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Type 2 diabetes mellitus and neurodegenerative disorders: The mitochondrial connection

Isabella R. Baduini [1], Jose E. Castro Vildosola [1], Sheida Kavehmoghaddam [1], Fatmanur Kiliç [1], S. Aiman Nadeem [1], Juan J. Nizama [1], Marietta A. Rowand [1], Dileep Annapureddy [2], Chris-Ann Bryan [2], Lisa H. Do [2], Samuel Hsiao [2], Sai A. Jonnalagadda [2], Akhila Kasturi [2], Nikhila Mandava [2], Sachin Muppavaram [2], Bryan Ramirez [2], Aleece Siner [2], Christina N. Suoto [2], Nasira Tamajal [2], Ernest R. Scoma [3], Renata T. Da Costa [3], Maria E. Solesio [*]

Department of Biology and Center for Computational and Integrative Biology, Rutgers University, Camden, NJ, USA

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ABSTRACT

The incidence of type 2 diabetes mellitus (T2DM) has increased in our society in recent decades as the population ages, and this trend is not expected to revert. This is the same for the incidence of the main neurodegenerative disorders, including the two most common ones, which are, Alzheimer's and Parkinson's disease. Currently, no pharmacological therapies have been developed to revert or cure any of these pathologies. Interestingly, in recent years, an increased number of studies have shown a high co-morbidity between T2DM and neurodegeneration, as well as some common molecular pathways that are affected in both types of diseases. For example, while the etiopathology of T2DM and neurodegenerative disorders is highly complex, mitochondrial dysfunction has been broadly described in the early steps of both diseases; accordingly, this dysfunction has emerged as a plausible molecular link between them. In fact, the prominent role played by mitochondria in the mammalian metabolism of glucose places the physiology of the organelle in a central position to regulate many cellular processes that are affected in both T2DM and neurodegenerative disorders. In this collaborative review, we critically describe the relationship between T2DM and neurodegeneration; making a special emphasis on the mitochondrial mechanisms that could link these diseases. A better understanding of the role of mitochondria on the etiopathology of T2DM and neurodegeneration could pave the way for the development of new pharmacological therapies focused on the regulation of the physiology of the organelle. These therapies could, ultimately, contribute to increase healthspan.

1. Introduction

Type 2 Diabetes Mellitus (T2DM) is predicted to affect 366 million adults worldwide by 2030, according to the International Diabetes Federation. Increased prevalence of obesity, and an aging population, seem to be main contributors to this rise in T2DM cases that is anticipated for the coming decades. Another contributor to the increased prevalence of T2DM cases could be the improvement of the treatments for some of the symptoms of the diseases, which increases the life expectancy of the patients. In fact, in recent years, interventions to prevent and treat typical micro- and macro-vascular complications associated with T2DM have improved; in turn, many patients are living longer with this condition. However, this increased life expectancy has exposed new complications associated with the disease, including dementia [1]. One of the mechanisms underlying this increased incidence of cognitive disorders in T2DM could involve insulin resistance (IR), hyperglycemia, and mitochondrial dysfunction. IR, defined as a limited or impaired response to insulin signaling, has been broadly described in T2DM [2], and it could be involved in the development of Alzheimer's disease, and Parkinson's disease (AD and PD; respectively) [3,4]. In fact, the

* Correspondence to: Rutgers University, Department of Biology, 201 Broadway, Camden, NJ, 08103.USA
E-mail address: m.solesio@rutgers.edu (M.E. Solesio).
[1] These authors contributed equally as co-first authors and their names are listed in alphabetical order.
[2] These authors contributed equally as co-second authors and their names are listed in alphabetical order.
[3] These authors contributed equally as co-third authors.

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deleterious effects of IR and hyperglycemia (two key molecular features of T2DM) on neurons, linking T2DM and neurodegeneration, have already been demonstrated [5]; and mitochondria could play an important role in this process.

The literature suggests that T2DM could be a risk factor for the development of both AD and PD [6–8]. On one hand, AD is the most common type of dementia, and it is estimated to affect 46 million individuals worldwide [8]. While the exact etiopathology of AD remains unknown, an increased presence of neurofibrillary tangles and accumulation of hyperphosphorylated tau and amyloid β (Aβ) deposits have been broadly detected in the brains of AD patients [4,9]. A progressive increase in IR and insulin deficiency in the central nervous system (CNS) are also found in AD patients [4], once again linking T2DM and neurodegeneration. In fact, AD has been described by some authors as "Type 3 Diabetes Mellitus" [10]. On the other hand, PD is the most common movement disorder worldwide, in which between 80 % and 90 % of PD cases have a sporadic origin. Some environmental factors such as exposure to toxic pesticides, frequent use of β-blockers, and brain injury have been proposed as risk factors for the development of PD and related parkinsonism [6]. The loss of dopaminergic neurons in the substantia nigra and the increased presence of aggregated α-synuclein (αSyn) are commonly present in PD [11]. Interestingly, using familial models of PD in *Drosophila* either fed a hypercaloric diet or knocked down for genes involved in insulin signaling to mimic T2DM; it has been demonstrated that T2DM symptoms are exacerbated in PD mutants. These symptoms include mitochondrial dysfunction and consequently, increased dopaminergic neuronal apoptosis, among others [12]. Moreover, IR has also been demonstrated in PD [13].

In this bibliographical review, we aim to present and discuss the literature regarding the crosslink between T2DM and neurodegenerative disorders, focusing on the mitochondrial connection between these diseases (Graphical Abstract). While this crosslink has been already described, a better understanding of the molecular mechanisms driving mitochondria to dysfunction and failure under these pathological conditions could unravel new pharmacological targets against T2DM, and neurodegenerative disorders.

2. Mitochondrial physiology in health and disease

Mitochondria are ancient endosymbiotic organelles [14], containing their own circular, double-stranded DNA (mtDNA) [15], which encodes 13 polypeptides that are mostly part of the electron transfer chain (ETC) [15,16]. Mitochondria play a crucial role in the regulation of many physiological processes, probably the best described of these processes is bioenergetics. In fact, the mitochondrial ETC is the site of oxidative phosphorylation (OXPHOS), which is key in glucose metabolism and the biggest net producer of ATP in mammalian cells [17]. Moreover, these organelles have intricated and delicate mechanisms to regulate many of the crucial metabolic processes closely related to bioenergetics, other than OXPHOS. Protein and calcium homeostasis are examples of this [18–24].

Mitochondrial dysfunction, which is multifaceted and complex, has been broadly described in many human diseases. These pathologies range from cancer to COVID [25,26]. As mentioned above, mitochondrial dysfunction has also been broadly described in T2DM, and in both AD and PD [27–29] (Fig. 1). The molecular mechanisms underlying mitochondrial dysfunction, and the consequences of this dysfunction in human pathologies, are multiple. For example, when mitochondria are

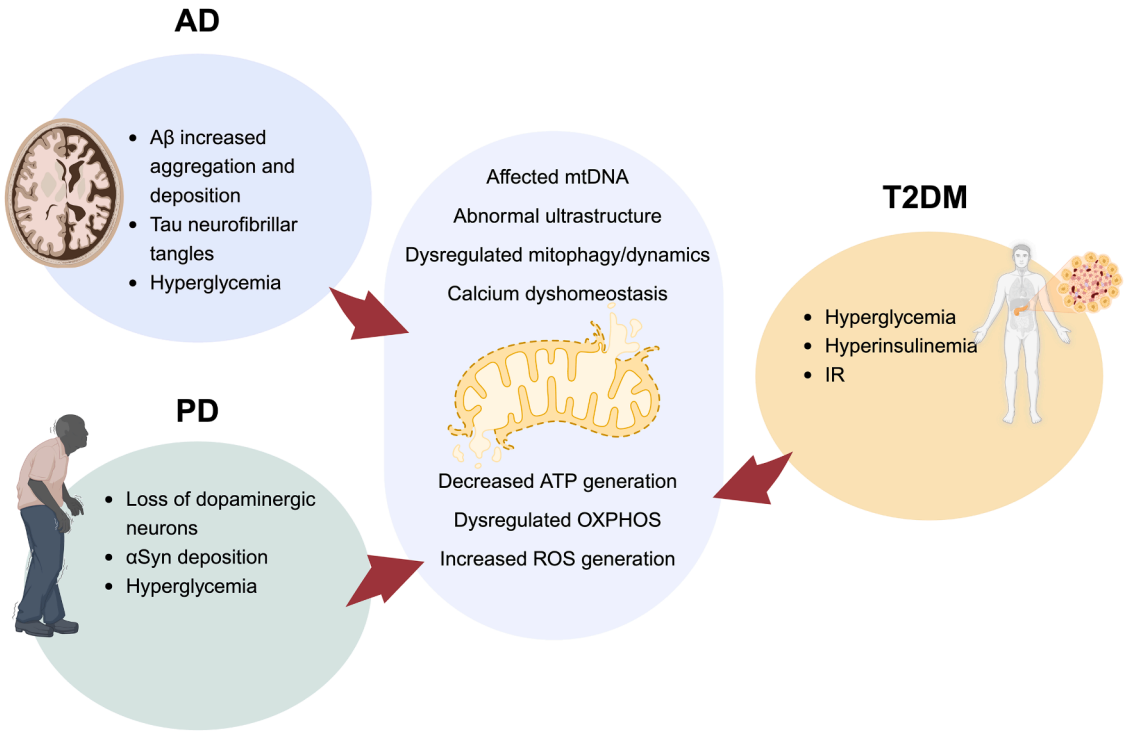

Fig. 1. *Mitochondrial dysfunction is present in the intersection between neurodegenerative diseases and T2DM.* Many epidemiological and molecular studies have already demonstrated the close relationship between T2DM and the main neurodegenerative disorders, which are, AD and PD. While the mechanisms that link these pathologies still remain unknown, the presence of mitochondrial dysfunction (including, for example, dysregulated bioenergetics, and mitophagy) has been broadly demonstrated in both types of disease. The study of the mechanisms that drive mitochondria to dysfunction in this intersection could provide the scientific community with further pharmacological targets to prevent or treat both neurodegenerative diseases and T2DM. The most representative and best characterized clinical features of AD, PD, and T2DM are listed in the side panels of this figure. Mitochondrial dysfunction could, at least partially, be involved in the onset and development of these clinical features, connecting the two main neurodegenerative disorders and T2DM. Specifically, the changes stated in the central part of the figure are different components of mitochondrial physiology that have been described in all these pathologies. Image was created using BioRender.com and an institutional license to Rutgers University.

dysfunctional, energy production often declines [19–21], while reactive oxygen species (ROS) generation and apoptosis increase, in a deleterious loop [30,31]. ROS are well-known byproducts of OXPHOS [32-34], produced next to the location of the mtDNA. This makes the mtDNA highly susceptible to oxidative damage [8], thus increasing the probability of mutations and further mitochondria dysfunction [31], especially considering that mtDNA lacks mechanisms to properly repair mutations [35]. Accordingly, some authors have proposed that changes in mtDNA levels and integrity could serve as biological markers for mitochondrial dysfunction. In fact, increased mtDNA is associated with inflammation, and it is present in the brain of T2DM patients; while decreased mtDNA often indicates reduced mitochondrial bioenergetics, and it is present in brains from AD patients [8]. Increased ROS has also been described as a consequence of neuronal IR, inducing a rise in the aggregation of αSyn in dopaminergic neurons [7]. Moreover, insulin, which could directly regulate the ETC [3], has a powerful effect in the modulation of the activity of the insulin-like growth factor-1 (IGF-1), a protein which protects astrocytes and neurons from increased oxidative stress [36]. In astrocytes, decline of IGF-1 receptor (IGFR) signaling has also been found to be associated with decreased glucose internalization and metabolism, therefore playing an active role in mitochondrial homeostasis [31]. Furthermore, knock-out (KO) mice for astrocyte-specific IGFR showed an elevated ROS production and increased susceptibility to oxidative stress [31].

Dysregulated mitophagy is also commonly present in T2DM and neurodegeneration [29,37]. Mitophagy facilitates the elimination of dysfunctional mitochondria through ubiquitin-mediated pathways, such as the PINK1/Parkin axis [38]. Under non-pathological conditions, mitophagy reduces the accumulation of AD-related amyloids, such as Aβ and hyperphosphorylated Tau, this in turn promotes proper brain energy metabolism [39]. However, dysregulated mitophagy has been described in AD and PD. Accordingly, urolithin A-induced mitophagy, can restore memory impairment in *C. elegans* [40]. Furthermore, delayed mitophagy has been described in axons from individuals with familial and sporadic PD [41]. However, some other authors showed increased defective mitophagy in pharmacological models of the same disease [28,42]. Further studies need to be conducted in this field to better clarify these points. The status of mitophagy is closely related to mitochondrial dynamics [28,29,42], which is mostly maintained by the equilibrium between fission and fusion. Fission is the process of division of mitochondria into two similar organelles, and it is mainly mediated by Drp1 [43]. Mitochondrial fusion, which is mediated by inner membrane protein OPA1, and outer membrane GTPases Mnf1 and Mfn2; is the process in which two different mitochondria merge [44,45]. Fusion allows for the exchange of small soluble molecules, including mtDNA [46]; while fission contributes to removal of dysfunctional mitochondria and to ensure proper ATP production in response to stress [47]. Dysregulated mitophagy and mitochondrial dynamics are well-known contributors to increased apoptotic cell death in human pathologies, including AD and PD.

3. T2DM and PD

PD is the most common movement disorder, it occurs in approximately 1–2 % of adults over the age of 60, and 3.5 % of adults 85 and older [48], an increasing burden as society ages. While approximately 20 % of PD cases have a genetic etiology, induced by relatively well-known mutations [49], most of the cases are sporadic and their causes remain insufficiently understood. At the cellular level, one of the hallmarks of PD is the increased aggregation and deposition of αSyn, and the consequent increased apoptosis of dopaminergic neurons in specific areas of the brain [50,51]. A connection between T2DM and the development of PD has been already proposed. For example, using *Drosophila* and mice models of T2DM created by high-sugar and high-fat diets respectively, T2DM has emerged as a risk factor for the development of PD, since increased neuronal dopaminergic dysfunction was present in both models, when compared to the control samples [12]. Moreover, the relationship between the levels of insulin and the activity of the neuronal dopaminergic transporter (DAT) has been demonstrated in the striatum of rats [52]. Specifically, decreased expression and activity of DAT, and decreased expression of D_2-dopaminergic receptors, was present in obesogenic rats, compared to the control animals.

In humans, increased incidence of PD in T2DM patients has been shown in a cohort study containing data collected from T2DM patients admitted for hospital care [53]. In this study, De Pablo-Fernandez et al., showed that PD patients with pre-existing T2DM experienced a rapid progression and a more severe phenotype of PD. Similar findings regarding increased risk for developing PD in T2DM patients (which was quantified at 36 %) was corroborated by another group of researchers who conducted their studies on a Danish population [54]. Moreover, Athauda et al., showed that individuals with both T2DM and PD exhibit greater dependency, compared to those with PD alone. Specifically, significantly increased motor and non-motor symptoms, and a faster progression of PD, was observed in individuals with PD and T2DM, compared to those individuals only suffering from PD [55]. Lastly, another example of the association between T2DM and PD is shown in a study aimed at better understanding the connection between IR and brain volume, an indicator for diagnosing and monitoring of the progression of various disorders of the CNS, including PD. The authors showed that, when compared to controls, PD patients had increased IR [56].

While the association between PD and T2DM seems clear, the specific molecular mechanisms underlying this association still remain far from being completely understood. However, multiple researchers have already provided scientific evidence for the important role of mitochondrial dysfunction in these mechanisms (Table 1). For example, dysregulated bioenergetics and mitochondrial ultrastructure alterations have been demonstrated in skeletal muscle from mice in which IR was triggered by a high-fat and high-glucose diet. The authors of this study stated that these deleterious effects were probably mediated by increased oxidative stress [57]. Moreover, hyperglycemia has been linked to unbalanced generation of ROS and increased damage to mtDNA, as well as to the activation of pro-inflammatory mediators and neurodegenerative markers in retinal ganglion cells [58]. Furthermore, using *Drosophila* models of PD (by inactivation of the DJ-1β gene, the

Table 1
The important role played by mitochondrial dysfunction in the intersection between T2DM and PD has already been demonstrated by different authors.

Mitochondrial link	Model	References
Increased neuronal apoptosis	Human samples	51
Dysregulated bioenergetics and mitochondrial ultrastructure as a consequence of increased oxidative stress	Mice	57
Unbalanced generation of ROS and increased mtDNA damage	Human cell lines	58
Mitochondrial dysfunction is similar in PD and T2DM models	*Drosophila*	12
Increased ROS generation and mitochondrial depolarization	Mice	7
Dysregulated cellular energy metabolism	Human samples	6
Dysregulated mitophagy	Mice	60
Treatment with insulin improves mitochondrial physiology	Rats	3
Streptozotocin-dependent increased ROS generation	Mice, human cell lines	63
Protective effects of glucagon-like peptide 1 could be exerted via its antioxidant properties	Rats	64
Protective effects of metformin could be exerted via its antioxidant properties	Mice	68
	Human cell lines, *Drosophila*	12

This role is exerted at different levels. The table synthesizes some of the studies mentioned in this review, including the model in which they were conducted and the specific mitochondrial targets that were assayed.

ortholog of human DJ-1), and T2DM (by feeding the animals with a high-sugar diet) similar effects were observed at the mitochondrial level in both models [12]; this suggest a common mitochondrial pathway that links the two diseases, which was further supported by another study conducted in mice. Specifically, Ekstran et al., fed MitoPark mice (a well-known model of PD [59]) for two months either with a regular diet or with a high-fat diet. The authors reported increased aberrant expression of αSyn in neurons from both control and MitoPark mice under T2DM-mimicking conditions. Moreover, in the same study, the authors modeled IR in differentiated dopaminergic neurons by pulse-stimulation with insulin. Using this method, they found that IR increased aggregated αSyn. Their findings suggest that the mechanisms underlying these observations include increased ROS generation and mitochondrial depolarization, in a molecular pathway mediated by the polo-like kinase-2 protein [7]. Lastly, a study conducted using fibroblasts obtained from healthy individuals and PD patients, which were grown under low and high-glucose conditions, showed increased levels of organic acids related to glucose metabolism, such as lactic acid, in fibroblasts from PD patients, especially under high-glucose conditions [6]. Activation of anaerobic glycolysis, usually as a consequence of decreased OXPHOS, results in the accumulation of these organic acids. Moreover, the authors showed that amino acids and fatty acids related to the tricarboxylic acid cycle (TCA), as well as to β-oxidation of fatty acids, were increased in samples obtained from PD patients under high-glucose conditions, compared to control conditions. These findings suggest that, while mitochondrial physiology is dysregulated in PD, pre-diabetogenic conditions could contribute to increase this dysfunction.

The study of the status of the dopaminergic neurons in models of T2DM and PD has also been addressed. For example, Su et al., using diabetic mice treated with MPTP, showed an increased loss of tyrosine hydroxylase positive neurons in the substantia nigra pars compacta of the mice modeling T2DM, which intensified the MPTP-induced bradykinesia [60]. Accordingly, dopaminergic neurons were more susceptible to hyperglycemic damage. The authors also showed that hyperglycemia significantly inhibited the PINK1/Parkin-dependent mitophagy in the midbrain of diabetic mice, which further contributed to mitochondrial dysfunction, connecting all these processes. MPTP is a drug commonly used to mimic PD because it induces an oxidative imbalance in dopaminergic neurons, ultimately leading to mitochondrial dysfunction and increased apoptosis [61]. Moreover, Iravanpour et al., studied the effects of the treatment with low doses of intranasal insulin for 14 days in rats injected with 6-hydroxydopamine (another pharmacological tool to model PD in animals [42]). Specifically, they addressed mitochondrial physiology and dopaminergic cell death, as well as motor performance in the animals. Their results showed that treatment with intranasal insulin did not only reduced motor dysfunction and dopaminergic cell death, but it also improved mitochondrial function, promoting mitochondrial biogenesis and fission [3]. Based on these findings, they proposed intranasal insulin as a plausible treatment for PD, further linking T2DM and PD, and placing mitochondria at a central point in that intersection. Furthermore, in the midbrains of mice in which T2DM was modeled by treatment with streptozotocin (a well-known diabetogenic), Parikh et al., showed upregulated thioredoxin-interacting protein (TXNIP, a protein involved in insulin regulation [62], and in increasing ROS generation [63]), as well as inhibition of autophagy. Additionally, they found an increased loss of dopaminergic neurons in the same animals [62]. The authors corroborated the upregulation of TXNIP, as well as decreased autophagy flux and increased ROS, in PC12 cells grew on a high-glucose medium. Lastly, using rats and pharmacological models of T2DM and PD, Elbassuoni et al., showed the deleterious effects of pre-existing T2DM in the severity of PD, which was evident by a significantly decreased number of striatal dopaminergic neurons in the brains of the animals [64]. In the same manuscript, the authors addressed the role of glucagon-like peptide 1 in their models, and they showed that the positive effects of this peptide in the striatal neurons could be exerted via its antioxidant properties, and therefore its positive effects against oxidative stress, rather than its direct hypoglycemic effect [64].

Another link between T2DM and PD could be found in the studies regarding the effects of metformin, an oral hypoglycemic agent commonly used in the treatment of T2DM, in PD. In many of these studies, mitochondrial physiology also arises as a crucial component of these effects. Metformin is an stimulator of AMP-activated protein kinase (AMPK), thus modulating cellular energy metabolism, including mitochondrial physiology [65,66]. Accordingly, the close relationship between the status of AMPK and mitochondrial physiology has already been demonstrated [65,67]. Using mice treated with MPTP and probenecid (an uricosuric agent known to increase the concentration of MPTP in murine brain by reducing the renal clearance of the drug [68]), Lu et al., showed that oral administration of metformin (5 mg/mL in drinking water for five weeks, starting on the third day of the treatment) protects dopaminergic neurons in the substantia nigra pars compacta, in a mechanism mediated by the enhancement of the AMPK-mediated autophagy and ROS clearance. Accordingly, metformin raised the striatal dopaminergic levels, considerably improved the MPTP-induced motor damage, and repressed the MPTP-induced microglial overactivation induced-inflammation [69]. Moreover, Catalan-Garcia et al., using SH-SY5Y cells knocked down for DJ-1, showed that the treatment with metformin increases cell viability. In the same study, using T2DM model *Drosophila*, the authors demonstrated that metformin decreased oxidative stress and suppressed impaired locomotor activity [12], further linking T2DM and PD, and showing the crucial role of mitochondrial physiology in this link.

4. T2DM and AD

AD is the most common type of dementia, and according to the "2020 AD facts and figures", the number of AD patients ($\geq$ 65 years) might increase to 13.8 million by 2050 in the USA, alone. The etiopathology of the vast majority of the cases of AD is still poorly understood, only a small subset of the cases has a clearly defined genetic origin (familial AD) [70]. Specifically, familial AD is a relatively uncommon autosomal dominant condition with an early onset [71], caused by mutations in some specific genes, such as those that code for the presenilin (PSEN) and the amyloid precursor protein (APP) [72,73]. The origins of sporadic AD remain unclear, but the development of the disease seems to be a consequence of a combination of environmental and genetic factors [74]. Probably one of the best-described pathological hallmarks of both familial and sporadic AD is the increased presence of Aβ plaques, and neurofibrillary tangles composed of hyperphosphorylated tau, in the brains of patients [75]. Whether Aβ accumulates in mitochondria is still debatable. However, it is known that the increased presence of aggregated Aβ and hyperphosphorylated tau in the brains of patients has deleterious effects on neuronal mitochondrial physiology, ultimately leading to increased cell death [76,77].

T2DM is a well-known risk factor for the development of dementia, including AD [78–80]; and shared pathobiological links between T2DM and AD have already been proposed at both molecular and epidemiological levels. For example, in the 90s, the Rotterdam Study found that the presence of T2DM almost doubled the risk of dementia and AD in aging individuals [80]. Moreover, in a longitudinal study that included 1138 subjects, Luchsinger et al., explored the relationship between the presence of a range of vascular risk factors and AD. The authors found that T2DM and smoking were the strongest risk factors to developing AD. They also concluded that the risk of AD associated with T2DM was stronger than previously reported, independently of any other vascular conditions [81]. Furthermore, a systematic analysis of longitudinal population-based studies found a 50–100 % increased risk for the onset of AD in diabetic patients, with no evident relation to ethnic origins [82]. This increased risk of AD in T2DM patients was corroborated by another manuscript, in which Kopf et al., also reported that studies conducted with a larger population size, early detection of T2DM, and

strict identification of dementia subtypes, are more likely to indicate a relationship between the two diseases [83]. Additionally, Xu et al., performed a community-based cohort study that lasted nine years and that included 1173 dementia- and T2DM-free individuals aged 75 years and older. The authors concluded that individuals with borderline diabetes (also known as pre-diabetes), a condition in which glucose tolerance is already impaired, showed a significantly increased risk of developing dementia, including AD [84]. Decreased glucose tolerance, which is not only reported in T2DM but also in AD [85], is usually associated to chronic hyperglycemia, a condition in which increased oxidative and nitrosative stress are present, deleteriously affecting the generation of ATP and further compromising mitochondrial physiology [86]. Lastly, not only has T2DM been proposed as a risk for developing AD, but also vice versa. In fact, in a cohort study conducted with patients in Minnesota, Janson et al., reported elevated occurrence of both T2DM and impaired fasting glucose in patients with AD [87].

At the molecular level, it has been demonstrated that treatment of rodents with streptozotocin increases the hyperphosphorylation of tau [88], as well as the aggregation of Aβ [89], further supporting a molecular link between AD and T2DM. Moreover, similarly to what was observed in PD, mitochondrial dysfunction has emerged as an important component in this intersection between these two diseases (Table 2). For example, using mice in which T2DM was modeled by treatment with streptozotocin, Ruegsegger et al., found decreased ATP generation in the cerebrum, hypothalamus, and hippocampus of the animals; as well as dysregulation of mitochondrial dynamics, and increased tau phosphorylation [90]. The authors also reported that intranasal administration of insulin in healthy mice increased mitochondrial ATP generation, and it improved neuronal development and neurotransmission. Moreover, using control and transgenic mice models of AD which were maintained under control or high-glucose diet for seven months to model T2DM, Carvalho et al., showed similar brain mitochondrial dysfunction in both AD and T2DM models [91]. Specifically, the authors described a comparable degree of compromised OXPHOS activity and calcium dyshomeostasis; as well as alterations in the ultrastructure of the organelle. Control mice, which were maintained in high-glucose diet, also showed increased levels of aggregated Aβ in their brains. The authors concluded that the metabolic alterations associated to T2DM could contribute to the development of AD-like pathologic features, which supports the hypothesis that mitochondria could serve as a fundamental link between these two pathologies.

To further address the molecular pathways linking T2DM and AD, some authors focused their efforts in the study of the regulation of insulin in these diseases. Mitochondrial dysfunction also emerged here as a link between the two pathologies. For example, Talbot et al., using post-mortem brains obtained from AD patients at different stages of the disease, showed decreased response to insulin signaling pathways in these brains. In fact, the authors noted that these signaling pathways were progressively more dysregulated as the samples were obtained from patients with more advanced AD, regardless of the presence of T2DM. The study also showed that Aβ could indirectly trigger IR, and rise oxidative stress as AD advances, and therefore the degree of IR increases, suggesting a molecular loop between these processes [92]. Moreover, Gasparini et al., showed that insulin can modulate both the trafficking of Aβ and the activity of APP, via regulation of the mitogen-activated protein kinase (MAPK) signaling pathway [93]. MAPK is involved in the downregulation of the IGF-1, which has been reported in the temporal cortex from AD patients [94]. The authors of this study also reported the involvement of the FoxO signaling pathway in this molecular pathway. Lastly, Wang et al., showed that the increased levels and activity of p38MAPK correlate with the duration and the severity of AD [95]. The MAPK signaling pathway is closely related to the status of mitochondrial physiology [67], and the regulatory role of p38MAPK in mitochondrial physiology, including fission and ROS generation, has been already demonstrated [96,97]. Moreover, short-term activation of FoxO by increased oxidative stress induces transcription of some of main mitochondrial antioxidant enzymes [98]. However, if oxidative stress persists, long-term activation of the FoxO signaling pathway could contribute to hyperglycemia and hyperinsulinemia, further increasing oxidative stress and apoptosis, in a deleterious cycle [99,100].

Hyperglycemia-induced vascular dysfunction is a crucial component of AD; in fact, AD has been defined as a vascular disorder with neurodegenerative implications (a “vascognopathy”) [101,102]. Accordingly, epidemiological studies have consistently demonstrated that nearly all the risk factors associated with AD are related to vascular health, and linked to cerebral hypoperfusion. The deleterious effects of high-glucose in blood vessels and in the endothelium can be mediated by several different molecular mechanisms; in some of this mitochondrial dysfunction has been already reported. For example, the activation of the polyol pathway due to hyperglycemia results in changes in plasma osmolarity, promoting tau post-transcriptional modifications, and ultimately, apoptosis [103]. This alternative metabolic pathway bypasses glycolysis by directly converting glucose into fructose, producing sorbitol as an intermediate metabolite [104]. Moreover, Wong et al., showed that treatment with resveratrol of individuals with T2DM, improved both their neurovascular status and their multi-tasking performance [105]. Resveratrol, a glucose and lipid regulator, has multiple functions in the mammalian cells, including a potent antioxidant effect [106]. Using a pharmacological model of T2DM in rats, the positive effects of resveratrol on cognition, as well as in reducing oxidative stress and preventing increased apoptosis, were corroborated by two research studies [107,108]. All these findings support the idea that mitochondrial dysfunction is present at the different levels in which AD and T2DM converge.

Table 2
The important role played by mitochondrial dysfunction in the intersection between T2DM and AD has already been demonstrated by different authors.

Mitochondrial link	Model	References
Dysregulated ATP generation	Mice	89
Compromised OXPHOS, calcium dyshomeostasis, and altered mitochondrial ultrastructure	Mice	90
Increased ROS generation and oxidative stress	Human samples	91
Dysregulated MAPK signaling pathway	Murine cell lines, human samples	92, 94
Increased mitochondrial-mediated apoptosis	Human cell lines	102
Positive results of treatment with resveratrol, probably exerted via its antioxidant effects	Human samples, rats	104, 106, 107

This role is exerted at different levels. The table synthesizes some of the studies mentioned in this review, including the model in which they were conducted and the specific mitochondrial targets that were assayed.

5. Other neurodegenerative diseases

While the number of studies that link mitochondrial dysfunction, T2DM, and neurodegenerative disorders other than AD and PD is not very high; the role of dysregulated glucose metabolism, which is closely related to T2DM and mitochondrial dysfunction, has already been addressed in many of these disorders (Table 3). Here, we critically review articles in which this relationship has been studied.

5.1. Amyotrophic lateral sclerosis (ALS)

ALS has been typically defined as a neurodegenerative disorder characterized by the loss of motor neurons and the onset of cognitive impairment, even though in the past decade the etiopathology of ALS has emerged as a much more complex system, and pleiotropic symptoms has been now broadly described. Various authors have already suggested a potential link between ALS, mitochondrial dysfunction, and dysregulated glucose metabolism, which is a hallmark of T2DM. For

Table 3
The important role played by mitochondrial dysfunction in the intersection between T2DM and other neurodegenerative disorders (different from PD and AD) has already been demonstrated by different authors.

Disease	Mitochondrial link	Model	References
ALS	Positive effects of trimetazidine via a mechanism that could involve preventing dysregulated mitochondrial metabolism	Mice	111
	Mitochondrial dysfunction (including impaired OXPHOS, increased oxidative stress, etc.)	Mathematical model	112
	Decreased ETC activity and increased levels of mtDNA	Human samples	112
MCI	Increased oxidative stress	Cybrids	118
	Mitophagy dysregulation	Human samples	119
MS	Increased oxidative stress	Human samples	124, 125
	Deficient ATP levels in the axons, and increased oxidative stress and calcium dysregulation	Mice	129
	Unbalanced TCA cycle and glycolysis	Human samples, mice	129
MELAS	Decreased activity of the ETC complexes	Human samples	135
HD	ROS-mediated mitochondrial dysfunction	Human cell lines	142, 143

This role is exerted at different levels. The table synthesizes some of the studies mentioned in this review, including the model in which they were conducted and the specific mitochondrial targets that were assayed.

example, Scaricamazza et al., using mice models of ALS, have investigated the potential therapeutic effects of trimetazidine; an anti-ischemic drug with potent effects in the metabolism of long-chain fatty acids, therefore affecting glucose metabolism [109]. Trimetazidine also promotes myogenesis and neuromuscular communication, via a mechanism mediated by the positive effects of the drug on mitochondrial metabolism [110]. Specifically, the authors of this study administered trimetazidine orally to $SOD1^{G93A}$ mice (which expresses a mutated form on SOD1 commonly linked to ALS and mitochondrial dysfunction [111]), starting from the onset of the disease. The authors reported that trimetazidine reduced the loss of motor neurons, therefore delaying paresis; and it improved muscle performance [112]. This treatment also improved glucose metabolism and decreased neuroinflammation in both the spinal cord and peripheral nerves, ultimately extending the overall survival of the mice. The authors concluded that the effects of trimetazidine in this mice model could be mediated by the positive impact of the drug on mitochondrial function. In fact, trimetazidine was also able to reverse the switch from glycolysis to OXPHOS, therefore regulating glucose metabolism; and to improve overall mitochondrial function in skeletal muscle and spinal cord in their mice model of ALS.

Additionally, using mathematical approaches, Burlando et al., created a three-loop model of ALS in which mitochondrial dysfunction and dysregulated glucose metabolism played a crucial role. The first loop, triggered by the misfolded mutant SOD1 in motor neurons, consisted of OXPHOS impairment, AMPK overactivation, increased 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFK3), and a shift from pentose phosphate pathway (PPP) to glycolysis. Consequently, mitochondrial dysfunction was further triggered, increasing oxidative stress, in a deleterious loop. This increased oxidative stress triggered the second loop, consisting in the activation of the excitotoxic glutamatergic cascade, which increased the levels of cytosolic calcium, expression levels of PFK3, and further swift from PPP to glycolysis. The increased levels of cytosolic calcium and their deleterious effects in mitochondrial physiology, including OXPHOS, closed the third loop [113]. Based on their model, the authors proposed that decreasing the levels and activity of PFK3 could represent a valid pharmacological strategy in ALS. Further evidence of the relationship between ALS, mitochondrial dysfunction, and dysregulated glucose metabolism, was provided by Wiedermann et al., using spinal cords obtained from healthy individuals and ALS patients. Their results show a significant rise in mtDNA content in ALS patients, which was interpreted by the authors as a compensatory effect to counteract the increased mitochondrial dysfunction observed in the same samples. In fact, the activity of the ETC complexes I, III, and IV was significantly decreased in spinal cord from ALS patients, which suggests compromised energy metabolism in the affected motor neurons. Increased oxidative stress, and mitochondrial morphological irregularitires (including swelling) were found in the spinal cords of these patients [114].

5.2. Mild cognitive impairment (MCI)

MCI is identified as an intermediate stage of cognitive impairment, which could be interpreted in some cases as a transitional phase from cognitive changes of aging to dementia [115]. Amnesic MCI, one of the types of this disease, has been often defined as a precursor of AD [116]. In individuals 50 years and older, the prevalence of MCI has been estimated at around 15 % [117]; this prevalence is higher in men than in women of similar age groups, and it decreases as the educational level increases [117]. Patients with T2DM are at higher risk for developing MCI. In fact, in T2DM patients aged 35–81, the prevalence of MCI is about 45 % [118]. As stated above, MCI seems to be prevalent in men; however, in T2DM patients, the prevalence of MCI is higher in women [118]. Interestingly, mitochondrial dysfunction has already been described as a component of the etiopathology of MCI, via a mechanism including increased oxidative stress [119].

Some authors have studied the molecular mechanisms that link MCI and T2DM. For example, a proteomics analysis of platelets from patients with T2DM and MCI (T2DM-MCI), and T2DM but not MCI (T2DM-nMCI), showed significant changes in the levels of proteins involved in insulin regulation. Moreover, the levels of optineurin, an autophagy receptor involved in the PINK1-mediated mitophagy and in the clearance of Aβ and tau, were increased in both hippocampus and platelets of the T2DM-MCI patients; and glycolysis was also increased in the same patients [120]. T2DM-MCI patients also showed elevated platelet ratio of glycogen synthase kinase β3 (rGSKβ-3) rGSKβ-3 and $A\beta_{1-42}/A\beta_{1-40}$ ratio. Changes in rGSK-3β-3 have been previously correlated to cognitive decline in T2DM patients [121].

5.3. Multiple sclerosis (MS)

MS is a chronic neurodegenerative disorder characterized by demyelination in the brain and spinal cord, and the consequent axonal degeneration and neuroinflammation [122]. In fact, patients with MS have significant higher plasmatic concentration of different proinflammatory cytokines, whose levels correlate with MS duration, inflammation stage, and number of relapses [123]. At the cellular level, active MS lesions are characterized by the migration of the macrophages to the outside of the lesion, while the center is demyelinated; inactive lesions are characterized by total demyelination, with microglia and macrophages no longer present [124]. Demyelinated axons show increased energy demands, probably in an attempt to maintain electrical conductance. Interestingly, IR and increased oxidative stress seem to be linked with increased disability in MS patients [125,126]. Moreover, approximately half of MS patients developed cognitive impairment, which has been associated with hyperinsulinemia [127].

To address the status of glucose metabolism in MS, the concentrations of sorbitol, fructose, and lactate (involved in extra-mitochondrial glucose metabolism), were assayed in human cerebrospinal fluid obtained from healthy individuals and MS patients. Increased levels of these metabolites were found in MS patients, and this elevation was shown to be associated with worsening of neurological symptoms [128]. Impaired extra-mitochondrial metabolism could be a compensatory effect against dysregulated mitochondrial physiology, which is a key contributor to glucose metabolism dysregulation in MS [129]. Furthermore, using mice models of the disease, Tai et al., showed that

neuroinflammation in the neuronal cord is in the basis of deficient levels of ATP in the axons. They also showed that insufficient ATP production precedes oxidative stress and calcium dyshomeostasis, in a deleterious cycle [130]. The authors reported that the decreased levels of ATP observed in these samples are not merely a consequence of impaired ETC, but also of an imbalance of the enzymes involved in the TCA. Moreover, using brain tissue, Nijland et al., reported increased expression levels of glycolytic enzymes in MS patients, while the expression levels of the enzymes involved in the TCA were increased in active MS lesions, but not in inactive lesions [131]. For example, aligning with the study from Tai et al., these researchers found that the TCA enzyme α-KGDH was significantly reduced in demyelinated axons. Down-regulation of the TCA has also been demonstrated in the peripheral nervous system of T2DM models [132,133], further linking these diseases. The authors also demonstrated that demyelinated axons may rely on astrocytes to supply lactate to axons [130].

5.4. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)

MELAS is a rare mitochondrial disorder that predominantly affects children and young adults [134]. It causes multiple symptoms, which might not been present in all the patients, including seizures, dementia, hyperglycemia, myalgia, etc. [135]. As these symptoms progress over time, they can potentially lead to chronic complications including glucose intolerance, hearing loss, and hypertrophic cardiomyopathy. The 3243 A>G mutation, located within the mitochondrial tRNA Leu (UUR) gene, is a particularly prevalent cause of MELAS, with approximately 80 % of cases being attributed to this mutation [135].

Increased lactic acid generation is a crucial component of MELAS, which further contributes to mitochondrial dysfunction. In fact, mitochondrial dysfunction, including decreased activity of all the complexes of the ETC, has been demonstrated in the muscle of MELAS patients, even though the percentage of mutated mtDNA does not seem to underly this effect [136]. While the bibliography regarding this disease is scarce, probably due to the very low number of MELAS patients, increased presence of T2DM has been described in clinical data obtained from some MELAS patients [137,138]. However, T2DM seems to follow an heterogenous pattern in these patients. For example, impaired insulin secretion is not affected in all the individuals suffering from this disease [139,140].

5.5. Huntington's disease (HD)

HD is an autosomal-dominant neurodegenerative disease caused by an abnormal increased number of CAG repeats in the gene coding the Huntingtin protein (Htt) [141]. This results in the aggregation of Htt and the subsequent increased cell toxicity and death, mostly in the medium-spiny GABAergic neurons in the striatum [142]. ROS-mediated mitochondrial dysfunction, including increased damage to mtDNA, has been broadly described in HD [143,144]. Additionally, through the use of mice models of the disease, it has been suggested that mitochondrial dysfunction could be the basis for higher rates of T2DM observed in HD patients [145]. However, the exact mechanisms linking these diseases are still not fully understood, although some models have been proposed. For example, Htt could increase adiposity as a consequence of mitochondrial dysfunction, a well-known risk for developing T2DM [146,147]. Moreover, the hypothalamus-pituitary-gonadal axis, the hypothalamus-pituitary-adrenal (HPA) axis, and the mechanisms in charge of the production of testosterone are all deleteriously affected in HD [148,149]. The impact of HD on the HPA axis, specifically on signal molecules like cortisol, could also contribute to the increased levels of T2DM observed in these patients. However, this link is debatable, since the timing and duration of the release of cortisol in the body are also critical factors to developing T2DM [150,151].

The exact relationship between HD and T2DM remains particularly poorly described. For example, in murine models of HD, increased presence of insulin receptor substrate-2 (Irs-2, a crucial downstream protein in the insulin signaling pathway) has been shown to be an accelerator of the progression of HD at different levels. In fact, mitochondrial dysfunction, neuronal damage, and overall organism motor function were deleteriously affected by increased Irs-2 [145]. However, in the same study and in other study also conducted in mice, decreased Irs-2 expression induced hyperglycemia and T2DM [145,152]. Moreover, Fain et al., showed that R6/2 mice (a well-known model of HD) fed a sugar- and fat-rich diet, failed to develop T2DM [153]. In fact, in this study, only one mouse showed increased IR, although the effect seemed to have been mitigated by increased insulin secretion. Another study conducted by Luesse et al., on the same mice model, but with animals fed a regular diet with six hours starvation periods, showed a greater co-morbidity between HD and TDM2, but even in this case, only 26 % of the mice developed T2DM [154]. Nonetheless, the correlation between the two disease is consistently observed in humans [155,156]. This discrepancy may be explained by the limitations of the R6/2 mice model to adequately replicate human HD. In fact, the limitations of the use of mice models in neuroscience have already been broadly described [157].

6. Conclusions, perspectives, and future directions

Neurodegenerative disorders and T2DM are highly prevalent diseases among the aging population, and they are expected to be more common in the coming decades as society ages, and new pharmacological approaches for symptomatic treatment emerge. The scientific literature that we comprehensively present in this bibliographical review demonstrates the crucial role that mitochondrial dysfunction plays in the intersection between neurodegeneration and T2DM. A better understanding of the regulation of the organelle under these pathological conditions, especially in senescent cells in the CNS, could provide us with valid and innovative therapeutic options to increase healthspan.

Specifically, the scientific manuscripts that we review here show that T2DM patients are significantly more prone to develop AD. It also shows that patients with T2DM and pre-existing PD often experience a more severe and rapidly progressing PD. In both cases, mitochondrial dysfunction seems to be in the intersection between T2DM and neurodegeneration. This dysfunction could contribute to the onset or the progression of the diseases via intricate mechanisms that seem to involve IR and the dysregulation of glucose levels. Specifically, reduced ATP generation and increased oxidative stress, with the consequent rise in cytotoxicity, have been broadly demonstrated in all these pathologies. Furthermore, mitochondrial dysfunction has been broadly described in the pathogenesis of other major neurodegenerative disorders, such as ALS, HD, MS, and MCI. The role of T2DM on the onset and/or development of these diseases has also been suggested.

7. Plausible new pharmacological approaches based on targeting mitochondrial dysfunction

Considering the crucial role played by mitochondrial dysfunction in the intersection between T2DM and neurodegeneration, targeting this dysfunction could constitute a promising therapeutic avenue against these pathologies. In fact, two of the leading drugs which have been tested on T2DM and neurodegeneration (metformin and resveratrol, see above for more details) exert, at least partially, positive effects on T2DM and neurodegeneration by regulating mitochondrial physiology (Fig. 2). As mentioned before, both T2DM and neurodegenerative diseases have a serious deleterious impact on human healthspan.

While a better understanding of mitochondrial physiology under pathological conditions, especially in senescent cells in the CNS, is needed before developing new and valid pharmacological therapies, some possibilities in this field are already found in the literature. For example, novel compounds designed to revert mitochondrial

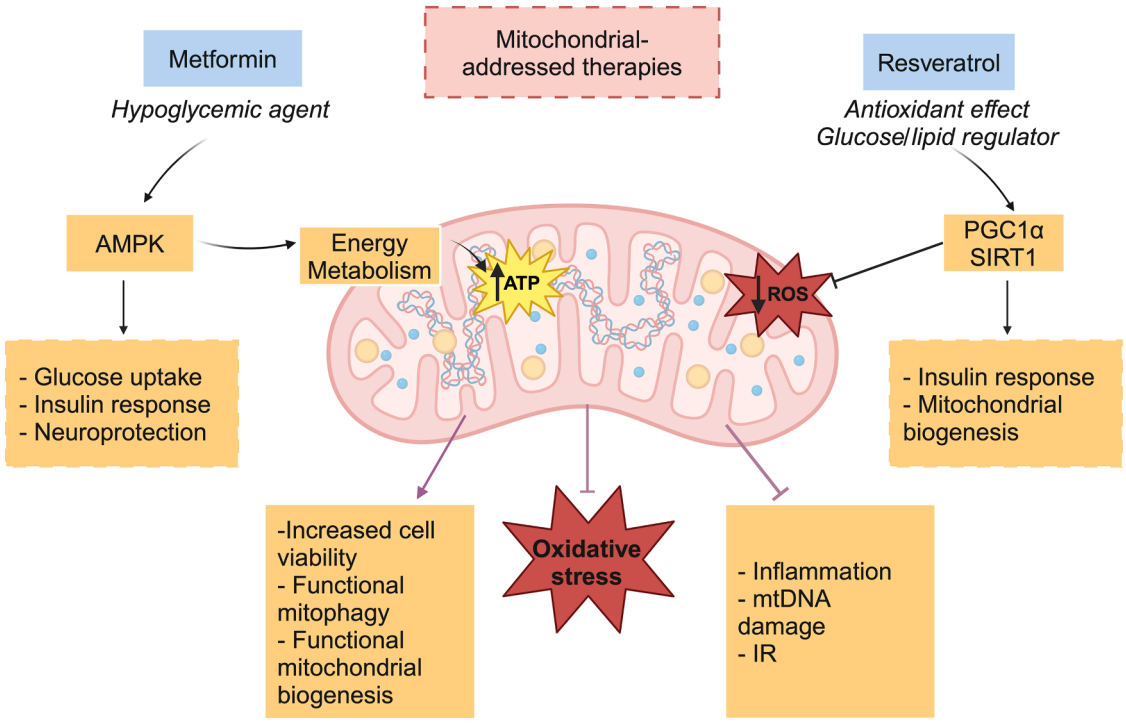

Fig. 2. Mitochondrial physiology is crucially involved in the molecular and cellular pathways affected by metformin and resveratrol. Metformin and resveratrol are two of the leading drugs that are currently being studied in patients suffering from T2DM and PD or AD. As described in this review, the positive effects of these drugs at the cellular and molecular level are exerted, at least partially, by their protective effect on mitochondrial physiology. Image was created using BioRender.com and an institutional license to Rutgers University.

dysfunction could prevent IR and hyperglycemia, which are two of the main mechanisms described in T2DM and discussed in this review. Both are also closely related to mitochondrial dysfunction [158,159]. In fact, the onset of IR in liver, skeletal muscle, and adipose tissue has been hypothesized to be closely related to reduced OXPHOS and mitochondrial biogenesis, as well as to increased oxidative stress and metabolic imbalance [160–164]. IR can in turn lead to hyperglycemia, which is highly correlated with elevated levels of oxidative stress, including increased damage to mtDNA and disrupted mitophagy [58,165–167]. All these could be prevented or reverted with the use of mitochondrial-addressed therapies, which have the potential to significantly improve healthspan in both T2DM and neurodegeneration. These therapies could work at different levels, from OXPHOS modulators and antioxidants; to mitochondrial translation regulators, and modulators of mitochondrial dynamics and mitophagy. Restoring mitochondrial physiology at any of these points has the potential to contribute to revert mitochondrial dysfunction, and hopefully, some of the clinical features of T2DM and neurodegenerative disorders.

Author's Contributions

Discussing the mainmanuscripts, in a journal club-type format; and writing this review was themain focus of a graduate-level class taught during the Fall semester of 2023,similarly to what we did in the previous semesters 22,25,167. All the students listed as authors in thismanuscript contributed equally to this work during the semester. However, thestudents listed as first authors, voluntarily extended their work into theSpring semester of 2024, participating in the final writing and review, andaddressing the comments from the reviewers. E.R.S. and R.T. D.C. are researchersat Dr. Solesio's laboratory, they read and edited the final draft of thereview, and contributed to respond to the comments from the reviewers. M.E.S.was the professor; she contributed to the selection of the manuscripts that thestudents discussed, structured the review, coordinated the writing process, andreviewed the manuscript before submission and re-submission. All authors haveread and agreed to the published version of the manuscript.

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CRediT authorship contribution statement

S Aiman Nadeem: Writing – original draft, Conceptualization. **Fatmanur Kilic:** Writing – original draft, Conceptualization. **Sachin Muppavaram:** Writing – original draft, Conceptualization. **Sheida Kavehmoghaddam:** Writing – original draft, Conceptualization. **Nikhila Mandava:** Writing – original draft, Conceptualization. **Jose E Castro Voldolosa:** Conceptualization. **Akhila Kasturi:** Writing – original draft, Conceptualization. **Isabella R Baduini:** Writing – original draft, Conceptualization. **Sai A Jonnalagadda:** Writing – original draft, Conceptualization. **Samuel Hsiao:** Writing – original draft, Conceptualization. **Maria E. Solesio Torregrosa:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Lisa H Do:** Writing – original draft, Conceptualization. **Renata T Da Costa:** Writing – review & editing, Conceptualization. **Chris-Ann Bryan:** Writing – original draft, Conceptualization. **Ernest R Scoma:** Writing – review & editing, Conceptualization. **Dileep Annapureddy:** Writing – original draft, Conceptualization. **Nasira Tamajal:** Writing – original draft, Conceptualization. **Marietta A Rowan:** Writing – original draft, Conceptualization. **Christina N Suoto:** Writing – original draft, Conceptualization. **Juan J Nizama:** Writing – original draft, Conceptualization. **Aleece Siner:** Writing – original draft, Conceptualization. **Bryan Ramirez:** Writing – original draft, Conceptualization.

Declaration of Competing Interest

Nothing to declare

Data Availability

No data was used for the research described in the article.

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