFS presentation revealed functional involvement of compromised mitochondrial health and immune system, shifted circadian rhythm / melatonin production and gut microbiome profiles, involvement of autonomic nervous and endogenous opioidergic systems, amongst others [18]. All the interacting systems involved suggest that an understanding of the CFS complicity may significantly contribute to the patient stratification and cost-effective PPPM implementation in management of fibromyalgia, depression, migraine and dementia, amongst others.

To achieve and study the CFS, a repeated forced swimming test has been applied to healthy mice. After 25 days of the forced swimming exercise, the level of fatigue has been investigated utilising mitochondria fraction in gastrocnemius muscle: the level of pyruvate dehydrogenase was significantly decreased in mitochondria of the forced swimming mice (CFS model) [19]. The authors proposed potentially beneficial effects by utilising sodium dichloroacetate for the treatment to prevent fatigue-like behaviour in CFS.

Studies dedicated to the adaptive mechanisms demonstrated that a well-controlled balance between fission and fusion is critical for maintaining mitochondrial health and functionality, when mitochondrial are exposed to excessive environmental and metabolic stressors. On the one hand, specifically the fusion is an adaptive mechanism for stress mitigation by mixing complementary contents of partially damaged mitochondria. On the other hand, fission is essential to create new mitochondria increasing the mitochondrial mass but also contributing to the mitochondrial health quality control by removal of severely damaged mitochondria and facilitating apoptosis [20], e.g., under non-compensated stress overload. Extracellular release of fragmented mtDNA is a reliable biomarker for the non-compensated stress overload and predisposition to downstream pathologies related to the compromised mitochondrial health. Chronic accumulation of damage-associated molecular patterns including mtDNA fragments have been demonstrated as inducing downstream inflammatory response via pattern-recognition receptors (such as NLRP3 inflammasome, TLR9, cGAS/STING and ZBP1) leading to chronic inflammation observed, for example in autoimmune disorders such as type 1 diabetes mellitus, Sjögren's syndrome and rheumatoid arthritis, amongst others [21].

2 Microvascular Deficits and Silent Lacunar Brain Lesions in Flammer Syndrome: A Case Presentation for Implementing PPPM Strategies

Individuals with the Flammer syndrome phenotype (FSP) are known to suffer from primary vasospasm, increased endothelin-1 level and pronounced sensitivity to psychological distress and cold stress provocation [22]. Several disorders have been associated with FSP such as connective tissue deficits, migraine, tinnitus, normal-tension glaucoma and highly aggressive cancer subtypes [23, 24], amongst

others—all, in turn, are tightly linked with mitochondrial impairments [5, 25, 26]. The best acknowledged FSP attributes associated with mitochondrial injury are shifted circadian rhythms, increased blood endothelin-1 levels and disturbed microcirculation resulting in subtle ischemia-reperfusion events [27, 28].

Recently, a detailed presentation of FSP was performed in the context of ischemic stroke vulnerability in the population and the call for multi-professional expertise for implementing advanced PPPM strategies [29]. The topic-dedicated case report demonstrated the spectrum of signs and symptoms of the Flammer syndrome including high stress-sensitivity and strong vasospastic reactions under stress conditions accompanied with a significantly increased endothelin-1 level (3.2 pg/mL) in blood serum, low body mass index, low blood pressure, migraine with aura, retinal ischemic lesions diagnosed early in life, connective tissue impairments and corresponding pregnancy complications. Mitochondrial test demonstrated strongly compromised health quality according to the expertise of 3PMedicon [29]. Recommended brain-MRI revealed micro-angiopathy, lacunar microinfarction zones and white matter hyper-intensities and micro-haemorrhages—see Fig. 2 [30]. Since brain lacunar microinfarction is an independent and best acknowledged predictor of ischemic stroke predisposition, the authors conclude the essentiality of PPPM

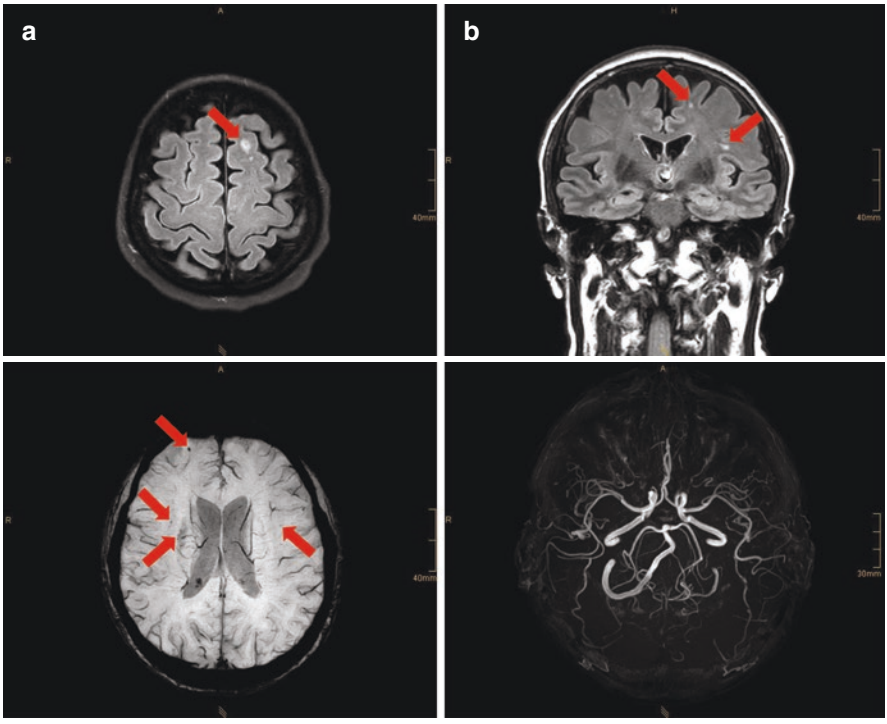

Fig. 2 FSP case report [30]: Brain-MRI demonstrated signs of micro-angiopathy; several lacunar microinfarction zones (**a**, **b**), white matter hyper-intensities and micro-haemorrhages

implementation to the FSP considered a suboptimal health condition. Obviously mitochondrial health quality control is highly appropriate for diagnostics and targeted prevention of downstream pathologies in FSP-individuals.

3 Compromised Mitochondrial Health in Critical Illnesses: Prominent Examples

3.1 Mitochondrial Dysfunction in the Ageing-Related Metabolic Disorders

Organismal ageing is associated with progressive metabolic changes, reduced cellular functions and systemic deterioration of multiple tissues synergistically causing vulnerability to the ageing-related disorders. Mitochondrial burnout plays the key role in accelerated ageing and associated pathologies, such as diabetes mellitus type 2, cancers, neurodegenerative and cardiovascular diseases. Accumulated research data suggest that accelerated ageing and related diseases are caused by insufficient energy supply associated with mitochondrial dysfunction that could be restored by a variety of interventions such as mitochondrial-targeted therapy also linked to the longevity-pathways [31].

3.2 Female and Male Reproductive Health

Infertility is frequently liked to an accelerated ageing. To this end, mitochondria create a high portion of the cytoplasm in oocytes which are the largest cells in mammalians. Furthermore, the number of mitochondria per cell is considered the highest in oocytes that is essential to effectively support oocytes' maturation, fertilisation and initial embryonic development [32]. The total number of mitochondria as well as the mitochondria functionality—both are decreasing in oocytes with progressing age. Consequently, mitochondrial dysfunction in oocytes negatively impacts their quality, fertility and embryonal development. On the other hand, preventive therapies tailored to the mitochondrial health have been proposed as promoting oocyte rejuvenation.

The mtDNA quantity inversely correlates to sperm quality being implicated in energy production, redox equilibrium and calcium regulation and apoptotic pathways—all essential for flagellar motility, capacitation, acrosome reaction and gametic fusion. Therefore, mitochondrial health is central for the spermatozoa metabolism and quality presenting an attractive target for the male fertility [33].

Specifically mitochondria-targeted antioxidants significantly improve semen quality and their overall reproductive performance utilised for artificial insemination [34].

Finally, mitochondria are the key regulator in the synthesis of sex hormones such as oestrogen that is decisive for phenotypic development and downstream regulation of mental and behavioural patterns [35]. Therefore, mitochondrial health is crucial for all aspects of reproductive function in humans.

3.3 Pathologic Pregnancy

Accumulated research data demonstrate the association between the maternal immune activation (MIA) during pregnancy and offspring neuropsychiatric disorder risks, where mitochondria play the role of the mediator. Furthermore, mitochondrial dysfunction is evident in preclinical MIA models and human neurodevelopmental disorders [36]. This is the new concept of the pathophysiology of mental health disorders which originate from the exposure to MIA and mitochondrial dysfunction during pregnancy that makes mitochondrial health to an attractive target for the pre-pregnancy check-up and adapted therapeutic approach [24].

3.4 Connective Tissue Dysregulation

Mitochondrial dysfunction has been demonstrated as the key player in the connective tissue dysregulation (CTD) [37]. Noteworthy, incidence of CTD tends to increase specifically in young populations and is attributed to changing environmental conditions such as an environmental stress that mitochondria are extremely sensitive to. Furthermore, there is a broad spectrum of pathologies linked to CTD and developing early in life including severe complications in pregnancy, eye disorders, aortic aneurism, pulmonary fibrosis and musculoskeletal disorders, amongst others [24, 38]. Intact energy metabolism and extracellular matrix functionality—together orchestrate and maintain tissue organisation. In turn, mitochondrial dysfunction, imbalanced hypoxic-ischemic events, extracellular matrix (ECM) remodelling and chronic low-grade inflammation are implicated in the disease progression. To this end, ECM remodelling is performed by metalloproteinases under mitochondrial redox control mechanism [39]. Shifted redox control by disordered mitochondria lead to abnormal / extensive ECM remodelling which has been implicated to the cancer progression and metastatic disease, ischemia/reperfusion injury, atherosclerosis, arthritis and neuro/degeneration.

3.5 Atrial Fibrillation (AF)

Worldwide AF is the most prevalent and progressive type of cardiac arrhythmias and an independent risk factor of the downstream development of heart failure and ischemic stroke. Despite steadily improving treatment modalities, still they are only moderately effective in the AF severity progression. Mitochondrial health is compromised in AF, due to highly increased demand towards the energy supply associated with the accelerated atrial activation (both electrical and mechanical) of the heart rate characteristic for AF. Mitochondrial damage and dysfunction are pre evidence the dominant contributor to the retarding cardiomyocyte function and cell population in AF. Contextually, targeted mitochondrial therapies are considered a promising approach for diagnostics and therapeutic interventions to advance overall AF management [40].

3.6 Ischemic Stroke

The pivotal role of mitochondria in ischemic stroke (IS) prediction, prevention and treatment has been recently demonstrated based on the abundant research data available [5]. Worldwide, stroke is the leading cause of physical and intellectual disability in adults, and a cost-effective and timely therapy approach are considered problematic. Mitochondria are a major target in hypoxic/ischemic injury, and the mitochondrial health quality control (MHQC) was proposed an attractive target for the ischemic stroke risk assessment, neuroprotective therapies and improved individual outcomes [5, 41–44]. Furthermore, (MHQC) is of great clinical utility for predicting and preventing cerebral small vessel disease causing one in five stroke cases and considered a leading cause of cognitive impairment and dementia [45]. Finally, compromised mitochondrial health was detected in the peri-infarct zone of young adults and associated with poor recovery prognosis [46].

3.7 Skin Disorders

At the organismal level, the skin has the main protector against foreign bodies and toxic invasions maintaining physiologic body homeostasis despite noxious environments. In the skin, there is a reciprocal relationship between the physiologic functionality of mitochondria and melatonin metabolism. To this end, mitochondria act as a central hub of melatonin metabolism which, in turn, is indispensable for physiological skin functions and for an effective protection of the cutaneous homeostasis against environmental invasiveness and toxicity. In the skin, melatonin-mitochondria axis attenuates adverse systemic effects such as those associated with the UV-light exposure, pro-inflammatory and carcinogenic processes [47]. Furthermore, specifically functional melatonin metabolism effectively operates against mitochondrial injury and dysfunction modulating mitochondrion redox control and bioenergetic homeostasis and demonstrating significant anti-apoptotic effects, therewith allowing for an adequate cellular adaptive response to skin injury and effective repair.

Contextually, there is a clear reciprocity between the mitochondrial and skin health: common as well as rare skin pathologies demonstrate mitochondrial involvement; in turn, there is a dermal manifestation of primary mitochondrial diseases. This reciprocity led to developing therapeutics targeted in the skin health utilising an ATP production boost and free radical scavenging highly attractive for both clinical and aesthetic purposes. Bioactive compounds effective for improving mitochondrial function have proved effective against aged and diseased skin [48].

3.7.1 Atopic Dermatitis (AD, Also *Atopic Eczema/Neurodermitis*)

AD is the most common inflammatory skin disease characterised by cutaneous inflammation and associated deficient epidermal barrier. Recently performed differential proteomics investigated epidermis of healthy versus AD skin lesions revealed an impaired activation of the NRF2-antioxidant pathway and reduced mitochondrial proteins in the diseased epidermis [49].

Moreover, an increased oxidative stress was demonstrated as being specific for AD-lesions. Treatment with MitoQ largely corrected the AD profile suggesting mitochondria as a specific target for mitigation AD-lesions [50]. Finally, dietary vitamin D supplementation has been proposed to be effective for AD treatment [51]. To this end, vitamin D-related metabolites support mitochondrial function [52], and the vitamin D—mitochondria cross-talk seems to be essential for maintaining skin health.

3.8 Impaired Wound Healing

During wound healing, stage-specific changes in mitochondrial metabolism coordinate the physiologic healing process: for the subpopulation of early-stage pro-inflammatory wound macrophages, an excessive mitochondrial ROS production and HIF-1alpha stabilisation are highly specific, whereas the late-stage wound macrophages are characterised by IL-4Ralpha-mediated mitochondrial respiration and mitohormesis [53]. Furthermore, factors which negatively influence mitochondrial health also may impair healing such as excessive environmental, psychologic and metabolic stress, oxygenation defects, ageing, alcohol overuse, smoking and nutritional deficits, amongst others. Therefore, treatments targeted to the mitochondrial health are of particular interest for maintaining physiological healing [54].

Finally, keloid scars are caused by tissue injury leading to impaired healing and predisposition to cancerous lesions. Research data demonstrated compromised mitochondrial health as being highly relevant for developing keloid scars [55] that is highly indicative for complex treatments involving mitochondria as the specific target.

3.9 Cancers

Under excessive stress, mitochondrial respiratory chain dysfunction induces NOX-associated overproduction of cellular ROS. The escalated ROS generation is utilised by cancer cells as a messenger to stimulate cell proliferation under oxidative stress conditions further promoting pro-carcinogenic genetic instability. As discussed above, mtDNA is more susceptible to the ROS-associated damage and mutagenesis than the nuclear genome, since mtDNA lacks histone protection, possesses highly limited DNA repair capacity, and is in close proximity to the electron transport chain. Consequently, the level of mtDNA mutations is 10–20 times higher than this of chromosomal DNA that plays an important role in the cancer initiation at the site of damaged mitochondria [56].

Accumulated evidence suggests that mitochondrial DNA copy number (mtDNA-CN) is considered an important indicator of mitochondrial dysfunction and an easily quantifiable parameter useful for the health risk assessment towards chronic diseases associated with mitochondrial impairment such as diabetes mellitus and cancer [57]. Indeed, an excessive mitochondrial fission promotes the

pro-tumorigenic phenotype [58]. However, meta-analytical studies demonstrate that mtDNA-CN may be increased in some malignancies but decreased in others [59] that argues against simplistic measurements and interpretation of mtDNA-CN alone.

3.10 Sleep Disorders

In mitochondrial disorders, sleep complaints are prevalent and amongst them specifically the sleep-disordered breathing (e.g., obstructive sleep apnoea syndrome OSAS associated with decreased microcirculation, impaired aerobic metabolism and muscle dysfunction and contribute to upper airway obstruction during sleep) was reported as being the most typical sleep disorder [60]. To this end, an excessive damage to the mtDNA was demonstrated for patients diagnosed with OSAS [61].

Mitochondria display circadian oscillation and are involved in the sleep-wake cycle [62]. Physiological sleep patterns and good quality of sleep is essential for systemic effects such as repair mechanisms and has a defensive role against oxidative damage. Contextually being linked to the oxidative stress, insomnia is associated with compromised mitochondrial health, depression and anxiety disorders as well as a severe damage to immune and cardiovascular systems [63]. Furthermore, molecular biological analysis of the fatal familial insomnia terminal stages confirmed severe impairments in the mitochondrial function and protein synthesis machinery associated with the extensive neuron loss detected in mediodorsal thalamus [64].

Also excessive daytime sleepiness investigated in persons diagnosed with the posttraumatic stress disorders (such as military personnel) demonstrated shifted expression patterns of genes involved in mitochondrial bioenergetics [65].

3.11 Psychiatric Disorders

Autism, Schizophrenia, bipolar and major depressive disorders share common epi/genetic risk factors as well as symptoms of metabolic alterations and mitochondrial dysfunction [66]. Being impaired to a various degree, mitochondrial function and downstream redox balance and brain energetics are implicated in pathophysiology of psychiatric disorders. Moreover, mitochondrial dysfunction was proposed to be circuit-specific for the developmental stage of corresponding pathology that makes mitochondria to the primary target for the patient stratification and cost-effective personalised treatment of psychiatric disorders. Specifically for the major depressive disorder this would be an excellent solution, since nearly 50% of these patients under treatment never reach remission [67]. The incidence of depression continues to increase worldwide and conditions associated with the COVID-19 pandemic have significantly accelerated these trends. The underlying

pathomechanisms demonstrate synergistic effects of social stress on mitochondrial injury and inflammation together facilitating the stress-related depression [67]: non-compensated stress overload damage mitochondria which in turn release cell-free mtDNA and trigger neuroinflammatory processes in brain [68]. At the cellular level, mitochondrial dysfunction is reflected in an impaired neuroplasticity and neurotransmission in brain [69]. Contextually, therapeutic interventions focused on modulating mitophagy are under development to treat depression effectively.

3.12 Endocrine Disorders

Mitochondria are critical organelles for endocrine health: the steroid hormone biosynthesis is performed in mitochondria which provide energy for hormone production and trafficking. Endocrine dysfunction is frequently observed in patients diagnosed with mitochondrial diseases and clearly reflected in significantly decreased intracellular production as well as diminished extracellular secretion of hormones. The most frequently described endocrine dysregulation in patients with inborn mitochondrial dysfunction is Diabetes mellitus. Other types of endocrine manifestations include growth hormone deficiency, hypogonadism, adrenal dysfunction, hypoparathyroidism and thyroid disease. Mitochondria-associated endocrine dysfunction generally occurs at the multisystem level that makes mitochondria to the unique target for developing innovative therapeutic approaches for maintaining endorine health [70].

3.13 Kidney Disease

The kidney function essentially demonstrates high level of dynamicity and therefore demands an extraordinary large amount of energy for performing the entire spectrum of activities including maintaining the body's metabolism, plasma haemodynamics, electrolytes and water homeostasis, nutrients reabsorption and hormone secretion. After the heart, kidney demonstrates the second highest mitochondrial count and oxygen consumption [71]. Contextually, the mitochondrial health status is pivotal for maintaining all kidney functions adequate, and mitochondria-targeted therapeutics attract a lot of attention for maintaining mitochondria homeostasis, in order to prevent downstream kidney injury and disease progression. One of the best examples is the diabetes associated kidney disease (DAKD) reported as the leading cause of end stage renal disease (ESRD) in the USA. Per evidence, massive alterations in mitochondrial bioenergetics of the kidney cells cause the disease progression from DAKD to ESRD [72]. The central contributing factors are alterations in the mitochondrial dynamics and energetics, non-compensated oxidative stress overload, shifted redox status and metabolic profiles—all innovative targets to delay health-to-disease transition in the kidney.

3.14 Liver Disorders

Due to the central organismal detoxification function of the liver, mitochondria is the key organelle in regulating hepatic redox status and all associated functions. Consequently, mitochondrial dysfunction underlies pathogenesis of acute and chronic liver disorders such as alcoholic and non-alcoholic fatty liver disease, ischemia-reperfusion and drug-induced liver injury, hepatitis and liver cancers [73]. Mitophagy of damaged mitochondria is the critical regulator in the liver patho/physiology. Disordered mitochondrial fusion and fission result in a progressive reduction of functional mitochondria leading to the excessive necrosis and apoptosis, organ failure and metabolic dysfunction of the liver—all clearly demonstrated for the ischemia-reperfusion injury as a main complication of hepatectomy, liver transplantation, trauma and hypovolemic shock [74]. Corresponding protective measures consider mitochondrial health maintaining therapeutic strategies as promising for prevention and cost-effective treatment of liver pathologies.

3.15 Eye Disorders

3.15.1 Retinal Microvascular Endothelial Cells Dysfunction

As discussed above, environmental and metabolic stress stimuli cause mitochondrial damage releasing mtDNA into the cytosol and cell-free mtDNA fragments. Released mtDNA then drives the activation of non-infectious (sterile) inflammation implemented downstream, for example, in the retinal microvascular endothelial cells (RMECs) dysfunction playing the central role in the inner endothelial blood–retinal barrier (BRB) and BRB breakdown. Per evidence, both RMEC dysfunction and BRB breakdown frequently occurs in posterior-segment eye diseases, causing loss of vision [75].

3.15.2 Myopia

Connective tissue deficits/disease is associated with mitochondrial impairments (upstream) and on the other hand with a broad spectrum of associated pathological conditions (downstream) such as myopia and glaucoma [24]. Although, the mechano-biology underlying connective tissue remodelling differs between both diseases, the asymmetric remodelling of the optic nerve head in a myopic eye significantly increases risks of glaucoma development and mechanical insult of retinal ganglion cell axons [76].

3.15.3 Glaucoma

Mitochondrial dysfunction is associated with normal- and high-tension glaucoma—both are multifactorial diseases with characteristic optic nerve degeneration leading to blindness. Dysfunctional mitochondria trigger sterile inflammation via NLRP3 inflammasome activation, liberation of IL-1β and IL-18 and interferon signalling. Mitochondrial associated ER membrane contacts and the mitochondria-associated adaptor molecule MAVS can activate NLRP3 inflammasome signalling. In parallel, the mitochondrial ATP production is significantly reduced that synergistically

results in downward spiral accelerating degeneration process. These pathomechanisms occur in retinal ganglion cells, microglia cells and astrocytes [77]. In several glaucoma models demonstrated upstream decrease in the mitochondrial mass and in the mitochondria-encoded electron transport chain transcripts prior to the hypoxic retinal ganglion cells loss (downstream) [78].

Finally, it has been demonstrated that glaucoma prediction is possible in vulnerable subpopulations such as individuals with the Flammer syndrome phenotype: disease-specific biomarker-panels are detectable in the body fluids including significant alterations in mitochondrial protein setup, stress response, ischemia-reperfusion signalling, blood–brain barrier breakdown and tissue remodelling associated pathways, amongst others [79–83].

3.15.4 Diabetic Retinopathy

Proliferative diabetic retinopathy (DR) is the leading cause of blindness in the working-age population. DR screening is currently ineffective, since the disease remains undetected until irreversible damage occurs. DM associated small vessel disease and neuro-retinal changes synergistically result in conversion of DR into PDR. Characteristic pathomechanisms include progressive mitochondrial and retinal cell damage, chronic sterile inflammation, neovascularisation and reduced visual field. Mitochondrial health control is strongly recommended for advanced DR management. To this end, particularly multiomic tear fluid analysis is considered as instrumental for predicting DR clinical manifestation and disease progression [84].

3.15.5 Early Cataract

Mitochondrial dysfunction is implicated to the cataract development—corresponding pathomechanisms involved shifted redox control [85].

To prevent early cataract manifestation, phenotype-specific screening has been suggested; compromised mitochondrial health is involved in the proposed phenotype [86].

3.16 Neurodegeneration

Accumulating research data have identified several overlapping pathomechanisms involved in a broad spectrum of neurodegenerative disorders such as cognitive decline, Alzheimer's and Parkinson's diseases, diabetic retinopathy and neuropathy as well as glaucoma, amongst others. Per evidence, these pathomechanisms include non-compensated oxidative stress, mitochondrial dysfunction, neuroinflammation and significant metabolic alteration [87, 88].

3.17 Musculoskeletal Degenerative Disorders

Musculoskeletal system disorders have been reported as associated with a degeneration of supporting tissues due to pro-inflammatory micro-environments. Affected chondrocytes, osteoblasts and synoviocytes exhibit extensive mitochondrial injury

and cell death, cartilage degeneration, bone erosion and musculoskeletal degeneration. An artificial transfer of exogenous functional mitochondria has been proposed as highly innovative and effective therapy approach to restore mitochondrial functionality by replacing malfunctioning mitochondria with their healthy and functional counterparts. This innovative approach is expected to reverse the failed metabolic status of musculoskeletal tissues by restoring mitochondrial bioenergetics [89].

3.18 Respiratory Diseases

Since mitochondria do sense and respond to the upstream processes pivotal for respiratory diseases such as environmental insults, exposure to toxic pollutants, infections and tobacco smoke, they are well-known modulators of patho/physiological processes influencing airway structure, functions, airway remodelling and hyper-responsiveness [90]. To this end, allergic asthma is tightly associated with mitochondrial dysfunction, reduced ATP production, imbalanced oxidative stress and abnormal calcium homeostasis. Particularly in the lung—an oxygen-rich organ, defective mitochondria play the key role in the pro-inflammatory mechanisms of lung fibrosis and excessive airways cells' apoptosis [91]. Due to the redox-dependent modulation of the cell signalling, antioxidant treatment were suggest to mitigate asthma-associated hyper-responsiveness of airways. However, general antioxidant compounds have proven clinically ineffective against asthma [92]. In contrast, specifically mitochondria-targeted medication (smooth muscle remodelling) is considered highly promising treatment for asthma prevention and mitigation of its severe forms [93].

3.19 Long COVID

Chronic fatigue syndrome (CFS) is highly relevant for a big portion of patients infected with SARS-CoV-2 who suffer from CFS symptoms for a couple of months that is called a "long COVID". Accumulated research data indicate mitochondrial involvement into pathophysiology of both CFS and "long COVID" suggesting high clinical utility of mitochondrial health check-up and therapeutic approaches focused on the mitochondrial health [94].

4 Conclusions and Outlook in the Framework of 3P Medicine

Mitochondria, as the "powerhouse" of eukaryotic cells, play the key role in the cell fate (proliferation, differentiation, growth and death) as well as systemic events and effects including stress response towards environmental changes, redox balance, the innate and acquired immunity as well as severity of the acute and chronic disorders.

This key role makes mitochondria to an attractive target in treating a variety of disorders ranging from metabolic alterations, ischemia-reperfusion events, chronic inflammatory and respiratory diseases, mood disorders, to neurodegeneration and malignancies. For example, metabolic alterations associated with the mitochondrial dysfunction are considered causal for the insulin resistance and type 2 diabetes mellitus. Metformin, which is the widely prescribed DMT2-medication, also retards aging in model organisms and reduces the incidence of aging-related diseases such as neurodegenerative disease and cancer in humans [95]. It is widely accepted that the mitochondrion is a primary target of metformin responsible for its anti-glycaemic effect. Furthermore, specifically due to its primary effects on the complex I of mitochondrial electron transport chain, metformin inhibits cancer cell growth that is particularly relevant for DMT2 patients strongly predisposed to particularly aggressive cancers with poor outcomes [96].

Well controlled mitochondrial dynamics (mitochondrial mass in corresponding tissue, fission, fusion, biogenesis and mitophagy) is pivotal for their functionality, and can be pharmacologically manipulated. In clinical trials, creatine, coenzyme Q10 and antioxidants targeted specifically to mitochondria demonstrate remarkable effects on restoring mitochondrial bioenergetics, for example, in treating neurodegenerative processes [97]. In case of mitochondrial deficient conditions leading to depleted energy production and ROS excess, proposed compensatory mechanisms of targeted treatments prompt mitochondria to enhance ATP production by overexpressed antioxidants and respiratory complex subunits, for example using bezafibrate (resulting in activation of the PPAR-PGC-1 alpha axis), resveratrol and metformin (AMPK activation), as well as using Sirt1 agonists (quercetin and isoflavone-derived compounds) [97]. Further pharmacological strategies utilise dietary antioxidant supplements targeted to mitochondria (L-carnitine, coenzyme Q10, MitoQ10) and triggering Nrf2/antioxidant response by oleanolic acid derivatives (triterpenoids).

Holistic treatment strategies considering mitochondria as the cellular genotoxic stress "sentinel", are focused on restoring and maintaining mitochondrial homeostasis utilising systemic effects by supervised physical activity, keto-diet application, mitigation measures focused on reduced exposure to stress and vitamin therapy, amongst others. Towards the latter, vitamin D—mitochondria axis is considered an attractive target for restoring mitochondrial-associated homeostasis stabilising downstream physiologic processes. To this end, vitamin D deficiency is a worldwide pandemic resulting in multifaceted pathological processes and development of severe disorders including cardiovascular deficits, malignant transformation and neuro/degeneration via non-compensated oxidative stress, pro-inflammatory signalling and mitochondrial damage. Vitamin D values below 25 ng/mL have been associated with abnormal vascular smooth muscle contraction and disturbance in calcium homeostasis and mitochondrial metabolism [98]. Vitamin D deficiency is frequently accompanied with symptoms of skeletal muscle myopathy such as muscle weakness and fatigue. Contextually, vitamin D- mitochondrial axis is pivotal for maintaining mitochondrial health and functionality within skeletal muscle and mitigating fatigue [52]. Furthermore, there is an evident association between microbiome abnormalities and mitochondrial stress [99].

Finally, there is an evident reciprocity between mitochondrial and organismal health status: compromised mitochondrial health is reflected in systemic damage as well as organismal health-to-disease transition is reflected in an altered mitochondrial signalling. Contextually, mitochondrion acts as a natural biosensor integrated into human cells, and the routine non-invasive mitochondrial health quality control test is a powerful tool for the holistic predictive diagnostic approach in PPPM-framework highly recommended at the level of primary and secondary care for

- the whole-body health quality check-up,
- pre-pregnancy check-up,
- health-to-disease transition check-up,
- accompanying diagnostics in sport medicine and supervised physical activities,
- accompanying diagnostics in physiotherapeutic and well-being services,
- therapy efficacy monitoring for personalised treatments (e.g., chronic fatigue; burnout syndrome and sleep disorders; eye, skin, kidney, liver and respiratory diseases, endocrine and cardiovascular impairments, musculoskeletal- and neuro-degenerative disorders, depression, etc.).

Table 1 presents prominent conditions which mitochondrial health quality test is essential for to predict disease development and progression, to apply targeted prevention and treatments tailored to the person as well as to monitor treatment efficacy.

Table 1 A brief list of conditions under which mitochondrial health is known to be compromised and, therefore, its monitoring may be of a great practical benefit in application of 3P medicine in future healthcare

Conditions	Prominent examples and clarifying notes
Environmental and professional occupation risks with adverse effects on mitochondrial health status	
Exposure to ionising radiation/aggressive particles	Professional occupation; environmental (geo-specific natural radiation and artificial) contamination; long and frequent flights
Toxic environment	Heavy metals; toxic chemicals; extensive air pollution, amongst others
Electromagnetic smog	Natural (geo-specific) and artificial (e.g., mobiles) sources of electromagnetic irradiation
Shift work	Changing physiologic circadian rhythms
Non-physiologic time-frame of the job performance	Different from an individual circadian rhythm
Socio-economic and lifestyle associated risks	
Malnutrition	Suboptimal/deficient dietary patterns
Suboptimal life style	Stress overload, sedentary lifestyle, deficits in physiologic needs
Extensive body activities	Physical distress

Table 1 (continued)

Conditions	Prominent examples and clarifying notes
Genetic risks	
Family predisposition to chronic/severe disorders	Inborn genetic information leading to metabolic shifts and increased risks of rare and major disorders such as diabetes mellitus type 1, autoimmune disorders, stroke, cancers and neuro/degenerative pathologies, amongst others
Highly relevant medical conditions	
Suboptimal health conditions	Health-to-disease transition linked to decreasing mitochondrial health quality
Vascular status associated conditions	Increased endothelin-1 level, vascular stiffness, primary and secondary vasospasm, low and high blood pressure, ischemia-reperfusion, Flammer syndrome, etc.—all potentially linked to mitochondrial damage
Migraine and headache	
Tinnitus	
Hormonal stress	
Psychologic distress, autism spectrum condition	Mitochondrial burnout
Burnout syndrome	
Chronic fatigue	
Abnormal sleep patterns	
Inadequate stress response and behavioural patterns	
Psycho-trauma and post-traumatic stress disorder	
Musculoskeletal deficits and impairments	Mitochondrial impairments to be diagnosed and treated
Frequent acute infections	
Chronic inflammation and associated conditions	
Prolonged and impaired wound healing	
Microbiome shifts and pathogenic bio-flora	Mitochondrial stress is highly indicative for systemic effects caused by bio-toxins; relevant sources of information: body fluids, skin, oral and vaginal cavities, digestive and urogenital tracts, airways, wounds, etc.
Digestion-associated deficits	Multifaceted involvement of mitochondria to be considered for diagnostics and treatments tailored to the person
Allergies	
Asthma	
Local deficits of unclear aetiology	Eyes, skin, hair, nails, connective tissue etc.
Accelerated ageing	Higher biologic age against chronologic one—decreased mitochondrial functionality
Major disorders in the population	Mitochondrial component is essential to be considered for the holistic approach
Rehabilitation	
Medications	

Table 1 (continued)

Conditions	Prominent examples and clarifying notes
Acute viral and bacterial infections	Anti-biotics, immunisation and pain-killers—all are known to cause mitochondrial damage and dysfunction
Vaccinations	
Frequent acute and chronic pain	
Complex treatment of multifactorial syndromes and diseases	Mitochondrial component has to be considered in secondary prevention and monitoring of the therapy efficacy
Routine health condition check-up recommended for targeted prevention	
Regular health status check-up	Protection against health-to-disease transition
Pre-pregnancy check-up	Preventable pregnancy complications
Sport medicine	Protection against negative side-effects
Physical exercise couching	Improved individual outcomes
High performance athletes couching	Reaching top-achievements and preventing life-threatening conditions

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