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REVIEW OPEN ACCESS

The Role of Exercise in Mitochondrial Remodeling as a Combatant to Muscular Dystrophy: A Literature Review

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Abstract

Introduction: Muscular dystrophy (MD) refers to a group of diseases characterized by the progressive degeneration and weakness of skeletal muscle. Mitochondrial dysfunction plays a central role in the pathology of many MD subtypes that arise from various genetic mutations. Elevated oxidative stress induced by MD is a key mechanism driving mitochondrial dysfunction in these conditions. This review explores the role of exercise-induced mitochondrial remodeling and its potential therapeutic implications in MD management.

Methods: This literature review covers a comprehensive scope of studies published between 2018 to 2024 that were found using PubMed and OVID MEDLINE databases. The studies selected for this review focus on the effects of exercise on mitochondrial biogenesis and function in the context of muscular dystrophy.

Results: Exercise and exercise mimetics were found to induce mitochondrial remodeling, improve oxidative metabolism, and reduce cellular oxidative stress in various preclinical MD models and MD patients. Aerobic and resistance training elicited increased mitochondrial mass, protein levels associated with oxidative phosphorylation (OXPHOS), and oxidative muscle fiber composition across different MD subtypes. However, variability in response was observed, suggesting exercise may not be beneficial for all MD patients.

Discussion: Exercise is a potential therapeutic intervention in addressing mitochondrial dysfunction in MD patients. Moderate-intensity aerobic exercise demonstrates benefits in enhancing mitochondrial respiratory complexes thus suggesting it has a key role in improving mitochondrial function. MD models showed increased mitochondrial mass and respiratory complex protein levels in response to resistance exercise which is correlated with improved strength. In combination with pharmaceutical or gene therapies, exercise shows promise in mitigating MD pathology.

Conclusion: Exercise-induced mitochondrial remodeling appears to induce several positive mitochondrial adaptations that play a role in mitigating MD pathology across various subtypes. Exercise prescription should be tailored to specific MD subtypes to optimize mitochondrial responses, and treatment should be focused on preserving muscle function in patients. Further research is required to support the use of a combination of exercise and pharmaceutical therapies as potential intervention for MD patients.

Keywords: exercise; dystrophy; muscular dystrophy; mitochondria

Introduction

Mitochondria play a vital role in providing energy to cells through oxidative phosphorylation (OXPHOS), a process which uses oxygen to generate adenosine triphosphate (ATP) [1]. Skeletal muscle cells have high demand for ATP, especially during exercise. Several diseases affecting skeletal muscle are linked to mitochondrial loss and dysfunction [2-4]. Fortunately, exercise can improve mitochondrial health which can protect against muscular diseases, such as muscular dystrophy (MD) [5, 6].

Exercise induces many mitochondrial adaptations such as changes in mitochondrial activity, mitochondrial biogenesis, mitochondrial turnover, and more [7]. Peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) is an important transcription co-activator involved in the regulation of mitochondrial biogenesis [8]. This transcription co-activator increases the expression of enzymes, such as catalase and thioredoxin reductase, that act to improve mitochondrial function [8]. It is well documented that exercise leads to increased levels of PGC-1α, signaling that exercise is associated with improved mitochondrial biogenesis [2-4]. Enzymes such as succinate dehydrogenase (SDH) and citrate synthase (CS) serve as biological markers for mitochondrial activity; they are increased by different types of exercise training programs, such as moderate intensity aerobic training [5, 6]. Overall, exercise has been shown to improve mitochondrial health in several ways.

This knowledge can be used to study the impact of exercise on muscular diseases associated with mitochondrial dysfunction, such as MD [1]. MD encompasses a group of

diseases that involve the degeneration and weakness of skeletal muscle, with subtypes stemming from distinct genetic mutations. Mitochondrial dysfunction is a vital factor in the pathology of many MD subtypes. Specifically, increased oxidative stress that occurs in MD is a major mechanism through which MD leads to mitochondrial dysfunction [9]. The exact molecular connection between oxidative stress and MD pathology is unclear, however various MD subtypes exhibit several markers of increased oxidative stress [9]. For example, the most common type of MD, Duchenne MD (DMD), causes increased levels of thiobarbituric acid-reactive products, antioxidant enzymes, and markers of free radical damage, which are all representative of increased oxidative stress [9]. This increase in oxidative stress damages mitochondria by disrupting the electron transport chain, mitophagy, and mitochondrial DNA, ultimately causing increased mitochondrial dysfunction [9].

While MD is a relatively rare disease, estimated to impact around 4 in every 100,000 people globally [10], there is a lack of approved treatment options available to those affected. Most patients with MD have a relatively short life expectancy, many not living past adolescence, however, research surrounding MD has increased substantially over the last decade [11]. A promising area of research is the potential impact of exercise on MD [12]. Many new studies show that exercise elicits therapeutic effects in MD patients [12, 13].

Exercise may help maintain mitochondrial health and help mitigate the effects of MD. Given the severity of MD and the limited treatment options, it is important to understand how lifestyle changes, such as exercise, can biologically slow the progression and regulate cellular dysfunction associated with MD. In this review article, we investigate the mitochondrial response to exercise in MD and summarize the importance of exercise in regulating mitochondrial health to better the lifestyle of MD patients.

Methods

This review examined relevant articles from 2018 to 2024 that were found using a computerized keyword and MESH term search on PubMed and OVID MEDLINE. Keywords included in the search were ‘exercise’, ‘physical activity’, ‘endurance training’, ‘resistance training’, ‘mitochondria’, ‘mitochondrial adaptations’, and ‘muscular dystrophy’. The same keywords were used for both PubMed and OVID MEDLINE. Articles were selected after thorough abstract and full-text screening using the Covidence platform (Figure 1). Emphasis was placed on primary research articles investigating exercise and mitochondrial health in MD, but some review articles were selected based on their relevance and content. Only full-length articles available in English were included.

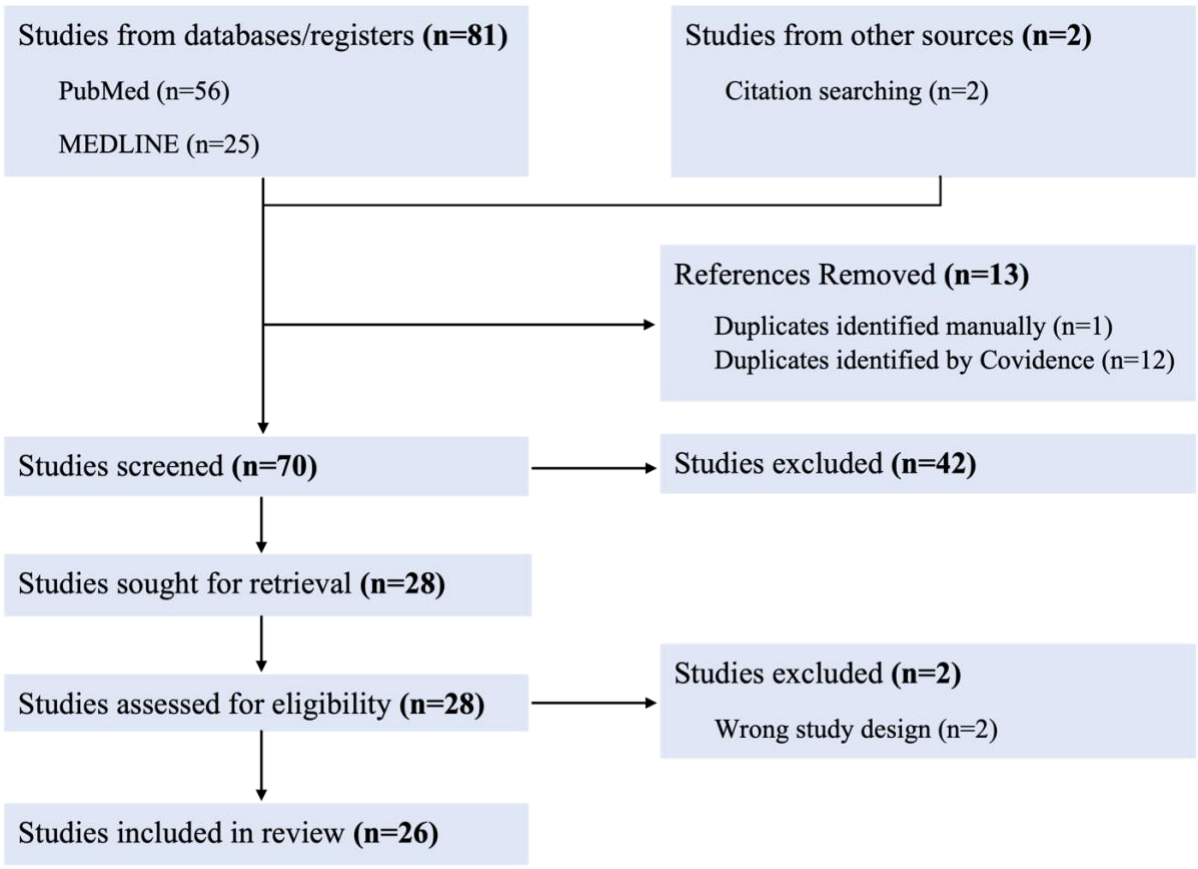

Figure 1. Article Review and Selection Process. This figure was created in Microsoft Word.

Results

Duchenne Muscular Dystrophy (DMD)

DMD is caused by mutations in the gene encoding dystrophin, a protein crucial for maintaining myofibril structure, leading to its depletion and subsequent progressive loss of muscle tissue and function [14]. High intensity interval training (HIIT) restored mitochondrial function in mdx mice, a preclinical model of DMD, through rescued mitophagy and mitochondrial biogenesis, which improved fatigue resistance and countered the histological damage from DMD [15]. Preclinically, HIIT, in the form of isometric contractions, increased the phosphorylation levels of AMP-activated protein kinase (AMPK), acetyl CoA, unc-51-like autophagy activating kinase (Ulk1), and many more positive biological factors related to mitochondrial function [15].

In mdx mice, exercise rescued mitochondrial function when combined with pharmaceutical and/or genetic treatments [16-19]. Mice showed an upregulation in PGC-1α and mitochondrial respiratory complexes when exercised on a treadmill and treated with the free-radical scavenger, Tempol [16]. This upregulation increased mitochondrial biogenesis and reduced oxidative stress in mdx mice [16]. An increase in PGC-1α prevents creatine kinase release and a reduced exercise capacity [20]. Voluntary wheel running, combined with an adeno-associated virus which carried microdystrophin, mitigated energetic deficits in mitochondria and increased mitochondrial respiration in mdx mice [17]. Additionally, exercise combined with the administration of an allosteric sarco-endoplasmic reticulum Ca^{2+} (SERCA) activator, CDN1163, reduced mitochondrial swelling and reactive oxygen species, which protected against exercise-induced muscle damage and restored mitochondrial function in mdx mice [19].

DMD causes lower levels of Perm1, a protein stimulated by exercise to enhance PGC-1α-induced mitochondrial biogenesis; this deficiency in Perm1 partially explains the altered exercise response in some mdx mice [21]. In other animal models of DMD, namely dys-1 *C. elegans*, exercise has been shown to cause muscle damage through increasing fibrosis and inflammation, leading to accelerated muscle degeneration [22].

Myotonic Dystrophy 1 (DM1)

DM1 is caused by a mutation in dystrophia myotonic protein kinase (DMPK) gene, which leads to muscle weakness and wasting [23, 24]. In DM1 patients and mouse models of DM1, aerobic exercise had rescuing effects on skeletal muscle mitochondria [25-27]. Voluntary wheel running in DM1 mice led to increases in mitochondrial density as measured by mitochondrial CS activity [25]. Specifically, the exercised DM1 mice exhibited a 63% and 88% increase in quadriceps CS activity compared to sedentary DM1 and wild-type mice, respectively [25]. Furthermore, exercised mice saw significantly higher levels of mitochondrial respiratory complexes I-V [25]. A single bout of aerobic exercise also had positive implications on mitochondrial health in DM1 mice [26]. When DM1 mice were ran to exhaustion, biogenesis was enhanced by the rapid activation of AMPK and PGC-1α in skeletal muscle [26]. Mitochondrial dynamics and turnover processes were activated by this single dose of aerobic exercise, leading to regulated mitophagy and augmentation of mitochondrial fusion and fission regulators within DM1 mice [26].

Similar results were seen clinically through aerobic exercise training in human DM1 patients [27]. Cycling significantly increased mitochondrial transcripts and the protein content of mitochondrial respiratory complexes in DM1 patients towards levels comparable to healthy individuals [27]. Cycling also partially restored balance among proteins related to mitophagy, mitochondrial fusion, and mitochondrial fission in human DM1 patients [27]. Overall, aerobic exercise rescued mitochondrial function and plasticity at the posttranscriptional level [27].

Two weeks of resistance training in human DM1 patients had positive influences on skeletal muscle strength through mitochondrial remodelling [28]. Resistance training significantly increased mitochondrial mass and protein levels of mitochondrial respiratory complexes; this significantly improved the oxidative capacity of mitochondria which rescued muscle fiber composition in DM1 patients [28]. The increase in mitochondrial mass was correlated with increases in one-repetition maximum strength in DM1 patients [28].

Limb Girdle Muscular Dystrophy (LGMD)

LGMD is an autosomal disorder which is caused by various genetic mutations and effects proximal skeletal muscles [29]. High-intensity aerobic exercise, such as running to exhaustion, has been used preclinically to induce mitochondrial remodelling in both healthy and LGMD muscles. In skeletal muscle of healthy mice, high intensity exercise increased Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) β levels, thus stimulating mitochondrial biogenesis and improving OXPHOS energy production and muscular endurance [30]. In calpain 3 (Capn3) knock-out (C3KO) mice, a preclinical model of LGMD, exercise did not induce CaMKII β elevation in muscle, as lack of Capn3 impairs calcium regulation and energy production within the muscle cell [30, 31].

Combining exercise with AMBMP (N^4-(1,3-benzodioxol-5-ylmethyl)-6-(3-methoxyphenyl)-2,4-pyrimidinediamine hydrochloride) treatment, a small molecule that mimics exercise by stimulating CaMKII β, leads to improved oxidative metabolism, endurance, and muscle performance in mouse models of LGMD [30]. AMBMP reverses the LGMD phenotype through increased CaMKII β activation which subsequently promotes OXPHOS and an increase in slow-twitch fiber size [30]. When C3KO mice were treated with AMBMP for two weeks with dosages ranging from 7.5-15 mg/kg, an

increased number of slow-oxidative fibers were found, assessed via NADH stain [30]. In addition, AMBMP-treated muscles showed significant improvements in mitochondrial respiration and increases mitochondrial complex I (39%) and II (36%) activities compared to baseline [30]. Research also shows that the C3KO phenotype is reversible through the effect of AMBMP on CaMKII β post-transcriptionally. This upregulation of CaMKII β subsequently increases oxidative metabolism and improves the LGMD phenotype [30].

While exercise-induced mitochondrial remodelling has shown some potential benefits in LGMD, research in mice has also shown that hypertrophy following exercise can be harmful [32]. Myostatin, a negative regulator of muscle growth, was inhibited in LGMD mice to induce muscle hypertrophy [32]. The results of the study showed that this led to a loss of oxidative capacity in muscles, compromising their ability to perform further exercise [32]. Muscle hypertrophy did not improve muscle strength or endurance and rather had the opposite effect, indicating that an increase in muscle mass without improved oxidative metabolism is not an effective treatment for LGMD patients.

Becker Muscular Dystrophy (BMD)

Similar to DMD, BMD involves mutations which hinder the expression of the dystrophin gene; however, involves a much milder phenotype as there is still some functional dystrophin protein expressed [10]. Clinical trials have explored the potential therapeutic effects of exercise management in BMD. (-)-Epicatechin, an exercise mimetic, is known to enhance mitochondrial biogenesis and support muscle regeneration [33]. In a study where human BMD patients received (-)-epicatechin treatment, there was a short-term improvement on tissue biomarkers, including AMPK and PGC-1α, associated with mitochondrial function [33]. Additionally, enhanced exercise testing parameters were observed indicating improved exercise capacity in the human patients, following treatment [33]. This suggests that (-)-epicatechin may help stimulate mitochondrial remodelling, leading to improved exercise tolerance in BMD patients.

Additional MD Subtypes

Facioscapulohumeral Muscular Dystrophy (FSHD)

FSHD is an autosomal dominant disorder which mainly effects muscles of the facial, scapular, and humeral regions [34]. Mitochondrial dysregulation in FSHD is characterized by a greater abundance, but slower turnover rate of mitochondrial respiratory complex subunits and ribosomal proteins [35]. This results in a greater number of dysfunctional mitochondrial proteins compared to unaffected healthy mitochondria, thus contributing to the reduced respiratory function observed in complex I caused by DUX4 mutation expression [35]. Treatment using a 2′-O-methoxyethyl modified antisense oligonucleotide has been shown to reverse the mitochondrial protein dysregulation in human FSHD models [35]. By targeting and silencing pathogenetic factor DUX4 mRNA expression, antisense oligomer treatment helps to improve mitochondrial quality and function in FSHD myoblasts [35]. The effects of exercise on mitochondrial remodelling in FSHD are not well studied.

Fukuyama Congenital Muscular Dystrophy (FCMD)

In a very rare subtype of MD, known as Fukuyama Congenital Muscular Dystrophy (FCMD), the electrical stimulation of exercise, in FCMD mice, resulted in insignificant changes to PGC-1α expression [36]. These findings indicate that exercise was not able to rescue dysfunctional mitochondria in FCMD.

Discussion

Muscular dystrophy (MD) is marked by progressive skeletal muscle weakness and degeneration, partially due to mitochondrial dysfunction [1]. This is primarily driven by elevated levels of cellular oxidative stress and leads the loss of functional mobility and ambulation [9]. Current therapeutic strategies aim to address the genetic and molecular defects in MD patients to preserve muscle function and quality of life [37]. The use of glucocorticoids, exon-skipping technologies, and gene therapies, which aim to mitigate specific genetic mutations and slow disease progression have been proven safe and effective in conditions such as DMD, BMD, and LGMD [37]. However, limitations in accessibility and long-term outcomes highlight the need for alternative therapeutic strategies. Exercise has been explored as a potential MD therapy due to its role in enhancing mitochondrial and muscular function [7]. Unlike many pharmacological and gene therapies, exercise can be a widely accessible and cost-effective form of treatment that requires minimal resources [38]. Its affordability and practicality make it a promising complement to existing medical treatments, particularly for patients with limited access to advanced therapies.

The results reviewed herein demonstrate that exercise appears to have a subtype-specific impact on mitochondrial function in both preclinical models of MD and MD patients. These findings are prevalent across various exercise types and intensities as well as distinct MD subtypes.

High intensity exercise was able to elicit several positive mitochondrial adaptations in both DMD, DM1, and LGMD mice models [21, 32]. However, in LGMD mice, high intensity exercise was only able to produce these responses with the aid of AMBMP treatment [30]. This highlights the importance of subtype-specific prescription of exercise and combined therapy as some subtypes only experience benefits to exercise when combined with pharmaceutical treatments [30]. Without these specifications, exercise may have minimal benefits and

potentially cause muscular damage. Moreover, the specific mechanisms eliciting these mitochondrial responses to high intensity exercise vary across subtypes [15, 26, 30]. In mdx mice, high intensity exercise led to increased mitochondrial biogenesis and mitophagy by targeting activation of AMPK, acetyl CoA, Ulk1, and other molecules [15]. Conversely, DM1 mice saw rescuing effects to both mitochondrial dynamics and turnover through both increased biological factors and increased mitochondrial respiratory complexes [26]. C3KO mice saw mitochondrial benefits elicited through activation of CaMKII β [30]. The different molecular responses to exercise across MD subtypes should be considered when designing exercise mimetics or pharmaceutical treatments to be paired with exercise.

The mitochondrial response to moderate aerobic exercise appears to be positive across preclinical and clinical DM1 models [25, 27]. Preclinical and clinical models showed an increase in mitochondrial respiratory complexes after moderate aerobic exercise [25, 27]. These trends show that this form of exercise plays a major role in mitochondrial remodeling within DM1 patients. Further studies are necessary to examine the functional impacts of mitochondrial remodelling. Moderate aerobic exercise was also beneficial for mitochondria in mdx mice and human BMD patients when combined with pharmaceutical or genetic therapies [16-19]. These findings demonstrate the strong potential for use of combined exercise and pharmaceutical therapies to mitigate disease pathology in BMD. This potential should be further examined in preclinical and clinical models to confirm the efficacy and safety of combined treatments in BMD therapy.

Resistance exercise in DM1 patients significantly increased mitochondrial mass and protein levels of mitochondrial complexes which was correlated with increased strength [28]. While these results are promising, additional studies are required to evaluate the reproducibility of these findings. The coinciding increase in strength and mitochondrial mass seen in resistance training indicate that mitochondrial remodelling has a role in driving the therapeutic effects of exercise. This is supported by the damaging hypertrophy seen in LGMD mice that did not exhibit the typical mitochondrial responses to exercise [32]. These findings suggest that exercise can have deleterious effects when mitochondrial adaptations are not simultaneously induced alongside other exercise-driven adaptations.

Additional preclinical and clinical trials are necessary to validate these findings. Although the literature appears to show significant evidence for exercise benefiting mitochondria, there is a lack of testing around the functional impacts of these molecular benefits within MD. Future research should conduct simultaneous strength and muscular function tests alongside the investigation of molecular signals to provide stronger evidence that exercise can lead to both functional and molecular benefits for MD patients. Exercise has also shown some harmful side effects in MD patients, such as a loss of oxidative capacity, increased fibrosis, and increased muscle degeneration [21, 22, 32]. Future trials should also be cautious of these potential exercise-induced side effects seen in some preclinical models. This can include monitoring muscle histology, quality of life, and motor function to help ensure that adverse outcomes are minimized.

A potential limitation to using exercise as a therapy for MD patients is the prevalence of reduced exercise capacity and the loss of ambulation in many MD subtypes [28, 33]. This is a frequent limitation in clinical trials involving exercise and MD as many trials require a baseline fitness level for participants to be eligible [28, 33]. Thus, the use of exercise may not be universally applicable to all MD patients, especially those with severe phenotypes. One way to mitigate this limitation is the integration of combined therapy. Combining exercise with medications that improve exercise tolerance could allow for exercise to become a more widely applicable treatment. An example of this was demonstrated through the improved exercise capacity in BMD patients receiving (-)-epicatechin therapy [33].

Conclusions

This review encapsulates the mitochondrial response to exercise across several MD subtypes. Overall, various exercise types and intensities appear to induce positive mitochondrial adaptations which play a role in mitigating MD pathology. The present findings provide several implications which should be considered when conducting research surrounding MD treatments and exercise. Firstly, it is crucial that exercise prescription for MD patients is subtype-specific to elicit appropriate mitochondrial responses. Secondly, mitochondrial remodeling should be monitored when engineering treatments for MD as they play a role in preserving muscular function. Lastly, combining exercise with pharmaceutical or genetic treatments should be further explored across MD subtypes, as combined therapy shows major potential for improved treatment outcomes in both preclinical models and MD patients. Future studies should provide further evidence for the functional benefits of exercise in MD and address concerns pertaining to exercise-induced adverse side effects in MD patients. With treatment options for MD patients being scarce and disease progression being rapid, additional therapies are critical. Integrating exercise or combined therapy is a promising avenue to expand the therapeutic network for MD patients, however, this is an area that requires further exploration to completely understand and maximize the potential therapeutic mechanisms associated with exercise and MD.

List of Abbreviations
AMPK: AMP-activated protein kinase
ATP: adenosine triphosphate
BMD: Becker muscular dystrophy
C3KO: calpain 3 knock-out mice
CaMKII: Ca^{2+}/calmodulin-dependent protein kinase II
Capn3: calpain 3
CS: citrate synthase
DM1: myotonic dystrophy 1
DMD: Duchenne muscular dystrophy
DMPK: dystrophia myotonic protein kinase
FCMD: Fukuyama congenital muscular dystrophy
FSHD: facioscapulohumeral muscular dystrophy
HIIT: high intensity interval training
LGMD: limb girdle muscular dystrophy
MD: muscular dystrophy
OXPHOS: oxidative phosphorylation
PGC-1α: peroxisome proliferator-activated receptor γ coactivator 1α
SDH: succinate dehydrogenase
SERCA: sarco-endoplasmic reticulum Ca^{2+} ATPase
Ulk1: unc-51-like autophagy activating kinase

Conflicts of Interest
The authors declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent
This study did not require ethics approval as it is a review article.

Authors' Contributions
AY: Made substantial contributions to the design of the study, article acquisition and analysis. Primary contributor to critically drafting and revising the manuscript; and gave final approval of the version to be published.
MMC: Contributed to study design, article collection, and analysis. Secondary contributor to the drafting and revising; and gave final approval of the version to be published.

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