Abstract

Purpose: The purpose of this study was to review the alterations in muscle fibers in Parkinson's disease (PD). The following were our review questions. (1) How has research on type I myofiber grouping in PD developed over time? (2) What kinds of muscles are affected in which patients? (3) What are some possible pathophysiology and mechanisms? Does type I myofiber grouping in PD differ from primary sarcopenia that occurs with aging? (4) What are the clinical implications and possible therapeutic approaches for type I myofiber grouping in PD?

Method: To investigate the questions, we used combinations of keywords such as “Parkinson”, “skeletal muscle”, “myofiber type”, “fast twitch”, “slow twitch”, “myofiber grouping”, and “motor unit” in PubMed and Google Scholar. Articles on PD patients and normal elderlies that dealt with type I myofiber grouping and motor unit alterations were included. References in the included articles were also considered.

Results: Research over the past five decades has identified various motor abnormalities and myofiber alterations in PD patients, including the hypertrophy of slow-twitch type I myofibers and atrophy of fast-twitch type II myofibers across different muscles. One important finding is that Type I myofiber grouping, which is common in aging, is more severe in PD, which could be due to the selective activation of low-threshold motor units and could be also linked to abnormal alpha-synuclein aggregation, a factor associated with PD.

Conclusion: Research suggests that type I myofiber grouping in muscles, not just dopaminergic cell damage in the substantia nigra, could influence motor symptoms of PD, indicating that alternative treatments beyond dopaminergic drugs, such as high-intensity exercise, might be beneficial. However, given the limitations in these studies, such as small participant numbers and the complexity of PD pathophysiology, future research is needed to fully understand the phenomena in different PD subtypes and to develop more effective treatments.

Keywords: Parkinson's Disease, Neurodegenerative Disease, Skeletal Muscle, Type I Myofiber Grouping, Scoping Review

1. Introduction

Parkinson's disease (PD) is the fastest-growing and second-most common degenerative brain disease, characterized by gradual degenerative changes in the central nervous system [1], but changes in muscle fibers are less well-known. Edström (1970) was the first to report that the sizes of red and white muscle fibers are altered in PD patients [2]. Edström discovered that the group of white muscle fibers was atrophied and the group of red muscle fibers was either unchanged or hypertrophied through muscle biopsy. According to the author, the change may be caused by decreased muscular strength and increased rigidity. In comparison to the damage to the nervous system in PD patients, the topic has received little attention since then, but ongoing studies are still being reported.
PD patients develop motor symptoms such as bradykinesia, rigidity, tremor, and postural instability, and non-motor symptoms such as constipation, depression, anxiety, insomnia, fatigue, pain, urinary symptoms, and autonomic dysfunction as the disease progresses[3]. Dopaminergic drugs such as levodopa can effectively help PD patients manage their symptoms. However, more than half of PD patients experience a wearing-off phenomenon 2 to 5 years after starting dopaminergic medication[4]. In a Korean study, about half of the patients who took dopaminergic drugs for more than 12 months complained of the wearing-off phenomenon, and the patients' Unified Parkinson's Disease Rating Scale (UPDRS) Part 3 score, a clinical scale of motor signs of PD, deteriorated significantly in the off state (8 out of a total score of 108 points) [5]. In the case of PD, a standard disease-modifying treatment has not yet been established. Therefore, there is currently an unmet need for methods and techniques for managing and treating the disease[6].

Meanwhile, recent research suggests that, when applied over time, various types of exercise may have disease-modifying effects on PD [7]. It has been well established through studies using several animal models that exercise has a neuroprotective effect, and studies using PD animal models have also revealed that exercise exhibits a dopamine neuroprotective effect. The reason for this effect is not fully understood, but researchers believe that exercise reduces the vulnerability of neurons by expressing neurotrophic factors [8]. On the other hand, there haven’t been many studies on the effect of exercise on the altered muscle fibers of PD patients. At this point, a recent study suggests that resistance exercise can reverse type I myofiber grouping in PD patients. It is anticipated that additional research will be conducted in the future [9]. Therefore, in this review, we aimed to thoroughly examine the changes in muscle fibers in PD and speculate on the clinical implications and potential therapeutic approaches to the phenomenon.

2. Methods

2.1. Review questions

i. How has research on type I myofiber grouping in PD developed over time?

ii. What kinds of muscles are affected in PD patients?

iii. What are some possible pathophysiology and mechanisms? Does type I myofiber grouping in PD differ from primary sarcopenia that occurs with aging?

iv. What are the clinical implications and possible therapeutic approaches for type I myofiber grouping in PD?

2.2. Study selection

In this review, we included studies involving patients with PD. To investigate the questions, we used combinations of keywords such as “Parkinson”, “skeletal muscle”, “myofiber type”, “fast twitch”, “slow twitch”, “myofiber grouping”, and “motor unit” in PubMed and Google Scholar. Articles on PD patients and normal elders that dealt with type I myofiber grouping and motor unit alterations were included. References in the included articles were also considered.

3. Results and Discussion

3.1. Type I myofiber grouping in parkinson’s disease

Edström (1970) first reported that in PD patients, muscle fibers with a high concentration of myofibrillar ATPase (fast-twitch, generally known as ‘white’, type II fibers) were atrophied while
fibers with a low concentration of myofibrillar ATPase (slow-twitch, generally known as ‘red’, type I fibers) were either unchanged or hypertrophied, as discovered through a muscle biopsy. The author suggests that the change may be due to muscular weakness and hypertonia in PD patients[2]. Years later, Sica and colleagues(1973) observed a decrease in the number of functional motor units and abnormal enlargement of the remaining motor units in the extensor digitorum brevis muscle of PD patients. The authors associated these phenomena with these individuals' loss and dysfunction of alpha-motor neurons[10]. Meanwhile, Grimby and Hannerz(1974) observed that PD patients experiencing bradykinesia demonstrate a reduced capacity to transition between tonic and phasic motor unit recruitment, and the reverse as well. The authors propose that passive stretching of the muscle could potentially normalize voluntary activity, while relieving the muscle load may rectify the abnormal termination of voluntary actions in PD patients[11]. In 1979, Edström and colleagues additionally found that in PD patients, type I and type IIA fibers showed normal levels of sulfur and phosphorus. However, type IIB fibers (usually referred to as Type IIX fibers in more recent literature), particularly the atrophic ones, displayed a marked reduction in sulfur content and an increase in phosphorus content. The authors attributed the findings to the disuse of high activation threshold fast-twitch type IIB motor units[12].

During the 1980s and 1990s, the idea again slowly developed. Dietz et al.(1981) observed that PD patients frequently exhibited synchronized bursts of electromyography in the leg muscles and increased muscle tone. The authors suggested that these observations may be partially attributed to the increase in slow muscle fibers in PD patients. These fibers, given their unique contractile properties, displayed a heightened resistance to stretching[13]. In 1991, Pedersen and colleagues found that in PD patients, the time taken for the adductor pollicis muscle to reach half tetanus contraction was notably shorter compared to a control group, a result unaffected by medication status. Moreover, the speed at which muscles relaxed in PD patients was notably increased compared to the normal control group, possibly indicating an elevated muscle metabolism due to higher muscle tone. The authors suggested that the shortened muscle contraction time and increased muscle relaxation rate could be factors contributing to muscle stiffness in PD patients[14]. In 1996, Rossi et al. indirectly evaluated PD patients’ muscle modification using surface electromyography and muscle biopsy. The researchers discovered that in PD patients, there was a tendency for type I fibers in the tibialis anterior muscle to hypertrophy. This was also associated with a reduced rate of conduction velocity and changes in median frequency during stimulated contraction of the same muscle in these patients[15].

In the 2000s, Nuyens et al.(2000) found that PD patients exhibited a decrease in resistive torque during repetitive tasks when compared to healthy individuals. The researchers hypothesized that this finding could be partially attributed to a reduction in voluntary muscle strength and a shift in muscle fiber types towards low-threshold tonic fibers due to hypertonia, coupled with the selective disuse of high-threshold phasic motor units[16]. In 2002, Inkster and colleagues conducted a study comparing lower leg strength and the capacity to stand up from a chair between PD patients and control subjects. Despite the PD patients in this study having mild PD and maintaining activity levels similar to the control group, the authors discovered that these PD patients exhibited lower extensor torques in their hip and knee[17]. Building on this, Pääsuke et al.(2004) also identified leg extensor muscle weakness in PD patients, a condition that was found to be associated with difficulties in rising from a chair. The authors underlined the multifaceted nature of muscle weakness in PD patients, pointing to abnormal motor unit discharge patterns and peripheral alterations in muscle fibers as potential contributing factors[18]. In 2004, another group of researchers explored if the muscle weakness observed in PD patients was a result of reduced agonist activation, the engagement of a pathological oscillator, or a combination of both. The researchers suggested that the high occurrence of type I fibers, which exhibit lower discharge frequency, in the muscles of PD patients might have influenced their findings[19]. In 2007, Mak et al. conducted a quantitative analysis of trunk rigidity in PD
patients. They proposed that in PD patients, the resistance of trunk muscle tone increased more noticeably with an increase in passive movement speed compared to the control group. Furthermore, the data was more consistent in PD patients than in the control group. The authors speculated that this could be attributed to alterations in the trunk muscles of PD patients[20].

In the decade of the 2010s, Mu et al.(2012) revealed that PD patients experiencing dysphagia showed signs of fiber atrophy, fiber type grouping, and a transition from fast to slow myosin heavy chain in their pharyngeal constrictor and cricopharyngeus muscles[21]. This research group also identified a link between these phenomena and damage to the peripheral motor nerves, such as nerve X, the pharyngeal branch of nerve X, intramuscular nerve branches, and axon terminals in the neuromuscular junctions. This damage was assessed by examining the histopathological marker of alpha-synuclein aggregates[22]. Kelly et al.(2014) investigated the muscle tissue phenotype and discovered that PD patients had a larger cross-sectional area of type I myofibers and greater type II myofiber size heterogeneity than non-PD controls[23]. Nishikawa and colleagues(2017) explored the spatial distribution pattern of electromyography during continuous contraction of the vastus lateralis muscle in both healthy individuals and those with PD. The investigators found that in PD patients, the variations and alterations in the activation pattern were less pronounced than in healthy individuals. The researchers theorized that there could be irregularities in the descending commands originating from the basal ganglia and directed to the motor neurons in PD patients, which may lead to aberrations in the recruitment strategies of motor units. Additionally, the researchers suggested the potential for fiber type grouping in PD patients, which could further impact changes in the amplitude distribution of spatial electromyography[24]. Krumpolec and colleagues(2017) examined the impact of aerobic-strength workouts on total body metabolism and the properties of skeletal muscles in PD patients and age-matched control subjects. The researchers found that the vastus lateralis muscle in PD patients showed hypertrophy of type II fibers after endurance training. Exercise could also reduce the type I/type II fiber ratio in both the control group and PD patients, according to the study[25]. Kelly et al.(2018) likewise studied the impact of resistance training on the remodeling of motor units of the vastus lateralis muscle in PD patients, as well as young and older adults without PD. PD patients showed greater motor unit remodeling than what is typically seen in normal aging, and resistance training could potentially reverse myosin heavy chain expression in some of the grouped type I myofibers[9].

In the 2020s, Lavin et al.(2020) studied the transcriptional networks in skeletal muscle that are associated with Type I myofiber grouping in PD patients, as well as in older adults who were matched for both age and sex, and young adults who were matched for sex. The researchers identified co-expression networks linked to phenotypes that were pathologically increased in PD muscle tissue. The networks were associated with the size of type I myofiber groups and another network was related to the percentage of type I myofibers found within these groups. These networks were related to various biological processes, such as neurotransmission, neural development, cell survival, regulation of the cell cycle, inflammation, and energy metabolism[26]. Nishikawa et al.(2020) examined the motor unit behavior in female PD patients using surface electromyography. The authors found out that compared to control subjects, PD patients exhibited laterality of motor unit activation in their legs. Furthermore, PD patients demonstrated reduced muscle strength and irregular motor unit activity, which included increased rates of motor unit firing and an abnormal relationship between the average motor unit firing rate and motor unit threshold[27]. The same group of researchers(2022) compared the vastus lateralis muscle activity in female PD patients and the healthy age-matched female controls. In comparison to the control subjects, those with PD exhibited considerably higher entropy and reduced heterogeneity in the electromyography signals from the more impacted side of the lower limbs. Furthermore, this asymmetry in motor patterns continued to be present even when the patients were on dopaminergic medications[28]. On another note, Ginanneschi
and colleagues (2021) studied alterations in the excitability of the corticomotor pathway following upper-limb exercise in patients with PD. They found that the score for Part 3 of the UPDRS improved after two months of training, and this improvement was linked to a higher plateau of the post-training input-output curve obtained through transcranial magnetic stimulation. The authors proposed that this outcome suggests that exercise training might rehabilitate the recruitment and firing rate of large motor units, specifically Type II motor units, which are capable of fast and powerful movements [29].

3.2. Type I myofiber grouping in various muscles of PD patients

Research spanning several decades has significantly enhanced our understanding of the type I myofiber grouping in PD patients. Early studies in the 1970s detected atrophy in fast-twitch muscle fibers and irregularities in shifting between motor unit types [1][9][10][11]. In the following decades of the 1980s and 1990s, observations included synchronized bursts of electromyography in leg muscles, faster muscle contraction and relaxation rates, and changes detectable through electromyography and biopsies. These phenomena were thought to be related to modifications in muscle fibers and a preference for low-threshold tonic fibers [12][13][14]. Research in the 2000s also highlighted decreased resistive torque, weakened leg muscles, and trunk rigidity alterations in PD patients, suggesting abnormal motor unit discharge and muscle fiber changes [15][16][17][18][19]. During the 2010s, studies by Mu and colleagues [20][21] underscored the presence of dysphagia in PD patients, indicating signs of fiber atrophy, fiber type grouping, and a shift in myosin heavy chain within their pharyngeal muscles. Additionally, other researchers during this decade observed alterations in muscle activation, and the possible advantages of resistance training [9][23][24][25]. In the 2020s, research delved into transcriptional networks in skeletal muscles, motor unit behavior, and the impact of exercise on large motor units. Findings highlighted asymmetric motor unit activation, irregular motor unit activity, and persisting asymmetry in motor patterns, even when under medication [26][27][28][29].

Table 1. The effect of type I myofiber grouping on specific muscles in Parkinson's disease patients.

<table>
<thead>
<tr>
<th>Muscle type</th>
<th>Fiber type</th>
<th>Type I myofiber</th>
<th>Type II myofiber</th>
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<tbody>
<tr>
<td>Biceps brachii muscles</td>
<td>Hypertrophy (in patients with marked rigidity) or atrophy (in patients who were affected by akinesia and had minor rigidity) [2]</td>
<td>Atrophy [2]; a significant decrease in sulfur in atrophied type IIB fiber [12]</td>
<td></td>
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<tr>
<td>Quadriceps femoris muscles</td>
<td>Type I myofiber grouping [9][23][24]; increased type I myofiber group size, cross-sectional area, and motor unit activation [9][23]</td>
<td>Atrophy (type IIB fibers), &amp; decrease sulfur concentration in atrophied type IIB fibers [12]; heterogeneous type II myofiber size [9][23]</td>
<td></td>
</tr>
<tr>
<td>Tibialis anterior muscles</td>
<td>Hypertrophy, which was associated with smaller conduction velocity, and median frequency of the power spectrum (non-invasive surface electromyography) [15]</td>
<td>Atrophy in some cases [15]</td>
<td></td>
</tr>
<tr>
<td>Pharyngeal muscles</td>
<td>Atrophy, type I myofiber grouping in the pharyngeal constrictor and cricopharyngeus muscles, associated with dysphagia [21]</td>
<td>Decrease in the number, and a transition from a fast to slow myosin heavy chain in the pharyngeal constrictor and cricopharyngeus muscles [21]</td>
<td></td>
</tr>
</tbody>
</table>
3.2.1. Biceps brachii muscles

Edström in the 1970s described that in the case of the biceps brachii muscle, there was a tendency for type II fibers to atrophy. For type I fibers, they appeared at normal size or even showed a tendency for hypertrophy in patients with marked rigidity. Conversely, atrophy was also observed in patients who were predominantly affected by akinesia and had minor rigidity[2]. In 1979, Edström et al. conducted fiber type analysis of the muscle based on stainability for alkaline and acid-stable ATPase and measured relative concentrations of phosphorus, sulfur, chlorine, and potassium. The authors discovered type IIB fiber atrophy and a significant decrease in sulfur in atrophied type IIB muscles in PD patients[12].

3.2.2. Extensor digitorum brevis muscles

Sica et al.(1973) discovered the functional motor unit loss and abnormally large remaining motor units in the extensor digitorum brevis muscle of PD patients. In some of the PD patients, the researchers discovered prolonged terminal motor latencies in the deep peroneal nerve and a decreased response of the extensor digitorum brevis muscle[10].

3.2.3. Quadriceps femoris muscles

Edström et al.(1979) also investigated the fiber type of the quadriceps femoris muscle. The researchers discovered that, like the biceps brachii muscle, type IIB fibers were atrophied in PD patients, and that the sulfur concentration in atrophied type IIB fibers of the quadriceps femoris muscle was decreased[12]. Later, Nishikawa et al.(2017) applied spatial electromyography and discovered that alterations and variations in the vastus lateralis muscle activation patterns were not as distinct in individuals with PD as in healthy subjects. This suggests that abnormal motor unit recruitment strategies may be in effect, along with fiber type grouping in the muscles of PD patients[24]. Kelly et al.(2014 & 2018) discovered that type I myofiber group size and cross-sectional area, as well as motor unit activation were increased in PD patients when compared to older and young adults. The researchers also discovered that type II myofiber size was more heterogeneous in PD patients than in non-PD controls[9][23].

3.2.4. Adductor pollicis muscles

Pedersen et al.(1991) discovered that the contraction time and relaxation rate were decreased and increased in PD patients, respectively. Because both muscle tone and metabolism are generally elevated in PD patients, the authors hypothesized that the phenomenon could have been caused by muscle stiffness. Because Parkinsonian medication did not affect muscle contraction time or force output, the authors hypothesized that secondary changes in PD patients’ muscles could influence muscle contraction characteristics in the long run[14].

3.2.5. Tibialis anterior muscles

Using muscle biopsy, Rossi et al. discovered a tendency for type I fiber hypertrophy and type II fiber atrophy in the tibialis anterior muscle of PD patients. The conduction velocity and median frequency of the power spectrum of the tibialis anterior muscle were smaller in PD patients with type I fiber hypertrophy, according to non-invasive surface electromyography[15].

3.2.6. Pharyngeal muscles

Mu et al.(2012) revealed that pharyngeal constrictor and cricopharyngeus muscles in PD patients with dysphagia showed signs of fiber atrophy, especially type I fibers, fiber type grouping, and a transition from fast to slow myosin heavy chain[21]. The same group of researchers also discovered a link between these phenomena and damage to peripheral motor nerves such as nerve X, the pharyngeal branch of nerve X, intramuscular nerve branches, and axon terminals.
in neuromuscular junctions. The histopathological marker of alpha-synuclein aggregates[22] was used to assess this peripheral nerve damage.

### 3.2.7. Paraspinal muscles

Wrede et al.(2012) biopsied the paraspinal muscles of PD patients with camptocormia and discovered hypertrophied type 1 fiber and loss of type 2 fibers, structural defects in the disorganized fibers, and loss of oxidative enzyme activity and phosphatase reactivity. The author hypothesized that such changes in the trunk muscles could result in camptocormia and diminished ability to maintain the trunk’s upright posture[30].

To sum up, the grouping of type I muscle fibers in PD seems to be muscle-specific and is associated with the disease’s duration, severity, and particular symptoms such as muscle weakness and rigidity. While there are instances where atrophy of type I muscle fibers is reported, a trend toward hypertrophy is often observed. Although hypertrophy of type I muscle fibers can sometimes be found in ungrouped fibers, it is more commonly seen in grouped fibers[21][30].

In certain instances, like in the pharyngeal muscles, type I muscle fiber grouping can be observed, but instead of hypertrophy, the muscle fibers may reduce in size[21]. Conversely, type II muscle fibers often show a tendency to atrophy. Exercise training has the potential to alter both the composition and size of type I and II muscle fibers. Overall, the proportion of type I myofibers increases while the proportion of type II myofibers decreases. These findings are attributed to motor unit denervation-reinnervation[2][7][9][15][23].

### 3.3. Postulated pathophysiology and mechanisms

Type I myofiber grouping is a common aging phenomenon caused by denervation-reinnervation of muscle fibers, but the degree of such muscle fiber modification is reported to be more severe in PD[9][31]. The following hypotheses have been proposed as the cause of muscle fiber modification in PD patients. First, individuals with PD often selectively engage low-threshold, tonic motor units, likely due to rigidity or decreased motor capability, and tend to keep high-threshold motor units less active[21][31][32][33]. Furthermore, a decrease in activity in PD patients may result in atrophy, particularly in specific muscles due to muscle fiber disuse. As a result, muscle fibers that are not used may atrophy, while remaining muscle fibers may undergo compensatory hypertrophy[21][31][34][35].

Next, according to Mu et al., Type I myofiber grouping appears to be associated with abnormal alpha-synuclein aggregation[22]. Alpha-synuclein is a presynaptic neuronal protein that is genetically and neuropathologically linked to PD. In PD patients, alpha-synucleinopathy is mostly studied in conjunction with damage to the enteric and central nervous systems[36]. However, the findings suggest that alpha-synucleinopathy-related peripheral nerve damage may be linked to motor unit remodeling in PD[21][22], and more research is needed in this area.

Recently, peripheral neuropathy has been identified in PD patients, alongside the simultaneous occurrence of phosphorylated alpha-synuclein accumulations and mitochondrial dysfunction. Multiple research efforts suggest that such peripheral nerve impairment may be an inherent trait of PD, although the exact mechanism is still unclear. The possible mechanisms behind these phenomena have been suggested to include comorbidity of diabetes, mitochondrial dysfunction, oxidative stress, and mutations in the Parkin gene[37]. Furthermore, aggregates of alpha-synuclein in the cutaneous nerves are proposed as a potential biomarker for patients with idiopathic PD. In 2014, Donadio and colleagues found that patients with idiopathic PD exhibited phosphorylated alpha-synuclein in their proximal peripheral nerves. This was associated with small-fiber neuropathy and denervation of the leg epidermis. Given that these alterations were not observed in other patients with parkinsonism, the researchers proposed that the presence of phosphorylated alpha-synuclein could serve as a potential biomarker to differentiate idiopathic PD from other forms of parkinsonism[38]. More recently, Corrà et al. noted a correlation...
between peripheral neuropathy and gait and balance impairments in PD patients\[39\]. While the direct link between peripheral nerve damage and type I myofiber grouping in PD patients remains unclear, it's noteworthy that these have been recently emphasized as characteristics in PD patients. Therefore, more research is needed to develop personalized treatments based on these findings. Motor unit remodeling caused by denervation-reinnervation of muscle fibers is known to precede functional deterioration of the muscles in PD\[9\]. Denervated muscle fibers either die or are reinnervated by the branching axons of nearby motor neurons. Motor unit size and number decrease in the latter case, resulting in abnormal groupings of muscle fibers expressing the same myosin heavy chain isoform. As a result, abnormal recruitment of motor units occurs in such grouped muscle fibers\[37\]. Dual innervation by two separate motor neurons occurs in some aged muscle fibers, particularly in the elderly, which may explain why type I to type II conversion is possible\[9\]. Furthermore, regardless of exercise or drugs, these skeletal muscle changes tend to occur from an early stage of the disease\[33][40\]. Muscle atrophy can be observed as early as the initial stages of PD, and PD-related neuropathology can lead to further muscle atrophy and weakness, creating a vicious cycle\[41\].

Type I myofiber grouping is found not only in PD patients but also in the muscles of the elderly. Grouped type I myofibers exhibit some of the characteristics of type II myofibers, such as recruitment-dependent hypertrophy, low capillary supply, and sarcoplasmic reticulum calcium ATPase expression. This implies that type II muscle fibers converted to type I muscle fibers via denervation-reinnervation are not fully converted to type I muscle fibers. Furthermore, type II muscle fibers converted to type I muscle fibers are thought to have a higher potential for hypertrophy than original type I muscle fibers. As a result, these factors may be responsible for the hypertrophy of type I myofibers in muscles where type I myofiber grouping has occurred\[40\].

The following may explain why the proportion and grouping of type I myofibers increase selectively during muscle denervation-reinnervation. First, while denervation may occur at the same rate for all myofiber types, it is reasonable to assume that preferential reinnervation to type I myofibers occurs because motor units with lower thresholds are recruited first. Furthermore, motor symptoms of PD, which activate motor units with a low threshold and increase skeletal muscle tone, may also facilitate reinnervation into type I myofibers by favoring the maintenance of low-threshold motor units\[2][9][42][43\]. In a study of gene transcriptional profiling of skeletal muscle samples, the increase in group size and the ratio of type I muscle fibers in PD was found to be related to altered gene expression, and skeletal muscle itself could play an active role in signal transduction to promote muscle fiber survival, nerve redistribution, and remodeling\[26\].

3.4. Possible therapeutic approaches

Motor symptoms such as bradykinesia, postural instability, and rigidity in PD are typically understood in relation to dopaminergic cell damage in the substantia nigra. However, according to the above-mentioned research findings, type I myofiber grouping in various muscles of PD patients also appears to affect motor symptoms such as rigidity or muscle weakness in the patients. For example, Mu et al. discovered that type I fiber grouping in pharyngeal muscles of PD patients was associated with dysphagia. Dysphagia is a symptom of PD that doesn’t respond well to drug treatment\[21\]. Other researchers, including Pedersen et al.(1991) and Nishikawa et al.(2022), also found PD-related motor patterns that appear to be related to type I myofiber grouping that was unaffected by medication status\[14][28\]. These findings indicate that dopaminergic drugs cannot effectively treat PD symptoms stemming from muscle fiber modifications. It is therefore critical to develop a variety of alternative disease-modifying interventions\[21\].

According to Kelly et al.\[9][23\], high-intensity exercise, such as resistance training, can improve the size of muscles, mitochondrial function, and physical fitness in PD patients. The authors discovered that after high-intensity exercise training, type II myofibers in their study
switched from more fatigable IIX to less fatigable IIA. In addition, there was hypertrophy in both type I and II fibers, and mitochondrial complex activity in the muscle fibers increased[23]. Resistance training may also help to stabilize neuromuscular junction and motor unit activity. Resistance training was found to reverse a portion of grouped type I myofibers in PD patients with the most advanced type I myofiber grouping by reversing their myosin heavy chain expression[9].

These findings suggest that some grouped type I myofibers in PD patients can be converted to type II myofibers via strength training or high-intensity exercise. However, there is a lack of research on how much exercise is most effective in grouped muscle fibers in PD patients. Furthermore, many type II muscle fibers in PD patients have already been grouped and converted to type I myofibers. It is also important to consider the possibility that it will be difficult for all the converted muscle fibers to recover to their original state. As a result, a variety of exercises that can activate both the patients’ remaining types I and II myofibers must be developed to ensure that the remaining motor units are not further damaged and are well maintained. Energy metabolism issues or neuroinflammation, according to Lavin et al.[20], can also affect type I myofiber grouping. As a result, it can be inferred that restoring impaired circadian rhythm and energy metabolism, as well as improving PD patients’ metabolic state may be beneficial in treatment.

Meanwhile, therapies such as bee venom acupuncture, known for its neuroprotective effects, could also be explored as options for PD patients to mitigate peripheral nerve damage. Studies by Cho and colleagues in 2012 and 2018 showed significant enhancements in the UPDRS score for PD patients who underwent bee venom acupuncture treatment[44][45]. While continuous exposure to bee venom may not halt neurodegeneration sufficiently to prevent the manifestation of PD[46], it might exhibit local neuroprotective effects on the peripheral nerves of these patients. Several animal-based studies have demonstrated that bee venom possesses a neuroprotective effect against peripheral neuropathy. Research by Baher & Abo-Zeid showed that administering bee venom during early stages served a neuroprotective role against the advancement of diabetic neuropathy and could also reduce blood glucose levels in a rat model of diabetes[47]. Er-Rouassi et al.(2023) showed that injections of bee venom could promote the recovery of section-sutured facial nerves. Furthermore, these injections also enhanced functional restoration and reinnervation, as seen in the improvements in whisker movement and normalization of nasal deviation[48]. These findings indicate that bee venom exhibits a local neuroprotective effect. When applied locally, it could potentially impede further type I myofiber grouping in individuals with PD. However, further research is needed to fully explore this potential.

4. Conclusion

Over the last five decades, research on PD patients has revealed a variety of motor abnormalities and muscle changes. Edström first reported selective changes in the sizes of red and white muscles in PD patients in the 1970s. Since then, researchers have been investigating atrophy in fast-twitch muscle fibers, inconsistencies in shifting motor unit types, synchronized bursts of electromyography, decreased resistive torque, weakened leg muscles, and changes in trunk rigidity. It appears that different muscles in the trunk, as well as the upper and lower extremities, are all affected in PD, with the general tendency being hypertrophy of slow-twitch type I myofibers and atrophy of fast-twitch type II myofibers.

Type I myofiber grouping, a common aging phenomenon, is markedly worse in PD, possibly due to selective activation of low-threshold, tonic motor units. This remodeling, which is caused by denervation-reinnervation, occurs before functional muscle deterioration in PD and results in abnormal recruitment of motor units in grouped fibers. This grouping is also associated with
abnormal alpha-synuclein aggregation, a neuronal protein linked to PD, suggesting that alpha-synucleinopathy-related peripheral nerve damage could be linked to motor unit remodeling.

While motor symptoms of PD are typically attributed to dopaminergic cell damage in the substantia nigra, research suggests that type I myofiber grouping in various muscles could also influence symptoms such as rigidity or muscle weakness. Symptoms such as dysphagia, which do not respond well to drug treatment, have been associated with type I fiber grouping. Consequently, dopaminergic drugs may not effectively treat PD symptoms arising from muscle fiber changes, highlighting the need for alternative interventions. High-intensity exercise like resistance training, has been found to induce beneficial changes in muscle fibers, potentially converting some grouped type I myofibers back to type II in PD patients. However, challenges remain, including determining the most effective exercise volume and addressing metabolic issues and neuroinflammation which can also affect type I myofiber grouping.

Meanwhile, according to some studies, the aggregation of alpha-synuclein and peripheral nerve damage have been linked to type I myofiber grouping in PD patients. Moreover, peripheral nerve damage has been recently associated with idiopathic PD. The relationship between the degree of peripheral nerve damage and type I myofiber grouping has not been thoroughly explored yet. Therefore, additional research is needed to understand this potential correlation. Bee venom acupuncture, known for its neuroprotective properties, might also be a potential treatment for peripheral nerve damage in idiopathic PD patients. This could potentially prevent type I myofiber grouping resulting from peripheral nerve damage in these patients, particularly if applied in the early stages.

The studies included in this paper have the following limitations. First, a lot of difficult work was required in studies that performed muscle biopsies on PD patients, typed the myofiber phenotype, and thoroughly evaluated the patient’s muscle-specific motor function. As a result, the number of subjects per study was typically limited to around ten people. As a result, the consistency of the results may have weakened from study to study. Furthermore, the pathophysiology of PD is heterogeneous and complex. There is a lack of understanding regarding how myofiber grouping manifests in different subtypes of PD. As a result, more research in this field will be required in the future to develop disease-modifying treatments for PD patients.

5. References

5.1. Journal articles

Aging and Parkinson’s Disease on Motor Unit Remodeling: Influence of Resistance Exercise


### 6. Appendix

#### 6.1. Author’s contribution

<table>
<thead>
<tr>
<th>Initial name</th>
<th>Contribution</th>
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<tbody>
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<td>Lead Author</td>
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#### 6.2. Funding agency

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