

Review Article

Metabolic Syndrome: An Important Risk Factor for Parkinson's Disease

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Metabolic syndrome is becoming commoner due to a rise in obesity rates among adults. Generally speaking, a person with metabolic syndrome is twice as likely to develop cardiovascular disease and five times as likely to develop diabetes as someone without metabolic syndrome. Increasing oxidative stress in metabolic syndrome and Parkinson's disease is mentioned in the comprehensive articles; however, the system review about clear relation between metabolic syndrome and Parkinson's disease is deficient. In this review, we will focus on the analysis that the metabolic syndrome may be a risk factor for Parkinson's disease and the preventions that reduce the incident of Parkinson's disease by regulating the oxidative stress.

1. Introduction

Metabolic syndrome is a prevalent and increasing public health problem worldwide related to many chronic diseases. Its components mainly include at least insulin resistance, central obesity, glucose intolerance, dyslipidemia with elevated triglycerides, low HDL cholesterol, microalbuminuria, predominance of small dense LDL-cholesterol particles, hypertension, endothelial dysfunction, high waist circumference, oxidative stress, inflammation, tumors, neurodegeneration, and atherosclerosis-based ischemic cardio- or cerebral-vascular disease. Meanwhile, recent studies have indicated that increased oxidative stress is the core and a general character of metabolism-related disease. Parkinson's disease, during the past decades, is one of the most frequent neurodegenerative disorders that cause dementia and it is one of the leading chronic diseases in all countries and it also displays the high level of reactive oxygen species (ROS). A growing body of evidence that has implicated the components of metabolic syndrome may contribute to the pathophysiology of Parkinson's disease. In the current brief review, we extend this work to search for findings from studies that provide evidence to clarify it and propose some

prevention to delay the progression of Parkinson's disease via regulating the oxidative homeostasis.

2. The Components of Metabolic Syndrome Act as the Risk Factors for Parkinson's Disease

Risk factors for Parkinson's disease are either the result of genetic susceptibility (e.g., SNCA, PARK, PINK, and LRRK2 single nucleotide polymorphisms) or environmental exposure of a person's health to an event that can accelerate or further worsen dysfunction of the central nerve system. Metabolic syndrome is a crucial element of the environmental exposure of the global human health. Following up we will, respectively, introduce the components of metabolic syndrome that act as the risk factors for Parkinson's disease.

2.1. Fat and Obesity. Obesity continues to increase rapidly in the United States [1] and it is well established that obesity can increase the risk of Parkinson's disease and decrease life expectancy. A study has proved that high skinfold thickness in midlife was associated with Parkinson's disease [2]. And

another study found that obesity in middle age increases the risk of future dementia independently of comorbid conditions. Perhaps adiposity works together with other risk factors to increase neurodegenerative disease [3]. In addition, some evidence shows that body mass index is associated with a risk of Parkinson's disease and the effect is graded and independent of other risk factors [4].

In an animal model of Parkinson's disease, high fat diet may lower the threshold for developing Parkinson's disease through affecting glucose transport and decreasing phosphorylation of HSP27 and degradation of $\text{I}\kappa\text{B}\alpha$ in the nigrostriatal system, at least following dopamine-specific toxin exposure [5, 6]. Moreover, increasing inflammatory signaling, adipokine levels, oxidative or nitrosative stress, mitochondrial dysfunction, and lipid metabolism have all been shown to occur with high fat feeding [7–9].

2.2. Glucose, Hyperglycemia, Insulin Resistance, and Diabetes. High glucose induced cell death is sustained by oxidative, nitrosative stress and mitochondrial superoxide generation through cleavage of the caspase 3 to regulate the apoptotic pathway [10–14]. In aging, hyperglycemia is also associated with Parkinson's disease through damage in central nervous system, a consequence of long-term exposure to glucose [15, 16]. Indeed, epidemiologic studies have implicated that prior type 2 diabetes is also the risk factor of developing Parkinson's disease [17]. Although, in different regions, the Parkinson's disease patients' brain exhibits similar cellular and functional changes with signs of increased oxidative stress, reduced mitochondrial function, reduced glucose uptake, and increased peroxidation of cellular membranes [18].

2.3. Hypertension. Many studies have been carried out on this topic: whether hypertension is the risk factor for Parkinson's disease. Much work, both theoretical and practical, has been reported recently in this field that hypertension is less frequent in Parkinson's disease patient than general population and others show that there is no difference between Parkinson's disease patients and healthy people [19, 20]. Nonetheless, a large prospective study suggested that Parkinson's disease risk is not significantly related to history of hypertension (RR = 0.96; 95% CI = 0.80 to 1.15) [21]. Although a lot of effort is being spent on proving the relation between Parkinson's disease and hypertension, the surely inerrable conclusion has yet to be reached.

2.4. Hyperhomocysteinemia and Endothelial Dysfunction. Hyperhomocysteinemia, a risk factor for endothelial dysfunction [22], has been involved in the pathophysiology of neurodegenerative disorders such as Alzheimer disease and Parkinson disease [23]. And homocysteine leads to endothelial dysfunction that hydrogen peroxide plays a critical role in mediating cell injury *in vitro* [24]. Large increases in cellular oxidative stress and inflammations occurred in response to high homocysteine that induced toxicity by decreased NAD⁺ [25–29]. In comparison, recent studies have

also demonstrated that homocysteine is largely involved in antioxidant and reductive cellular biochemistry [30].

2.5. Inflammations. The involvement of inflammation in Parkinson's disease was initially proposed by McGeer et al. [31] who described the upregulation of HLA-DR-positive reactive microglia in the substantia nigra of Parkinson's disease patients in 1988. Additionally, they also reported that activated microglia was a contributor of proinflammatory and neurotoxic factors in Parkinson's disease patients [32]. Neuroinflammation which was induced by exposure to either toxicants or infectious agents with proinflammatory characteristics as a major factor in the pathogenesis of PD is widely accepted at present. Plenty of cytokines such as tumor-necrosis factor- α (TNF- α) [32, 33], interleukin 1 β (IL-1 β) and IL-6 [32, 34–36], and the quantities of ROS [32] have been postulated to be involved in the etiology of Parkinson's disease. Furthermore, recent evidence indicates that endoplasmic reticulum (ER) stress [37–40] and inflammation coordinate the pathogenesis of Parkinson's diseases.

3. Targeting Oxidative Homeostasis as a Therapeutic Strategy against Parkinson's Disease

A growing number of studies have been completed to confirm that stimulation of oxidative stress that initiates apoptosis in many cells and animal models [11, 14, 41] is pivotal to the evolution of metabolic syndrome, diabetes, diabetic neuropathy, and several neurodegenerative disorders, such as Parkinson's disease and Alzheimer disease [42–46]. Though application of antioxidants and some measures in the field of preventing Parkinson's disease have proliferated in recent years, a phyletic classification is lacking. Here we introduce the potential mechanism under a variety of antioxidants or other therapeutic strategies to reduce the oxidation stress.

3.1. Plant Extract. Previous works, such as Bournival et al. [41, 47], Bureau et al. [48], and G elinas and Martinoli [49], reported that several plant extracts are powerful in neuroprotective activity of dopaminergic neurons against the oxidative burden provoked by administration of the potent parkinsonian toxin MPP⁺ *in vitro* or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) *in vivo*. The plant extract, which contains resveratrol and quercetin and sesamin [41, 47, 48], fermented papaya preparation [50], cinnamon polyphenols [51], and estradiol and phytoestrogens [49], was inhibited by oxidative stress that damages the normal physiological function of cellular organelle by regulating caspase 3, DNA fragment, estrogen receptors, cytokines, Akt, p38, MAPK, and ERK pathway.

An additional research which focuses on the extremely important antioxidant properties of cannabinoids, extract of hemp plant, may contribute to the neuroprotective effect in Parkinson's disease through banding the canonical cannabinoid CB1 and CB2 receptors [52–55].

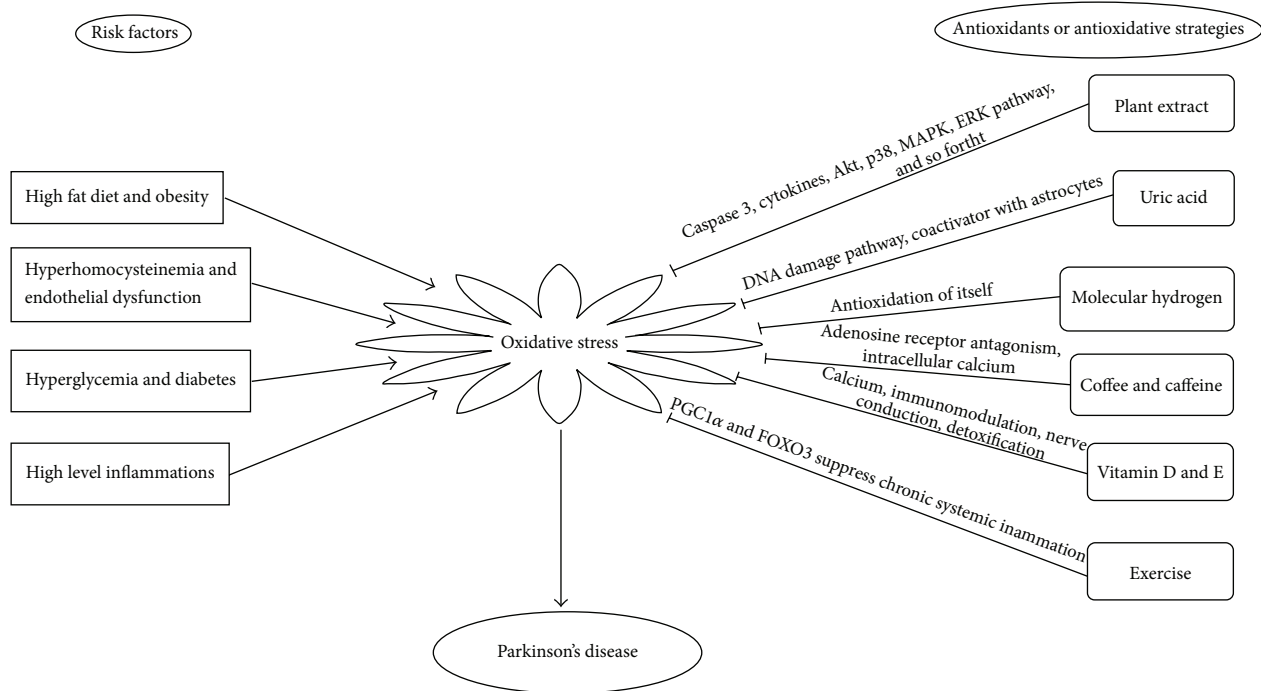


FIGURE 1: Summary of this review about oxidative stress and Parkinson's disease.

3.2. Uric Acid. A large community-based survey indicated that the associated higher serum uric acid was able to decrease the prevalence of Parkinson's disease [56]. Similarly, it has been observed that UA levels in the serum of patients with Parkinson's disease are lower than in controls and that increased levels of UA are associated with a lower risk of Parkinson's disease [56–59]. Evidence was also proved that physiological concentration of uric acid would exert antioxidant effects, attenuating neuronal lesions caused by oxygen radicals, generated during an acute ischemic stroke and in cases of Parkinson's disease [60]. It had been established that the protective mechanisms of uric acid may be through regulating the DNA damage pathway [60–62]. The recent study from Massachusetts General Hospital found that the urate's ability to protect neurons requires the presence of astrocytes in Parkinson's disease unexpectedly [63].

3.3. Molecular Hydrogen. Hydrogen has great potential for improving oxidative stress-related diseases by inhaling H_2 gas, injecting saline with dissolved H_2 , or drinking water with dissolved H_2 [64]. Recent basic and clinical research has revealed that hydrogen is an important physiological regulatory factor with antioxidant, anti-inflammatory, and antiapoptotic protective effects on cells and organs [65]. Meanwhile, a large number of studies report that molecular hydrogen acts as a novel antioxidant and prevents or ameliorates diseases associated with oxidative stress in animal experiments [66–77] and clinical tests [78–81]. Molecular hydrogen improves obesity and diabetes by inducing hepatic FGF21 and stimulating fatty acid and glucose expenditure in mice [64]. Another research reported that molecular hydrogen is protective against 6-hydroxydopamine-induced

nigrostriatal degeneration in a rat model of Parkinson's disease [75]. However, little is known about the mechanism that H_2 acts on to prevent oxidative stress in Parkinson's disease.

3.4. Coffee and Caffeine Intake. Higher coffee and caffeine intake is associated with a significantly lower incidence of Parkinson's disease as discussed by Ross et al. [82]. Caffeine, a well-known central nervous system stimulant, inhibits the dopamine neurotransmission through adenosine receptor antagonism and mobilizes of intracellular calcium [83–85]. In addition, caffeine was regarded as an antioxidant against all the three reactive oxygen species, hydroxyl radical, peroxy radical, and singlet oxygen [86].

3.5. Vitamin D and Vitamin E. Individuals with higher serum vitamin D concentrations showed a reduced risk of Parkinson disease. The relative risk between the highest and lowest quartiles was 0.33 (95% confidence interval, 0.14–0.80) [87]. Even so, the exact mechanisms by which vitamin D may protect against Parkinson disease are not fully understood [87]. High vitamin D status, however, has been shown to exhibit neuroprotective effects through antioxidative mechanisms, neuronal calcium regulation, immunomodulation, enhanced nerve conduction, and detoxification mechanisms [88–90]. Furthermore, the central issue in all these studies is to declare that high intake of dietary vitamin E [91, 92] may protect against the occurrence of PD, but vitamin C or β carotene does not [92]. And the protective influence for Parkinson's disease was seen with both moderate intake (relative risk:

0.81; 95% CI: 0.67–0.98) and high intake (0.78, 0.57–1.06) of vitamin E [92, 93].

3.6. Exercise. Inadequate physical activity has also been shown unequivocally to increase the morbidity and mortality rates of associated chronic disorders [94–96]. Exercise reduces the level of systemic inflammation by increasing the release of adrenaline, cortisol, growth hormone, prolactin, and other factors that have immunomodulatory effects and decreasing expression of toll-like receptors at the surface of monocytes, which have been suggested to be involved in mediating systemic inflammation [97–99]. Many results of the present research synthesis support the fact that the patients with PD improve their physical performance, activities of daily living [100, 101], and the effect of pharmacologic therapy [102] through exercise. The transcriptional coactivator PGC1 α controls muscle plasticity and suppresses chronic systemic inflammation via repressing FOXO3 activity, increasing vascularization, ROS detoxification, and mitochondrial and metabolic gene expression [95]. The more specific mechanisms of the fact that exercise mediates the beneficial and advantageous effects for Parkinson's disease remain enigmatic.

4. Summary

This review summarizes the data to support a link between oxidative stress and Parkinson's disease (Figure 1). Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting the elder population mainly and its pathophysiology as well performs a metabolism-related dysfunction. It has been believed generally that oxidative stress was found during Parkinson's disease development when it occurs in early stage. Oxidative stress also is a crucial feather of metabolic syndrome. Undoubtedly, Parkinson's disease should be treated as a metabolic disease. Numbers of antioxidants are effective and efficient in the prevention and treatment of Parkinson's disease by modulating the oxidative stress, but Parkinson's disease whether or not is a metabolic syndrome still needs further epidemiological, basic science and clinical research. At present, considerable studies in a new direction are guiding future research on the relationship between Parkinson's disease and metabolic syndrome.

Conflict of Interests

The authors declare that they have no conflict of interests regarding the publication of this paper.

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