Our Dermatology Online

Review Article

Mitochondrial dysfunction in metabolic syndrome and inflammatory skin disease

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ABSTRACT

Metabolic syndrome is a multifactorial process characterized by obesity, hypertension, hyperlipidemia, hyperglycemia, and insulin resistance, significantly increasing the risk of cardiovascular disease (CVD), type 2 diabetes mellitus, and other chronic health conditions. The prevalence of metabolic syndrome is rising globally due to sedentary lifestyles and poor dietary habits. Inflammatory skin diseases, including psoriasis, atopic dermatitis (AD), rosacea, acne vulgaris, lichen planus, acanthosis nigricans, androgenetic alopecia and hidradenitis suppurativa are closely linked to metabolic syndrome and mitochondrial dysfunction. These skin conditions are characterized by dysregulated immune responses and increased activation of inflammatory cytokines and immune cells. Additionally, mechanisms resulting in the induction of mitochondrial apoptosis influence the pathogenesis of these inflammatory skin diseases, while oxidative stress, inflammation and insulin resistance further interlink mitochondrial dysfunction and metabolic syndrome. Understanding the role of mitochondrial dysfunction in the pathogenesis of metabolic syndrome and inflammatory skin diseases is crucial for developing targeted therapies. Further research is needed to explore the contributing pathophysiology and develop strategies for preventing and treating these conditions. Genomic studies have also identified mutations associated with mitochondrial dysfunction and insulin resistance, offering potential targets for personalized therapies.

Key words: Mitochondrial dysfunction, Metabolic syndrome, Insulin resistance, Autoinflammatory skin disease, Oxidative stress

INTRODUCTION

Metabolic syndrome is characterized by a combination of factors, including obesity, hypertension, hyperlipidemia, hyperglycemia, and insulin resistance. These interrelated metabolic irregularities greatly increase the likelihood of developing CVD, type 2 diabetes, and various chronic health disorders [1]. The incidence of metabolic syndrome has steadily risen due to sedentary lifestyles, poor dietary habits, and the global obesity pandemic. The prevalence of metabolic syndrome varies across populations and age groups, but it is estimated that approximately one billion adults worldwide have this condition [1]. Early detection, lifestyle modifications, and appropriate medical interventions are crucial in managing metabolic syndrome and reducing the risk of associated health problems.

Metabolic syndrome is a risk factor for various inflammatory skin diseases, including psoriasis, atopic dermatitis (AD), acne, rosacea, androgenetic alopecia, acanthosis nigricans, lichen planus and hidradenitis suppurativa. The link between metabolic syndrome and inflammatory skin disease is thought to be mediated, in part, by mitochondrial dysfunction [2]. Mitochondrial

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dysfunction in skin diseases is thought to be caused by disruption of the mitochondrial membrane potential, reduced adenosine triphosphate (ATP) production, and induction of mitochondrial apoptosis [3]. This dysfunction may result in cutaneous activation of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF-α), c-Jun N-Terminal Protein Kinase 1 (Jnk1), interleukin-6 (IL-6) and IL-8, which can lead to reduced expression of the insulin receptor substrate (IRS1) and Glut4 insulin receptor genes, as well as decrease insulin stimulated glucose uptake in adjacent liver, skeletal and adipose tissue. [4] These factors therefore contribute to insulin resistance and metabolic syndrome. Conversely, metabolic syndrome also induces endoplasmic reticulum (ER) stress, contributing to mitochondrial dysfunction and inflammation in the cutaneous environment. This can cause an accumulation of unfolded or misfolded proteins in the ER, activating the unfolded protein response (UPR) [5]. UPR activation initiates restoration of normal ER functions by reducing ER stress, however persistent activation can lead to mitochondrial dysfunction and inflammation [6]. For example, UPR activation leads to activation of the nuclear factor-κB kinase (NF-κB-IKK) pathway. Activated NF-κB translocates into the nucleus and switches on the expression of various genes involved in inflammatory pathways, such as IL-1 and TNF-α. The ER stress in psoriasis may therefore contribute to increased TNF-α and contribute to the inflammation in psoriasis.

This article will address mitochondrial dysfunction and its association with metabolic syndrome and inflammatory skin disease.

MITOCHONDRIAL DYSFUNCTION WITH CORRELATES TO METABOLIC SYNDROME

Mitochondrial dysfunction compromises the mitochondrial respiratory chain, reducing ATP production, increasing oxidative stress, and altering mitochondrial dynamics [7]. These abnormalities constitute hallmark features of metabolic syndrome, and the underlying mechanisms of mitochondrial dysfunction are multifactorial. The three primary factors contributing to mitochondrial dysfunction in metabolic syndrome include oxidative stress, inflammation, and insulin resistance:

Oxidative stress: In the mitochondria, through the process of oxidative phosphorylation, more than 90% of cellular ATP is produced as protons, which diffuse along their concentration gradient from the matrix across the intermembrane space [3]. Oxygen is the acceptor of electrons, and the process ultimately results in the formation of water and energy. However, a very small fraction of high-energy electrons leak from the electron transport chain and directly react with oxygen rather than following this coordinated path. This deviation results in a cascade of events, subsequently contributing to metabolic syndrome, as summarized in (Fig. 1).

Excessive mitochondrial nitric oxide synthase (mtNOS)-derived nitric oxide (NO) can produce ROS, such as peroxynitrite, which may also play a key role in apoptosis. Additionally, under oxidative stress conditions, the enhanced activity of inducible NOS (iNOS) in vascular smooth muscle cells induces chronic metabolic inflammation [8]. ROS production is increased in metabolic syndrome due to an additional combination of factors, including increased oxidative metabolism in adipose tissue via increased nicotinamide adenine dinucleotide phosphate (NADPH) activity, reduced antioxidant defenses, and impaired mitochondrial biogenesis [9]. ROS-induced damage to cellular components, such as mitochondrial DNA, further potentiates mitochondrial dysfunction, promoting further ROS production, thus creating a vicious cycle that can contribute to inflammation.

Inflammation is another major contributor to mitochondrial dysfunction in metabolic syndrome. Chronic low-grade inflammation is a hallmark of metabolic syndrome and is believed to contribute to the development of insulin resistance, dyslipidemia, hypertension and CVD [10]. Inflammatory cytokines such as TNF-α and IL-6 impair mitochondrial function by disturbing the mitochondrial membrane potential, reducing ATP production, and inducing mitochondrial apoptosis. Furthermore, TNF-a and IL-6 contribute to the shared pathogenesis of obesity and inflammatory skin diseases such as psoriasis, as well as enhance local oxidative stress. This increased oxidative stress causes atherogenic plaques to become less stable, and the cytokines also contribute to the dysfunctional CD4+ FoxP3 regulatory T cells associated with the inflammation of adipocytes in the obese population [11]. In metabolic syndrome, adipose tissue produce the pro-inflammatory adipokines leptin and resistin [11]. Concomitantly, there is decreased secretion of the anti-inflammatory hormone, adiponectin. Together, alterations in adipokine

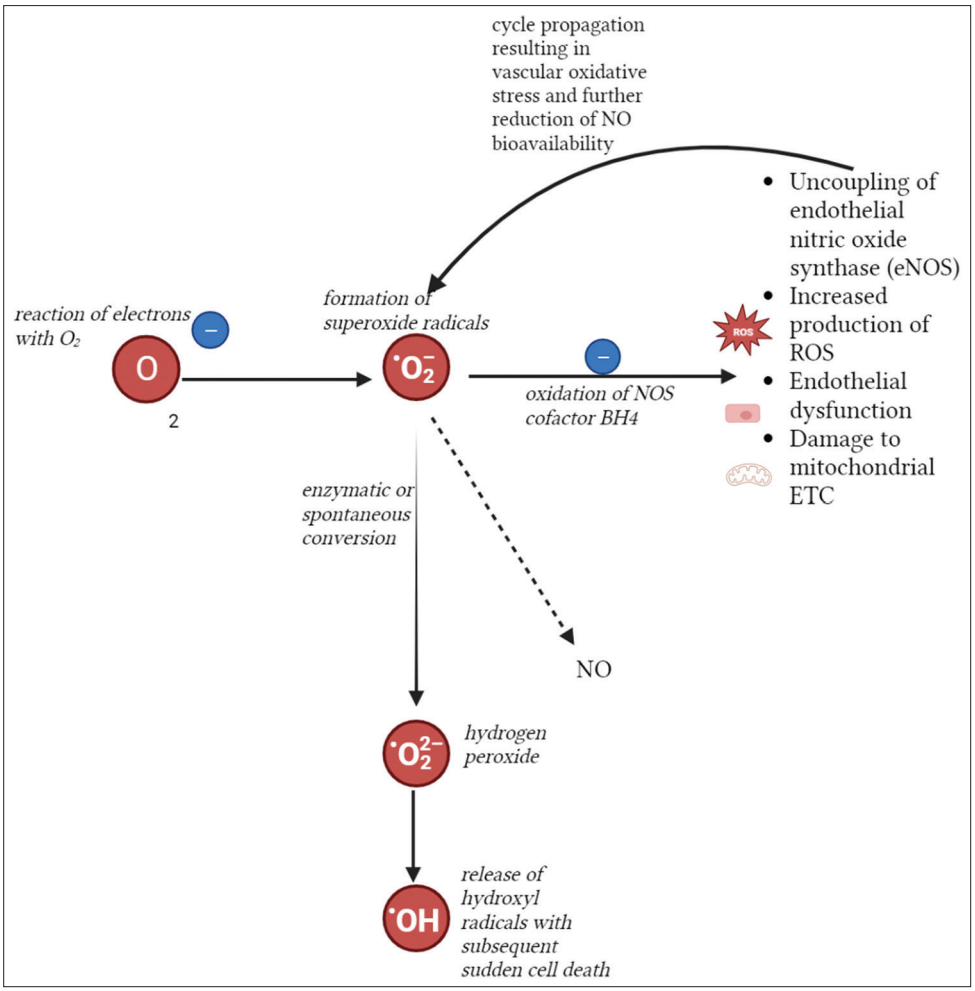

Figure 1: A graphical representation of a cascade of events in the electron transport chain with contribute to oxidative stress. Made with RioRender.

production and immune dysregulation contribute to mitochondrial dysfunction and inflammation, as seen in (Fig. 2).

Additionally, mitochondrial dysfunction can contribute to inflammation through basic science mechanisms such as inflammasome activation and ER stress. Inflammasomes serve as receptors and sensors in the innate immune system, responsible for regulating the activation of caspase-1 and initiating inflammation when exposed to pathogenic substances and signals generated from hosts [12]. Mitochondrial dysfunction can directly trigger inflammasome activation, producing the pro-inflammatory cytokines IL-1β and IL-18, which trigger inflammation. Metabolic syndrome also induces ER stress, contributing to mitochondrial dysfunction and inflammation, with subsequent activation of the UPR.

Insulin resistance, another key feature of metabolic syndrome, is also closely linked to mitochondrial dysfunction. Two pathways of insulin receptor signaling exist in cardiovascular tissues: the phoasphatidylinositol-3-kinase PI(3)K pathway and the mitogen activated protein kinase (MAPK) pathway. In states of insulin resistance, the PI (3)K-dependent insulin signaling pathway is inhibited, however the MAPK pathway in endothelial and vascular smooth muscle cells remains intact. This latter pathway is mitogenic, resulting in inflammation, cell proliferation, differentiation, and survival. Preferential signaling along this pathway may therefore contribute to the progression of inflammatory skin diseases via pro-inflammatory cytokines, and atherosclerosis is propagated via increases in the expression of cell adhesion molecules and cell interactions between vascular cells and macrophage/monocytes. [13] Reduced peripheral blood flow, commonly seen in people with sedentary lifestyles, additionally causes endothelial dysfunction and subsequent insulin resistance, as there is decreased peripheral insulin-mediated glucose uptake.

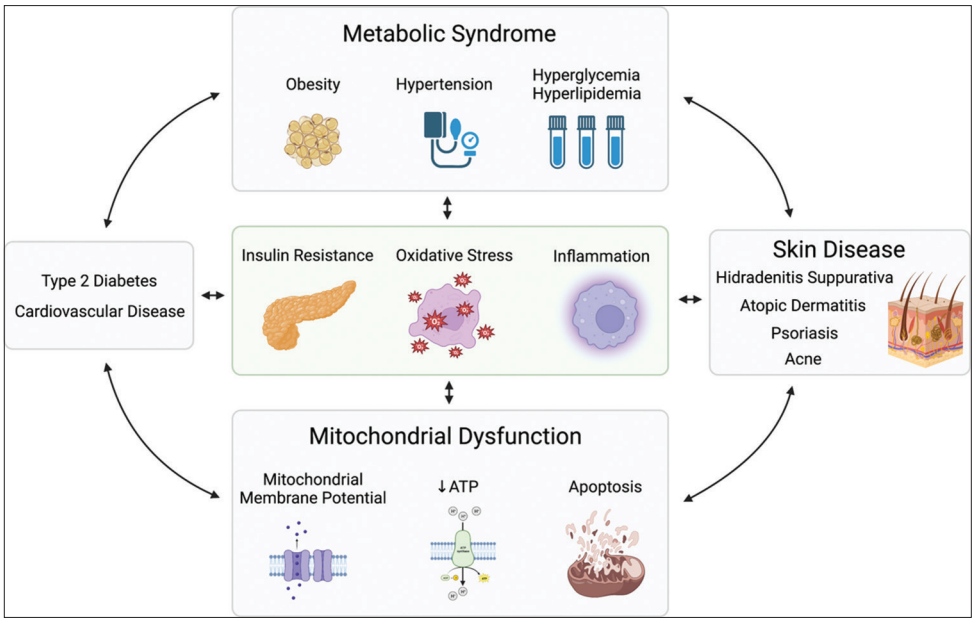

Figure 2: Graphical depiction of the complex interplay between metabolic syndrome, mitochondrial dysfunction, and skin disease. Created with BioRender.com.

MITOCHONDRIAL DYSFUNCTION WITH CORRELATES TO INFLAMMATORY SKIN DISEASES

Acne Vulgaris

There has been data citing insulin or insulin-like growth factor-1 (IGF-1) signaling pathway in the involvement of acne vulgaris' pathogenesis, both directly and indirectly, via increased androgen synthesis and involvement of rapamycin complex 1 signaling pathway [14,15].Certain foods, and elevated levels of insulin, which trigger sebaceous gland lipogenesis, may activate the IGF-1signaling pathway. Additionally, there was a cross-sectional case control study examining the relationship of metabolic syndrome and acne. They identified that systolic blood pressure ($p<0.04$), fasting blood glucose ($p<0.03$), and serum HDL depression ($p<0.008$) were associated with severe acne [16].

Androgenetic Alopecia

Androgenic alopecia (AGA) has been reported multiple times in patients with metabolic syndrome. Insulin resistance and a propensity for dyslipidemia is paramount in the pathogenesis. One study cited that high density lipoprotein cholesterol had the highest significant positive correlation with AGA while another cited that increased waist circumference was the most significant risk factor. However, in females, hypertension and central obesity had the most statistically significant correlation with AGA [17,18].

Atopic Dermatitis

A study by Ali et al. aimed to explore the relationship between AD and metabolic syndrome, reviewing 14 studies for this association [19]. While a causal link between AD and metabolic syndrome seems unlikely, findings indicate a stronger association of AD with central obesity, particularly in women. The study concludes that, despite inconsistent results in other metabolic syndrome components, AD is notably associated with central obesity, more so in women than in men.

Mitochondrial dysfunction is also implicated in AD. In the epidermis of non-lesional atopic dermatitis (ADNL) skin, an upregulation of oxidative stress markers is observed, implicating dysregulated mitochondrial activity [20]. Findings by Leman et al. demonstrate that ADNL keratinocytes exhibit a metabolic shift towards increased utilization of glycolytic substrates, resulting in augmented mitochondrial respiration and consequent oxidative stress. [20] Therapeutic intervention with mitochondrial-targeted agents, tigecycline or MitoQ, effectively mitigated these metabolic disturbances, highlighting the mitochondria as a strategic target for AD intervention.

Acanthosis Nigricans

The presence of acanthosis nigricans correlates strongly with the components of metabolic syndrome, including obesity, dyslipidemia, hypertension, and hyperglycemia, risk factors for cardiovascular disease and type 2 diabetes [21]. Moreover, acanthosis nigricans is largely attributed

to hyperinsulinemia, which reduces insulin sensitivity and elevates insulin levels, promoting keratinocyte and fibroblast proliferation. Mechanistically, increased IGF-1 receptor activation on skin cells and elevated leptin levels due to obesity contribute to developing a hyperplastic epidermis, manifesting as dark, velvety patches in skin folds. In a study by Philip et al., of those with acanthosis nigricans, 78.3% had metabolic syndrome, and 56.66% showed insulin resistance [22]. There was a significant correlation between the severity of axillary acanthosis nigricans and both metabolic syndrome ($P = 0.001$) and insulin resistance ($P = 0.03$). However, the severity of neck acanthosis nigricans did not show a significant link with either metabolic syndrome ($p = 0.4$) or insulin resistance ($p = 0.08$).

Rosacea

Rosacea is increasingly recognized as a possible indicator of metabolic syndrome [14]. A study by Duman et al. revealed a higher occurrence of dyslipidemia and cardiovascular diseases among individuals with rosacea [23]. Similarly, a study by Rainer et al. highlighted a link between moderate-to-severe rosacea and various metabolic disorders, including hypertension and hyperlipidemia [24]. This connection is thought to be driven by shared mechanisms such as: chronic inflammation, which is a hallmark of both conditions; insulin resistance, contributing to skin changes characteristic of rosacea; oxidative stress, causing cellular damage and exacerbating skin symptoms; vascular alterations inherent in metabolic syndrome, which may aggravate the vascular symptoms of rosacea; and potential gut microbiota imbalances [14]. These overlapping pathways suggest that rosacea could serve not only as a dermatological issue but also as a cutaneous marker for underlying systemic metabolic disturbances, highlighting the importance of a holistic approach in managing patients presenting with rosacea.

Psoriasis

In ultrastructural studies, the ER in the keratinocytes of patients with psoriasis is abnormal and has increased contents of proteins associated with ER stress. This leads to increased production of pro-inflammatory cytokines, such as TNF-α, demonstrating the shared inflammatory markers produced by ER stress in both psoriasis and metabolic syndrome [17]. This underlying shared pathogenesis may therefore be a contributor to their frequent co-occurrence. Additionally, iNOS is upregulated in psoriasis, contributing to chronic metabolic inflammation and resulting in significant overproduction of nitric oxide in psoriatic skin.

Hidradenitis Suppurativa

The inflammation seen in hidradenitis suppurativa is a result of the genetic, anatomical, immunological, and environmental influences. Cytokines such as TNFa, IL-1b, IL-6, IL-8, and IL-17A, which are elevated in MetS and cardiovascular diseases, are also overexpressed in HS [18]. Additionally, a shared "HS-MetS adipokine profile," specifically raised leptin (structurally homologous to IL-6), resistin, and visfatin levels together with low serum adiponectin level may represent a common adipokine milieu which predisposes patients to both syndromes. These agents result in a positive feedback loop as IL-6, TNFa and other cytokines, mediate the proinflammatory effects exerted by the resistin, which is itself under the positive influence of leptin [25]. This positive feedback loop is also observed in patients with an excess lipid pool, which triggers inflammatory signaling pathways such as JNK, IκBα kinase β (IKK β) and NF-κB, resulting in the production of proinflammatory cytokines, such as TNF-α, IL-6, IL-1β, leptin and resistin, and a reduction of adiponectin levels [26]. Of note, raised IL-6 levels have also been associated with more severe forms of HS as well as an HS phenotype characterized by obesity [27].

Lichen Planus

The data linking metabolic syndrome and lichen planus is inconclusive. However, the inflammatory cellular infiltrate in lichen planus, which consists mainly of CD4+ lymphocytes, is a well-known source of ROS [28].This increased ROS upregulates the expression of intercellular adhesion molecule (ICAM)1, further propagating T lymphocytes at sites of inflammation [28]. TNF-a also plays an important role in the pathogenesis, with the epidermal keratinocytes containing this cytokine producing hydrogen peroxide and superoxide anions, thus theoretically correlating this condition to mitochondrial dysfunction, inflammatory disease and consequently metabolic syndrome.

GENOMICS IN MITOCHONDRIAL DYSFUNCTION WITH CORRELATES TO METABOLIC SYNDROME AND INFLAMMATORY SKIN DISEASES

mtDNA is maternally inherited, with no alteration in the genetic structure during replication [29].

Nearly all cells in the human body contain abundant mitochondria, each containing multiple respective genomes. Therefore, pathologic mtDNA tends to be present in only a proportion of total mtDNA genomes within a cell or tissue, resulting in heteroplasmy. Heteroplasmy varies between individuals in a family due to a random bottleneck phenomenon that dramatically reduces total mitochondrial number from the oocyte to the embryo or organ progenitor cell.

Reduced mitochondrial function is associated with decreased insulin sensitivity. Genome-wide association studies (GWAS) have identified various genetic mutations which are associated with a decline in mitochondrial function, such as decreased human N-acetyltransferase, paraoxanase2 (PON2), Nuclear factor-erythroid factor 2-related factor 2 (NRF2), dynamin related protein-1 (Drp-1), calcineurin, mtDNA and SLC16A11 mutations[3, 30-34]. These mutations clinically correlate to decreases in insulin sensitivity, basal metabolic rate, exercise capacity and fat utilization, with subsequent increases in glucose, insulin, and hepatic and intramuscular lipid content. Further, additional mutations which can be targeted to prevent mitochondrial dysfunction are detailed below:

- Superoxide dismutase (*SOD*): The mitochondrial antioxidant mechanism involves SOD, which converts superoxide radicals to hydrogen peroxide, which is then converted to oxygen or water by catalase or glutathione peroxidase. This antioxidant mechanism reduces the risk of cell damage from hydroxyl radicals. *SOD* exists in three forms: *SOD1* (located in the cytoplasm, nucleus and lumen between the outer and inner membranes of mitochondria), *SOD2* (located in the matrix of the mitochondria) and *SOD3* (located extracellularly). Total antioxidant capacity (TAC) of plasma, erythrocyte SOD activities and catalase level in plasma has been identified to be decreased in patients with psoriasis. For example, Bozó et al demonstrated a two-fold increase in cytochrome C and two-fold decrease in SOD2 in psoriatic-involved skin [31]. Similarly, expression of SOD2 in macrophages was demonstrated to be reduced by 60% in psoriatic mice. This may promote enhanced oxidative stress in cells, aggravate cell damage and promote the formation of atherosclerotic plaques, an attribute already prescribed to macrophages due to the secretion of microparticles [35]. Therefore, people with disorders associated with mitochondrial dysfunction are more prone to have decreased SOD2 expression and could potentially benefit from supplemental antioxidants in the form of N-Acetyl cysteine (precursor of glutathione), lutein, zeaxanthin, curcumin, vitamin A, vitamin C, vitamin E or manganese [36]. Preclinical studies have demonstrated potential utility of SOD supplementation in acute and chronic inflammation. However, SOD's instability, high immunogenicity, low cellular uptake, and diminished half-life have limited the rate of progress in this area [37]. Additionally, the single nucleotide polymorphism (SNP) in the *SOD2* gene, rs4880, sometimes called T47C or A16V, is associated with increased risk of diabetes, CVD and cancer [36]. In this polymorphism, The T (GTT) allele produces a valine amino acid which does not allow *SOD2* to move readily into the mitochondria, therefore leading to reduced superoxide processing and subsequent mitochondrial damage [36]. Therefore, isolation of this isoform could potentially benefit screening for both mitochondrial dysfunction, inflammatory skin disease and consequent metabolic syndrome.
- Catalase: Esmaeili et al observed a significant decrease in expression of the catalase gene in patients with psoriasis ($P = 0.02$), likely due to sustained exposure to ROS leading to decreased expression of the catalase gene. This finding could provide utility of PPARγ agonists, as PPARγ regulates catalase production and is decreased in patients with psoriasis [38].
- Peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α): This transcriptional co-activator has been shown to be crucial for mitochondrial biogenesis, network dynamics, and removal of damaged mitochondria. Urra et al found that mutations in PGC-1α promoted mitochondrial fragmentation and decreased density of the extracellular matrix (ECM), and Handschin et al have suggested that a decrease in PGC-1α gene expression in skeletal muscle due to sedentary behavior can set off a low level but chronic pro-inflammatory response [39,40]. Additionally, Lira et al have demonstrated that modest (25%) upregulation of PGC1-a, whether in vitro or via exercise or cold exposure, improves mitochondrial biogenesis, fatty acid oxidation and insulin sensitivity in healthy and unhealthy skeletal muscle [41]. These findings highlight another potential target in the treatment and/or prevention of inflammatory skin disease [42]. Uncoupling protein 1 (UCP1): UCP1 expression has been associated with reduced

production of ROS [43]. UCP1 has also been shown to be an important regulator of non-shivering thermogenesis in brown adipose tissue by increasing mitochondrial density and proton dissipation as heat. According to Klingenspor et al, suppression of UCP1 in mice resulted in markedly decreased thermogenesis and mitochondrial density [44]. Thus, mutations in the UCP1 gene can promote inflammatory skin disease and should be an important consideration in its prevention. Furthermore, gene expression of uncoupling protein 2 (UCP2), another mitochondrial regulatory protein, is decreased in psoriatic lesional skin compared to non-lesional skin, demonstrating the loss of inhibition of inflammatory cells, including mast cells and macrophages [33].

Major Open Questions

The mitochondria are intricately involved in homeostasis through the establishment and termination of inflammatory responses. When excessive inflammation occurs and the mitochondrial outer membrane is permeated, a cascade of events occur which lead to regulated cell death via autophagy and caspase activation [45]. However, when the homeostatic capacity of this regulatory system is exceeded or is defective, inflammatory reactions elicited by mitochondria can become pathogenic and contribute to diseases linked to autoreactivity. Given the complexity surrounding the role of mitochondrial dysfunction in metabolic syndrome and inflammatory skin conditions, the questions exist of how to prevent and/or mitigate this dysfunction. Suggestions involve improving mitochondrial biogenesis and the antioxidative capacity through nonpharmacologic and pharmacologic interventions. [3]. Nonpharmacologic approaches are considered the first line intervention and combat metabolic syndrome by restricting calories and implementing exercise, consequently supporting healthy mitochondrial function. The summary of each non-pharmacological and pharmacological intervention is outlined in Table 1 below. The level of evidence presented, and their associated strength of recommendation was developed using the Strength of Recommendation Taxonomy (Appendix A).

In summary, addressing the dysfunction of metabolic disorders can be focused on nonpharmacologic and pharmacologic interventions including caloric restriction, exercise, metformin, antioxidant therapy and PPARγ agonists to alter the NADH to NAD+ ratio to activate the sirtuins or the AMP/ADP/ATP ratios to increase AMPK within the mitochondria and inhibit the production of mitochondrial ROS. This occurs due to the increase in PGC-1α subsequently contributing to mitochondrial dysgenesis [3]. Additionally, physicians can routinely undertake screening interventions in patients with increased predisposition to metabolic dysfunction, and its underlying mitochondrial dysfunction. For example, in patients with auto-inflammatory diseases such as psoriasis, it can be presumed that they are at intermediate risk of CVD and insulin resistance and screened with biochemical markers such as CRP, lipid profile and glucose tolerance testing with the calculated homeostasis model assessment for insulin resistance (HOMA-IR) index [47].

Global health disparities are potential limitations of both pharmacological and non-pharmacological measures discussed. Patients in food deserts generally do not have ready availability of foods rich in antioxidants, such as fruits which contain resveratrol. Additionally, mitochondrial dysfunction is associated with depression, anxiety, attention-deficit/hyperactivity disorder (ADHD) among other mental health disorders.[48] Patients with chronic inflammatory diseases developed because of mitochondrial dysfunction may have reduced health-seeking behavior due to these comorbidities. These barriers to healthcare and sustainable lifestyle interventions are, therefore, challenges that require multidisciplinary approaches for patient support.

CONCLUSIONS AND PERSPECTIVES

Mitochondrial dysfunction results in widespread inflammation and dysregulation of the immune system, leading to the manifestations of the components of metabolic syndrome and their reciprocal influence on the skin. Moreover, the interplay between oxidative stress, inflammation, and insulin resistance creates a vicious cycle that worsens mitochondrial dysfunction

Appendix A: Outlining the requisites for the SORT grading system [46].

Evidence Quality	Recommendation Strength
Level 1= Good quality, patient-oriented	A= Based on consistent and good quality patient-oriented evidence
Level 2= Limited quality, patient-oriented	B= Based on inconsistent or limited quality patient-oriented evidence
Level 3= Other evidence (i.e usual practice, opinion, disease-oriented evidence)	C= Based on consensus, usual practice, opinion, disease-oriented evidence or case series.

Table 1: Interventional recommendations to decrease mitochondrial dysfunction and combat metabolic syndrome

Intervention	Mechanism of Action	Recommendation	Level of Evidence/Strength of Recommendation
Caloric Restriction	1. Modulation of Sirtuin (SIRT) Signaling: • SIRT3: reduces production of mtROS during caloric restriction [49]. • SIRT1: Involved in deacetylation of NAD+, as a increased energy demand, propagates cycle of increased activation of sirtuins and optimized utilization of energy in the mitochondria [49]. 2. Further modulation of protein expression: reduces the production of free radicals and oxidative stress, thus improving cellular health. 3. Prevention of heat shock protein (HSP) compromise: with excess nutrient intake into the cellular energy system, the heat shock response system is compromised. This compromise results in 'nutri-stress' leading to diseases involving insulin resistance, such as type 2 diabetes mellitus [50].	Both intermittent fasting, continuous fasting, and restricted calorie intake can have cardiometabolic benefits for patients with elevated body mass index (BMI). The benefits also extend to patients with normal BMI through the autophagic destruction of senescent cells [51,52].	Level 1/A
Exercise Training	1. Increased HSP expression (mechanism unknown) [53]. 2. Active restoration of HSP72 content in insulin resistant tissues containing low endogenous levels of HSPs: HSP72 expression is markedly decreased in the skeletal muscle of patients with insulin resistance, type 2 diabetes mellitus and non-alcoholic fatty liver disease. Additionally, a positive correlation between HSP72 mRNA expression and mitochondrial enzyme activity has been observed in human skeletal muscle [53]. 3. Activation of AMPK: activates PGC1-α within the mitochondria enhancing biogenesis and inhibition the production of ROS, similar to the sirtuin pathway [3,49].	A combination of aerobic activity and at least twice weekly muscle-strengthening activities of moderate or greater intensity is recommended [54].	Level 1/A
Cold Exposure	Increased expression of PGC-1α, through the activation of AMPK, in skeletal muscle in addition to adipose tissue. This triggers mitochondrial activity through increased cellular demand, thereby enhancing mitochondrial biogenesis and inhibiting the production of ROS [55].	Activation of PGC-1α through cold exposure in areas with brown adipose tissue, which in adulthood is primarily located in the neck, mediastinum, kidneys and adrenal glands, can contribute to mitochondrial regulation [55]. Cold exposure can include cold showers, cold plunging, cryotherapy or even submerging the upper body in cold water.	Level 2/B
BH4 or sepiapterin supplementation	Reduces oxidative stress by targeting NOS uncoupling [8].	Further studies are needed to demonstrate utility: The role of exogenous NO exogenous via administering NO-donating substances, such as organic nitrates also requires further investigation, as current research demonstrates accelerated endothelial dysfunction and oxidative stress through supplementation [8].	Level 3/C
1. Glutathione (GSH) supplementation 2. N-Acetyl cysteine (NAC) supplementation 3. Lutein, zeaxanthin, curcumin, vitamin A, vitamin C, vitamin E or manganese supplementation	Increases concentration of SOD [36].	1. The sublingual form of GSH has demonstrated significant superiority over the oral form at the dosage of 150mg tds for at least 21 days, both in terms of bioavailability and positive effects on oxidative stress [56]. Further research is needed to determine efficacy in patients with inflammatory skin diseases and metabolic syndrome [57]. 2. Two amino acid precursors of GSH (cysteine and glycine) administered IV as NAC 0.81 mmol/kg/day, and 1.33 mmol/kg/day of glycine significantly lower oxidative stress and damage in patients with hyperglycemia [58]. Therapeutic oral dosages of NAC range from 1.8-3g daily for improvement of glycemic homeostasis, HDL-cholesterol, inflammatory status, and body antioxidative defense system. However, further studies are needed to clarify optimal dosing and potential adverse events [59]. 3. Further studies are required to assess optimal dosages of the additionally listed supplements.	1. Level 2/B 2 Level 2/B 3. Level 3/C

(*Contd...*)

Table 1: (*Continued*).

Intervention	Mechanism of Action	Recommendation	Level of Evidence/Strength of Recommendation
Biguanides	Decrease NADH at high concentrations, activate AMPK, contributing to the increase in PGC-1, enhancing mitochondrial biogenesis and function. By modulating mitochondrial activity, metformin may reduce the production of free radicals and oxidative stress, ultimately enhancing cellular health [60]. Of note, the precise mechanisms by which metformin influence mitochondria and free radical production remain elusive and require further mechanistic evaluation.	Consider a starting dose of 500mg metformin p.o, as tolerated, in patients with diabetes mellitus. Use as an adjunct to lifestyle change.	Level 1/A
MTOR inhibitors	1. Rapamycin promotes autophagy and mitophagy, the selective degradation and removal of defective mitochondria, maintaining a healthy mitochondrial population and promoting bioenergetic homeostasis. Additionally, rapamycin has been shown to stimulate mitochondrial biogenesis, subsequently enhancing mitochondrial function. This counteracts the effects of Mtorc1 activity, which promotes adipogenesis, inhibits insulin signaling and causes insulin resistance [61]. Rapamycin also reduces ROS generation within mitochondria, thus mitigating oxidative stress and protecting mitochondrial components [62]. Furthermore, rapamycin can modulate cellular metabolism, including nutrient sensing and energy metabolism pathways, promoting metabolic homeostasis, and optimizing mitochondrial function [63]. 2. Resveratrol: Same as above + activates SIRT1, AMPK + possesses antioxidant properties [64,65]. However, further studies are needed to clarify the effect on additional pathways, as well as optimal dosing and adverse effects [66].	1. Popular dosing for anti-aging/longevity ranges from 5-7mg/week [67]. However, further human studies are needed to identify the optimal dosage of rapamycin. 2. Resveratrol p.o ≥100mg/day may have utility in improving glucose homeostasis and systolic blood pressure levels.	1. Level 3/C 2. Level 2/B
1. PPARγ agonists 2. Glucagon-like Peptide (GLP)-1 Agonists	1. PPARγ agonists promote increased mitochondrial fatty acid oxidation via PGC1α activation, subsequently improving the sensitivity of insulin within adipose tissue and enhancing oxidative phosphorylation within the mitochondria [3]. 2. GLP-1 agonists exhibit antiatherogenic effects by altering leukocyte-endothelium reactions and promoting anti-inflammatory activity in vascular smooth muscle cells [68]. One of the mechanisms by which this is done is via stimulation of PPARγ [69].	1. The dosages and indications for PPARγ agonists and GLP-1 agonists to treat hypertriglyceridemia and type 2 diabetes mellitus are in accordance with national guidelines [70,71]. 2. The ideal dosing of GLP-1 agonists for antiatherogenic activity in patients without type 2 diabetes mellitus is not yet described. However, *Akkermansia mucinophilia* has been demonstrated to increase GLP-1 activity and doses of 10^8–10^{10} colony forming units/day have been shown to improve metabolic diseases [72].	1. Level 1/A 2. Level 3/C

in metabolic syndrome (Fig. 2). Further research is required in the form of GWAS to assess all the genetic components responsible for mitochondrial dysfunction, with potential future utility in screening patients at risk. Additionally, potential exists for the development of additional therapies which target chemokines and receptors involved in metabolic dysregulation. In current clinical practice it is important for physicians to understand the implications of using accurate screening tools to properly classify patients at risk and using biochemical markers and imaging to detect underlying inflammation.

Non-pharmacological interventions are first line for managing metabolic syndrome and are considered more effective than pharmacological treatment when patient adherence is high. However, it is important to note that patient adherence to lifestyle modifications, such as maintaining a healthy diet, can be influenced by various socioeconomic and psychosocial barriers. Socioeconomic factors play a significant role, as individuals from lower socioeconomic backgrounds may face limited access to affordable nutritious food options. The high cost of healthy food, especially in underserved communities, can make it challenging for individuals to follow a healthy diet consistently.

Additionally, limited resources, such as lack of transportation to grocery stores or limited availability of fresh produce in local areas, can further reduce adherence rates. Emotional factors, such as stress, depression, and anxiety, all of which are often associated with metabolic syndrome and chronic medical disease, can influence eating behaviors, leading to emotional eating, or seeking comfort in unhealthy food choices. Educational gaps and limited health literacy are also significant barriers to adherence. These factors should be considered when counseling patients on non-pharmacological approaches, coupled with patient education and engaging a multidisciplinary team for patients with perceived barriers to adherence.

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