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Creatine supplementation and exercise as possible therapeutic treatments in Parkinson's Disease: A review

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Parkinson's disease (PD) is the second most common progressive neurodegenerative condition after Alzheimer's Disease. It is characterized by a progressive loss of dopaminergic neurons in the substantia nigra region of the brain. Symptoms and signs manifest as motor disorders affecting balance and physical capacity, and non-motor symptoms such as cognitive decline and mood disorders. People with PD face considerable difficulties coping with associated physical and psychological changes that affect their quality of life. The main form of treatment is pharmacological, which alleviates some of the symptoms but does not slow the progression of the disease. Creatine monohydrate (Cr) may have therapeutic benefits in conditions where energy dysfunction and high rates of apoptosis are present. Cr supplementation may provide a protective effect by augmenting cytosolic high energy phosphate stores, thereby prolonging the survival of 'at risk' cells of neurodegenerative diseases. Emerging evidence suggests supplementation may offer specific benefits in the treatment of mood disorders associated with PD. Many different types of exercise improve physical capacity, balance, and quality of life. Research has recently demonstrated the potential benefits in PD of diverse modes of exercise, such as aquatic exercise and boxing. Combining exercise with Cr supplementation can enhance exercise induced muscular strength and power adaptations and may further improve exercise capacity and neuromuscular function. This review will critique evidence relating to the potential efficacy of Cr supplementation and exercise as a putative therapeutic approach in the treatment of the physiological and psychological challenges presented by PD.

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Key Words: Parkinson's disease; mood disorders; creatine; supplementation; oxidative stress; exercise training

1. INTRODUCTION

Parkinson's disease (PD) is the second most common degenerative neurological disorder after Alzheimer's disease (43). This complex, multi-layered disease has large individual variations in severity and symptoms. The primary pathology involves central dopaminergic neuronal loss, causing distal neurological dysfunction in skeletal muscle (99).

Cardinal motor signs and symptoms manifest as bradykinesia, tremors, rigidity, postural instability, and dyskinesia (79). Co-morbidities, including cognitive decline and depression (86), may be present in ~40-50% of patients; these numbers increase with greater disease severity (107, 125) and advanced age at disease onset (104).

The causes of PD are not fully understood; however, environmental toxins and genetic susceptibility are implicated (28, 42). Interference with complex I activity of the mitochondrial electron transport chain increases oxidative stress and augments the death of the dopaminergic neurons in the substantia nigra pars compacta (1, 14, 43, 76, 145). In addition, there is characteristic accumulation of abnormal proteins known as Lewy Bodies in the surviving neurons (24, 51, 64). In familial and idiopathic PD conditions, increased accumulation of the protein α-synuclein in dopaminergic neurons in the substantia nigra may

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augment apoptosis via an increase in reactive oxygen species (ROS) initiated by endogenous dopamine metabolism (143).

Surface electromyography (EMG) studies demonstrate that people with PD have slower extension movements compared to flexion, whereas individuals without PD show no significant difference between extension and flexion movements (116). Typically, increased and inappropriate co-contraction of agonist and antagonist muscle groups contribute to joint stiffness and rigidity, which results in energy inefficient and impaired movements (92).

Currently, there is no cure for PD: drug therapy is the main line of treatment, which alleviates some of the symptoms but has no effect on the deterioration of the condition over time. Indeed, therapies that slow the progression of this disease have not yet been found. Greater drug doses are required as the disease progresses, but after 5 years of treatment, dyskinesia and 'freezing' episodes worsen in ~40% of patients (64). The development of adjuvant interventions that could ameliorate the symptoms of PD would represent a major breakthrough.

2. CREATINE

Creatine (Cr), or methyl guanidine acetic acid, is a nitrogenous compound synthesized from the amino acids arginine, glycine, and methionine (16). The role of Cr is pivotal in the transfer of high energy phosphate bonds; it is phosphorylated by the enzyme creatine kinase (CK) to form phosphocreatine (PCr), which can rapidly re-phosphorylate adenosine diphosphate (ADP) to adenosine triphosphate (ATP) (139). This reversible reaction facilitates short duration high intensity muscular activity (25); in addition, Cr shuttles energy from the mitochondria to the cytosol in tissues such as brain and skeletal muscle, which have high and fluctuating energy demands (139). When the demand for energy is very high, rapid hydrolysis of PCr increases the Cr concentration of the cytoplasm. Cr diffuses to the mitochondria through the concentration gradient present in the cytoplasm, where the subsequent interaction of Cr with mitochondrial CK is instrumental in up-regulating mitochondrial oxidative phosphorylation (96). Consequently, the importance of Cr in the regulation of cellular energy metabolism is evident.

An average 70kg adult has a total Cr pool of ~ 120g, comprised of ~40% free creatine and ~60% PCr (46). Cr at a rate of 1-2%, and PCr at a rate of 6%, are continuously degraded to creatinine by non-enzymatic reactions and excreted in urine (103). Daily replenishment of the total Cr pool is achieved endogenously via the liver and pancreas (~1g) and ingested from food sources, predominantly fish and meat (~1g) (15).

3. CREATINE SUPPLEMENTATION

Supplementation with creatine monohydrate has been used extensively for two decades. A number of studies demonstrate improvements in high intensity short duration exercise, strength, power, and work performed (30, 70, 82, 90, 136). The ergogenic effects of supplementation are thought to be from increasing formation of muscle Cr and PCr levels (74, 80), leading to improved ATP turnover during intermittent high intensity muscle contraction and accelerated ATP resynthesis during periods of recovery (68). Approximately 20-30% of individuals do not experience any effects from Cr supplementation and are referred to as non-responders (69). Non-responders are proposed to be individuals whose muscular Cr stores are optimal and no further increase is physiologically possible (67, 74). However, some studies report no improvement in performance tests despite an increase in intramuscular Cr levels (60, 100, 124). Wide ranges in study populations, methodologies, and statistical interpretations might contribute to the considerable variation found in response to Cr supplementation (53, 87).

3.1. Creatine Supplementation as a Therapeutic Agent

Supplementation may be of greatest benefit to clinical populations in which direct and indirect energy deficits contribute markedly to the pathology of the disease; specifically, conditions featuring neuronal loss, muscle atrophy, and/or fatigue. For example, supplementation has resulted in significantly improved exercise capacity and functional performance in heart failure. Supplementation is rationalised in this disease due to impaired muscle cell metabolism, low oxidative capacity, and a reduction in total creatine content of skeletal muscle; as a result, patients experience exertional fatigue (7). A randomised crossover design with 13 participants taking 20g of Cr per day for 6wks showed no change in aerobic capacity, anaerobic threshold, or the 6 minute walk test. However, a 15% increase in elbow flexor muscle strength did occur (91). Furthermore, Gordon et al. (65) reported a 10-20% increase in leg muscle strength and endurance in heart failure patients after taking a dose of Cr of 20g per day for 1wk. Twenty grams for 5 days significantly increased contractions in the forearm (75% maximal voluntary contraction), with improvements in muscle metabolism demonstrated by a significant reduction in the formation of ammonia (6). Presently, it is unknown if Cr supplementation can

directly influence cardiac performance, but it is suggested that potential for this may be limited (59).

In a cardiac rehabilitation group, no additional benefits were gained from Cr supplementation in conjunction with exercise. This may in part have been due to the large initial benefits of exercise, which included resistance training, overwhelming the potentially modest additional benefits of Cr (37). Similarly, no improvement in exercise capacity has been found in Cr supplemented chronic obstructive pulmonary disease (COPD) rehabilitation (2, 44, 61), despite improvements in peripheral strength and muscular endurance (61); however, no large scale clinical trials have been conducted.

In idiopathic myopathies, low levels of PCr and intracellular calcium leakage can exacerbate excitotoxicity (73). Chung et al. (34) reported a placebo controlled 6 month supplementation (20gm/day for 8 days followed by 3gm/day for the remaining period) in conjunction with a home-based exercise regimen; this improved both the ability to sustain repeated bouts of high intensity exercise (e.g., stair climbing and descent, sit to stand, and walking challenges) and measures of endurance capacity (functional index in myositis). Metabolic myopathies have not shown any beneficial effects from supplementation (87), possibly due to defects in creatine uptake in the muscle (71). Muscle myopathies have many subgroups and phenotypes with high variation in pathology; this presents complex scenarios, particularly as the majority of studies are parallel in design with small participant numbers. Similarly, the effectiveness of Cr in Amyotrophic lateral sclerosis (ALS) remains under scrutiny. ALS is a progressive neuromuscular disease causing weakness, dysfunctional muscle control, and paralysis. High levels of glutamate in this condition are neurotoxic and cause excitotoxicity, which leads to increased levels of reactive oxygen species. Resulting free radical damage augments oxidative damage and contributes to mitochondrial dysfunction; subsequently, motor neurons die, leading to progressive muscle weakness (26). Other neurodegenerative conditions, such as HD and PD, also feature these characteristics (32). A review by Ellis et al. (89) examined the findings of animal and clinical research into Cr supplementation in ALS. The authors found that, despite problems with recruitment, study design, and inconclusive results regarding effectiveness, Cr does show potential to protect vulnerable neurons and improve physical ability.

In Chung's (34) study, exercises were home-based and resulted in improvements in functional activities; whereas in Cornelissen's (37) cardiac rehabilitation study, physical measurement outcomes consisted of a graded cycle test and isometric and isokinetic knee extension strength and endurance. A study comparing exercise and supplementation with exercise alone in PD patients found that although knee extension strength improved similarly in both groups, only the Cr group improved in the functional sit to stand test (75). This highlights the impact study design variations can have on findings and suggests functional measures of physical performance should be included in testing parameters in non-athletic and clinical populations.

The benefits of supplementation may extend beyond enhancements in skeletal muscle performance. Brain function, such as memory accumulation and recall, is energy dependant (106). As such, Cr supplementation may be beneficial in conditions of increased metabolic demand; for example, in the aging brain (101). Improvements in simple cognitive performance tests in the elderly occurred after 20g of Cr per day for 2 weeks (101). The authors hypothesised that reductions in excitotoxicity and increased neuroprotection may have facilitated these improvements. Furthermore, depressive states have responded favourably to supplementation [see section 4.1] (4, 71, 118).

The effects of Cr in Huntington's disease (HD) are equivocal at present. Animal models of Cr supplementation show improvements in brain atrophy, reductions in intranuclear inclusions (5, 45, 58), and biomarkers of HD pathology (144). Despite these encouraging findings, clinical trials have found no changes in disease status (137); however, administration of 8-10 weeks of Cr supplementation did result in a reduction in glutamate and glutamine in the brain of HD patients. This suggests Cr may reduce levels of excitotoxicity, which are abnormally high in HD, warranting further investigation (17). The CREST-E clinical trial currently underway in the U.S. is evaluating the safety, tolerability, and effectiveness of large doses (up to 40g/day) in slowing the progression of functional decline in HD.

Despite variable results, and at times speculative theories surrounding the potential therapeutic benefits of Cr supplementation in clinical populations, a number of conditions, particularly those featuring high levels of oxidative stress, vulnerable neurons, and energy depletion, may benefit from Cr supplementation.

3.2. Creatine Supplementation and Neurodegenerative Disease

The brain accounts for 2% of total body mass, whilst using 20% of its total resting energy output (72). Cr is required to meet high energy demands; mental retardation and neurological dysfunction may develop in conditions of significant Cr deficiency (6). Many neurodegenerative conditions share similar

biochemical pathological characteristics, including energy dysfunction and depletion, increased oxidative stress, excitotoxicity, and mitochondrial dysfunction. Mitochondrial dysfunction appears to play a central role in some of the most common neurodegenerative diseases (43), leading to abnormally high rates of apoptosis (1) and accelerating loss of specific neurons (13).

Exogenous supplementation may increase endogenous Cr levels and provide greater energy supply to cells by augmenting cytosolic high-energy phosphate stores, thereby exerting a protective effect and prolonging the survival of 'at risk' cells (27). Cerebral creatine deficiency disorders (CCDs), such as X-linked creatine transporter deficiency (SLC6A8 deficiency), which causes mental retardation, speech and language delay, and epilepsy, highlight both the importance of adequate Cr levels in the brain and the central role of the creatine transporter in maintaining Cr levels in the CNS (126). Clearly, this transport system will be saturable and so the scope for exogenous supplementation may be limited in situations where no Cr deficiency is present but such supplementation would at least ensure saturation of the transport system. Studies have shown that an increase in brain Cr level is possible following supplementation (3).

Whether or not creatine has a direct effect on the pathology of PD is unknown. More likely, it exerts its influence via enhanced bioenergetics, helping make cells more resilient to damaging environments. Cr supplementation may, therefore, extend the survival of cells; however, progression of the neurodegenerative disease will likely still occur (27, 142). As yet unknown is whether or not long term Cr supplementation down-regulates endogenous Cr synthesis.

3.3. Creatine as an Adjuvant Therapy in Parkinson's Disease

In vitro and animal studies demonstrate the neuroprotective capacity of Cr supplementation against neurotoxicity (88, 98) and the attenuation of motor symptoms in models of PD (133). Animal studies have generated potentially promising data; however, species-related differences make extrapolation of results from animal models to meaningful clinical improvements in humans complex. Bender and colleagues (18) conducted a 2 year, double-blind, placebo-controlled pilot study with 60 PD subjects (Hoehn and Yahr Scale $\leq$ 2.5). Subjects were supplemented with 20g of Cr per day or placebo for 6 days, followed by 2g per day for 6 months and 4g per day for the remainder of the 2 year period. Single-photon emission computed tomography (SPECT) was used to measure the extent and degree of dopaminergic nerve cell loss from baseline to the end of the study period. Supplementation was well tolerated by the subjects in the Cr group; however, it had no significant effect on SPECT variables or total Unified Parkinson's Disease Rating Scale (UPDRS) scores when compared to the placebo group. Importantly, a significant effect ($P = 0.046$) occurred in the UPDRS subscale 'depression' in the Cr group, suggesting a positive improvement in mood state as a result of supplementation. The Cr group also had a significantly ($P < 0.05$) smaller dose increase in dopaminergic therapy at the end of the trial (18), which implies a possible benefit to disease status that may not have been detected by the techniques used in this study.

A randomized, double blind, futility clinical trial in early PD assessed the ability of Cr to alter the progression of PD relative to a pre-determined threshold. Subjects ingested 2 x 5 g Cr or placebo per day and a baseline UPDRS score was recorded and re-evaluated at 1, 3, 6, 9, and 12 months. The mean change in disease status for the Cr group from baseline to either 12 months or the commencement of symptomatic treatment was 5.6 (SD 8.69); this was lower than the pre-determined threshold value of 7.46 (30% less than the expected change). As a result, Cr supplementation could not be rejected as futile. Supplementation was well tolerated by the subjects with 91% compliance, and none reported serious side effects (132).

Subsequently, a Phase III clinical trial by The National Institute of Neurological Disorders and Stroke Exploratory Trials in Parkinson's Disease (NINDS NET-PD) commenced in 2007 (21). The aim of this study was to evaluate the efficacy of Cr supplementation (10g/day) in a cohort (n = 1741) of individuals in the early stages of PD, who had been receiving dopaminergic treatment $\leq$ 2years. The primary outcome measurement was to determine if 5 years of Cr supplementation slows the progression of PD to a greater degree than standard drug therapy alone. In addition, the safety and tolerability of long-term supplementation would be assessed.

A Global Statistical Test (GST) model was applied in September 2013 by the researchers to determine the efficacy of the Cr treatment in reducing overall changes in disease state. This was necessary to justify continuation of the clinical trial. The analysis found no significant difference between the treatment and placebo groups. A finding of futility was declared and the trial was terminated (105). In other words, 5 years of supplementation statistical testing suggested that no significant difference in disease progression existed between the treatment and placebo groups. The five measure GST model selected encompasses overall disease status changes. This increases the power of detection when any treatment effect occurs across all measurement domains; however, power is lost if a

single measure demonstrates change. Under such conditions differences may not be detected, and individual aspects of the efficacy of supplementation could be present but not be detected (81).

Although this finding is disappointing, this study crucially provides important information regarding the tolerability and safety of long term Cr supplementation in PD. Evidence from animals studies suggests that there are relatively low concentrations of creatine transporters in the substantia nigra area of the brain, which could limit the potential for Cr to slow the progression of the disease (97). Future publication of the full findings of this clinical trial should inform other studies examining Cr supplementation in neurological disorders.

3.4. Antioxidant Effects of Creatine

Free radicals and reactive oxygen species can impair protein turnover (113) and augment muscle fatigue (93). In vivo experiments suggest Cr may have antioxidant properties (93), thereby providing some level of protection from the deleterious effects of increased levels of oxidative stress and fatigue associated with PD (62). Cr may augment antioxidant and neuroprotective effects by enhancing cytosolic high energy phosphates that maintain ATP levels under high oxidative stress conditions (130) (see Figure 1).

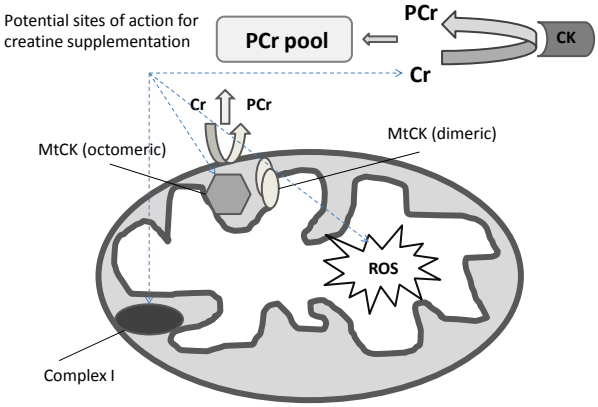

Figure 1: Mitochondrial dysfunction in Parkinson's Disease. Adapted from Adhihetty and Beal. Creatine and its potential therapeutic value for targeting cellular energy impairment in neurodegenerative diseases. Neuromolecular Medicine 2008; 10 p23 Fig.3. Springer/Kluwer Academic Publishers with kind permission of Springer Science and Business Media (12).

Kingsley et al. (84) reported that supplementation in conjunction with 5 days of endurance exercise in healthy males had no effect on oxidative stress levels. However, Bloomer et al. (22) reported 8 weeks of resistance training reduced oxidative stress in subjects with PD. Endurance exercise cannot be directly compared to resistance training; however, this study provides evidence that the oxidative status of people with PD can be altered and suggests a longer time frame may be necessary to observe adaptations. The effect of supplementation on oxidative status in human PD trials has not been evaluated.

3.5. Creatine and Musculoskeletal Abnormalities in Parkinson's Disease

Motor dysfunction is primarily related to central dopamine depletion; however, histological studies suggest pathology may not be restricted to the brain (141). Individuals with PD can also have musculoskeletal mitochondrial abnormalities, inflammatory myopathies, and necrotizing myopathies with no obvious link established between these pathologies and adverse drug side effects (63, 141). Therefore, increased free radical damage in PD may have a direct effect on skeletal muscle mitochondria (141).

A reduced capacity for muscle torque and force production associated with a prolonged muscle relaxation time (36) and lower levels of EMG activity during isometric voluntary contractions (119) are common in PD. Longer EMG relaxation times have been linked to more pronounced bradykinesia (66). Whether extended muscle relaxation time is directly related to the pathology of the disease or due to drug related side effects is unknown.

Five days of Cr supplementation improved neuromuscular function in moderately trained healthy men (12). Peak torque (PT) increased 33.4% ($P < 0.05$) more in the Cr group than in the placebo group, whilst time to reach PT in the Cr group decreased 54.7% ($P < 0.05$) more than the placebo group. Measured maximal torque was significantly increased at the highest angular velocities (180o·s-1 and 240o·s-1). Conduction velocity increased 15% ($P < 0.05$) in the Cr group at all velocities, remaining unchanged in the placebo group, and with no changes reported in measures of fatigue in either group (12).

Supplementation has been shown to decrease muscle relaxation periods in healthy individuals during isometric contractions (134). A decrease in muscle relaxation time may reduce energy expenditure, reduce co-contraction activity, and increase cross-bridge cycling efficiency, potentially improving muscle power during rapid repetitive maximal muscle contractions with no pause between contractions (134). The proposed mechanism for decreased muscle relaxation time is via an improvement in calcium (Ca2+) kinetics, enhancing muscle contractile properties (12, 134) (see Figure 2). There may be

potential for Cr to improve neurological function in individuals with PD; however, to date no studies evaluating the effect of Cr on neurological function in PD have been published.

Interestingly, although considered a pathological manifestation in PD, prolonged muscle relaxation time is regarded as a mechanism that delays fatigue during isometric contractions in healthy muscle (96). In PD, this may be an adaptive condition that paradoxically results in energy inefficient states during dynamic movements, whilst fatigue in postural muscles is reduced.

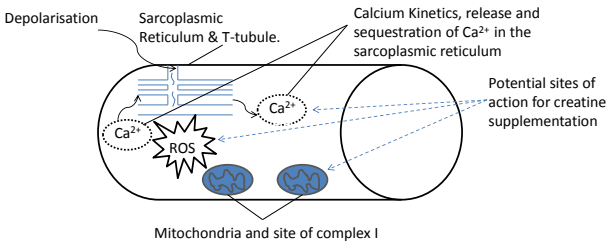

Figure 2: Muscle Cell and Potential Sites of Action for Creatine Supplementation. Adapted from Powers et al. Reactive oxygen and nitrogen species as intracellular signals in skeletal muscle, The Journal of Physiology 2011; 589, with kind permission of John Wiley and Sons (113).

4. MOOD DISORDERS IN PARKINSON'S DISEASE

Mood disorders affect most people with PD at some stage in the progression of the disease, the most prevalent being depression, anxiety, and apathy (127). Depression is considered to be the most common mood disorder symptom in PD (39), with an incidence of ~35%; however, this figure may be as high as 90% in some sub-groups (49). Silverman and Henry (122) propose similarities between common symptoms in PD and those of depression; e.g., slowness in movement, blank expression, stooped posture, and slowness in cognitive function could lead to overdiagnosis of depression. In contrast, other authors suggest these similarities may lead to confusion and a prevalence of underdiagnosis (121). Subtle symptomatic differences in PD patients and non-Parkinson's populations diagnosed with clinical depression mean that the use of valid assessment tools are essential when investigating depression in PD. Additionally, depression in PD is often accompanied by anxiety disorder (140). The prevalence of anxiety in PD is estimated between 40-60% (115); cognitive dysfunction and anxiety are not related in PD. Approximately 17-70% of individuals with PD have symptoms of apathy (111). Those with this condition experience low motivation, lethargy, difficulty completing tasks, and a high incidence of fatigue (127). The incidence of apathy can be related to depression, but can also occur independently (85).

Disease status is related to the presence of clinical depression in PD (110). Impairment of activities of daily living (ADL) is more strongly associated with depression than specific motor symptoms (129), meaning the overall impact the disease has on an individual's quality of life and well-being presents the greatest difficulty. This is closely related to the person's own perception of having poor health and low quality of life; in fact 'illness belief" can predict psychological outcomes in PD (123).

The causes of mood disorders in PD are not completely understood; they are thought to result from a complex interaction between psychological and neurobiological processes (127). An organic origin is evidenced by early presentation of symptoms in a significant number of individuals long before manifestation of motor symptoms and diagnosis of PD (77). Genetic variations in a serotonin transporter gene implicate inherited aspects of PD mood disorders in some individuals (102). Defects in the neurocircuitry (110) of the frontal subcortical region of the brain in neurodegenerative diseases are linked to neuropsychiatric symptoms that may be directly or indirectly implicated in mood disorders (23). These neurological abnormalities in PD are hypothesized as being linked to dysfunctional neurotransmitters of the dopaminergic, serotonergic, and noradrenergic systems (127).

4.1. Creatine Supplementation and Mood Disorders in Parkinson's Disease

Recent intriguing evidence examining the potential effects of Cr supplementation in a number of psychiatric conditions may signal benefits for PD that have not yet been fully realized. A topical review of Cr metabolism in psychiatric disorders suggests the effect of psychological stress in some of the most common mental health conditions, resulting in augmented energy demands within the brain. This may lead to depletion of total Cr and PCr in the brain and subsequent mitochondrial dysfunction, triggering a cascade of neurological events that could cause, or exacerbate, thought or mood disturbances.

Emerging evidence suggests neurons may be vulnerable to damage in conditions of energy imbalance and result in increased oxidative stress. Indeed, production of neurotransmitters such as dopamine and serotonin may be compromised when there is an energy deficit (3). The implications in PD are evident.

Allen (3) examined the potential benefits of Cr supplementation in psychiatric conditions such as depression and some anxiety disorders. Two weeks of Cr supplementation increased brain concentrations of

Cr and PCr (20, 95) and may have had the potential to improve brain energetics. Enhanced brain metabolism could protect vulnerable neurons associated with mood and emotion, which may be at risk in psychologically stressful conditions present in PD. In addition, Cr supplementation may help optimize neurotransmitter production, which would be beneficial in depleted states. These theories may explain the findings of Bender and co-workers (18), who reported an improvement in depression scores following Cr supplementation without an overall improvement in disease status. Recently, individuals with PD suffering from depression benefited from supplementation with omega -3 fish oils (39). This is encouraging as it provides evidence that people with PD respond positively to nutritional supplementation targeted to improve mood disorders.

5. EXERCISE AND PARKINSON'S DISEASE

Physical activity levels are likely to be reduced in individuals with PD compared to individuals without PD due to lower exercise capacity related to metabolic inefficiency and earlier onset of fatigue (9). Inactivity contributes to increasing disease severity, poor walking performance, and more difficulty performing the activities of daily life (135). Individuals with PD who experience the highest levels of fatigue tend to be the most sedentary and possess lower levels of functional capacity and physical function (62). Sedentary lifestyles are also linked to increased ROS production (38), immunosuppression, pathological inflammatory conditions, and accelerated brain aging (10). A complete understanding of the potential benefits of exercise in brain health is emerging (8). Erickson et al. (56) reported that moderate intensity aerobic exercise 3 days per week for 1 year increased hippocampal volume by 2% in adults without dementia compared to a control group who only performed stretching exercises. Increased hippocampal volume is associated with higher serum levels of brain derived neurotrophic factor (BDNF), which mediates neurogenesis in the brain and usually declines with age (56). Evidence suggests that exercise may elevate dopamine receptor expression in PD (138) and may reduce overall levels of skeletal muscle ROS, despite increased ROS production in muscle fibres as a result of contraction (38).

Dynamic, functional, high intensity movements with many repetitions and increasingly complex movements have successfully increased the UPDRS score of 20 patients with mild to moderate PD by a clinically significant mean of 5.05 (52). Exercise training improves strength, balance, and functional capacity and can enhance QOL in individuals with PD (47, 48, 52, 57, 120). Better QOL in PD is associated with increased fitness levels, improved social interactions, and greater independence (11).

A variety of exercise modalities are well tolerated by people with PD. These include high intensity resistance (47, 48) and aerobic training (19, 78). Recently, more diverse types of exercise have shown efficacy in PD. Tai Chi (94), aquatic exercise (11), and boxing training (35) have improved balance, functional capacity, and ADL. Music therapy has also had positive effects in measures of motor and non-motor symptoms (50, 109). Low expectations of any worthwhile benefits from exercise contribute to poor engagement in exercise participation (54) and levels of self-efficacy predict whether or not ambulatory individuals with PD engage in exercise (55). The fear of falling is one of the main barriers to exercise reported by people with PD (54); appropriate aquatic exercise may increase exercise choice and reduce the fear of falling. Longitudinal information regarding adherence to exercise in PD from early in the disease to later stages is not available, but the information available suggests it is crucial to design exercise interventions that offer a variety and choice to meet the various physical and psychological needs of those with PD.

5.1. Exercise and Creatine Supplementation in Parkinson's Disease

Cr supplementation can allow more work to be performed during high intensity repetitive exercise (30, 31, 70), increase exercise induced muscular strength and power adaptations (33, 40), and augment lean body mass (136). Combining strength training and creatine supplementation up-regulates myogenic activity in skeletal muscle and may optimize muscle fibre growth more than strength training alone (108). Additionally, exercise can augment Cr accumulation in exercised skeletal muscle (74), possibly by enhancing the Na+-Cr transporter system (117). To date there have been no studies published evaluating the effect of exercise on brain concentrations of Cr.

Currently one study has measured the effect of Cr supplementation and exercise in PD. Hass et al. (75) combined supplementation with resistance training in a randomized, double-blind study of twenty subjects (n = 17 males, n = 3 females) classified as the Hoehn and Yahr scale $\leq$ 3. Subjects performed one set of 8-12 reps at 70% of 1RM for the upper and lower body to volitional fatigue for 12 weeks; in addition, subjects performed one set of leg extension and flexion at 50% of 1RM, which allows faster movements to be performed. Load was progressively increased by 5-10% when subjects were able to perform 12 reps during strength training, and 20 reps for low resistance power training. Post exercise chest press, leg

extension, and bicep curls increased 9%, 16%, and 18%, respectively, in the placebo group, and 21%, 18%, and 23%, respectively, in the Cr group. Both groups significantly improved leg extension endurance ($P \leq 0.05$) and increased fat-free mass ($P = 0.002$); no significant differences were found between groups (75).

Combining resistance training and supplementation improved muscular strength and endurance compared to resistance training alone. Despite an increase in leg extension strength, in both groups only the Cr group significantly improved the chair stand test. Supplementation may have had a greater effect in the chair stand test as this test involves repeated high intensity movements. In the Cr supplemented group, neurological function as well as strength may have been improved.

Cr supplementation - in conjunction with different types and intensities of exercise - may augment the benefits of exercise alone (see Figure 3). Performing high intensity exercise such as boxing, aquatic resistance training, deep-water running, or aquatic cycling with supplementation may improve training effects, which would be transferred to improvements in QOL and ADL in PD. Ultimately, real improvement in a person's quality of life is the most important aspect, both to PD patients and to their caretakers.

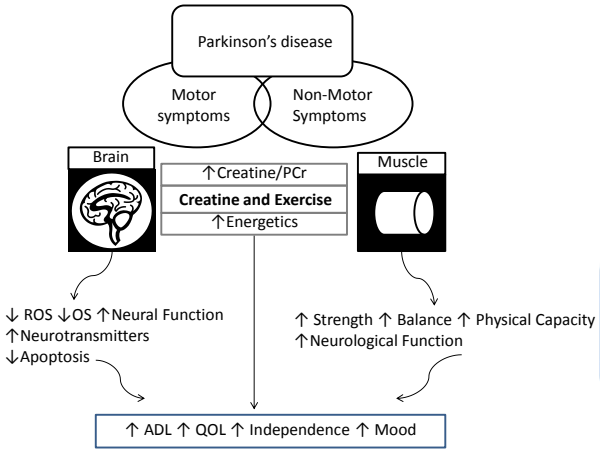

Figure 3: Potential Synergistic Relationship between Exercise and Creatine Supplementation in Parkinson's Disease. Reactive Oxygen Species (ROS). Oxidative Stress (OS). Activities of Daily Living (ADL). Quality of Life (QOL).

6. SAFETY OF ORAL CREATINE SUPPLEMETATION

No serious adverse effects have been documented as a result of short term supplementation (29, 37, 41, 75, 87), or long term studies of up to 2 years duration (17, 71, 90, 132), in healthy and clinical populations.

The most consistently reported side effect of supplementation is weight gain of 1-2 kg, which is attributed to an increase in intracellular water in muscle tissue (80). In an extensive review of safety issues and concerns by Wyss et al. (142), evidence of muscle cramps, increased thirst, stomach cramps, diarrhoea, and rashes have been isolated cases and subjective reports. Reports of renal dysfunction linked to supplementation have been confined to case studies (114, 128, 131). In Pritchard et al. (114) subjects had a previous history of renal dysfunction, whilst the subject in Thorsteinsdottir et al. (131) had consumed multiple supplements in addition to creatine. The affected person in Taner et al. (128) had no prior renal problems, nor had they reported consuming any other supplements; on cessation of supplementation renal function returned to normal. Individual case studies should not be dismissed, but they lack controls that would provide more conclusive evidence. A recent comprehensive review concludes Cr supplementation does not impair glomerular filtration rate or glomerular membrane permeability in healthy or neurodegenerative subjects (83). Nevertheless, individuals who may have existing renal disease, or an increased risk of kidney dysfunction, should be regularly monitored (83, 112).

7. CONCLUSION

Parkinson's disease presents a challenging scenario for those directly affected. Additionally, it presents complex demands for the scientific community, supporting professionals in their quest to elucidate the aetiology of the disease and devise the best prevention and treatment strategies. The individual variability of the condition and multi-layered symptomatology determines that a holistic approach is required.

Cr is central to the transfer of energy bonds in tissues with highenergy requirements. Many neurodegenerative diseases, including Parkinson's disease, demonstrate electron pathway pathologies that are possible targets for the pleiotropic effects of Cr. In vitro and animal models of PD demonstrate that Cr has neuroprotective effects, and clinical trials suggest a promising impact on mood and disease state. Exogenous Cr may augment cytosolic high energy phosphate stores, thereby rendering vulnerable cells more resistant to environmental stress and prolonging their life. The highly specialized energy buffering capacity of Cr may protect brain cells from the deleterious effects of stressful mood disorders, which have been found to deplete endogenous brain Cr concentrations. Energy deficiency in specialized brain cells may lead to increased oxidative stress conditions and reductions in neurotransmitter production. Supplementation with omega-3 fatty acids has been found to improve depression in PD patients,

demonstrating potential efficacy for nutritional supplementation strategies in this condition. It is hypothesized here that Cr supplementation may offer benefits in the treatment of mood disorders in PD.

Additionally, the ergogenic effects of supplementation may improve functional capacity, reduce muscle atrophy, and be of specific benefit to PD sufferers. Individuals with PD have demonstrated energy inefficient and impaired movements associated with longer relaxation times. Musculoskeletal mitochondrial abnormalities, inflammatory, and necrotizing myopathies may also present. Supplementation may improve muscle efficiency and neuromuscular function by up-regulating Ca2+ kinetics and enhancing muscle contractile properties.

A variety of exercise modalities improves functional capacity and quality of life in individuals with PD. Greater exercise options should help address particular problems associated with engagement in exercise. Combining supplementation with exercise may have synergistic effects by accelerating Cr uptake and augmenting the beneficial effects of exercise alone. No serious safety issues have been associated with creatine supplementation; however, a greater understanding of the optimal application of supplementation is necessary to realize the full potential of this nutritional supplement.

Further, well controlled studies are required to investigate the potential effects of Cr supplementation in mood disorders and assess the combined effects of supplementation and exercise on functional capacity and QOL in people with PD.

This review concludes that creatine supplementation, particularly in conjunction with exercise, presents the potential for a safe, inexpensive, and effective adjuvant treatment that may improve quality of life in PD.

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