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Stress and Changing Life-Style can Aggravate Neurodegenerative Disorders - An Emphasis on Parkinson's Disease

Begum F, Pal R, Sengupta S and Basu BR*

Department of Physiology, University of Calcutta, India

***Corresponding author:** Barnali Ray Basu, Associate Professor, Department of Physiology, Surendranath College, University of Calcutta, Kolkata, West Bengal, India, Email: braybasu@gmail.com

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Abstract

Changing lifestyle and dietary patterns , constraint due to COVID-19 pandemic have shifted life to more home confined with restricted mobility, which could contribute to an increase in the burden of neurodegenerative disease like Parkinson's Disease (PD). This neurodegenerative disease, which stood second among brain disorders, is rapidly affecting the geriatric population. There are reports on accelerating the early onset of this disease. As the disease advances, the symptoms become more difficult to control and deteriorate, having an impact not only on the quality of patient's life but also on that of their family and caregivers. Therefore, society has a pressing need to be aware of other factors like oxidative stress (OS) and inflammation that may be influencing the disease's development and detecting the disease in its prodromal stage. Chronic psychological stress acts like a roller-coaster in the body and alter the balance of oxidants/antioxidants leading to oxidative stress followed by inflammation. Other two lifestyle conditions, Insulin resistance (IR) and a Vitamin D Deficiency D(VDD) are also contributing to the enhancement of neurodegeneration. Insight molecular mechanisms of PD are intertwined with epigenetic factors like IR-T2DM, VDD, obesity, OS, and inflammation that lead to the death of DA neurons and disease onset. As the said altered health profiles are reversible and with due attention can be reverted or to some extent be arrested, the progressive neurodegenerative disease like PD can be prevented or slowed down by taking early preventive measures.

Keywords: Parkinson's Disease; Insulin Resistance; IGF1; Oxidative Stress; Inflammation; Vit D Deficiency

Abbreviations: PD: Parkinson Disease; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; T2DM: Type 2 Diabetes Mellitus; VDD: Vitamin D Deficiency; SNpc: Substantianigra Pars Compacta; OS: Oxidative Stress; DA: Dopaminergic Neurons; ROS: Reactive Oxygen Species; IR: Insulin Resistance; IGF1: Insulin Like Growth Factor 1; IGFBP: Insulin like Growth Factor Binding Protein; BBB: Blood Brain Barrier; CNS: Central Nervous System; FFA: Free Fatty Acids; GH: Growth Hormone; TNFα: Tumor Necrosis Factor Alpha; IL-6: Interleukin- 6; IL-1β: Interleukin-1 Beta; MCP-1: Monocyte Chemoattractant Protein-1; IRS1: Insulin Receptor Substrate 1; INSR: Insulin Receptor; IGF1R: Insulin Receptor Growth Factor 1 Receptor; PI3K: Phosphoinossitide-3-Kinase; PIP2: Phosphatidylinositol 4,5-Bisphosphate; PIP3: Phosphatidylinositol 3,4,5-Bisphosphate; PDK1: 3-Phosphoinositide-Dependent Kinase-1; NOX4: NADPH Oxidase 4; GLUT4: Glucose Transporter Type-4; FOXO1: Forkhead Box Protein 01; TLR4: Toll-Like Receptor 4; ETC: Electron Transport Chain; GSK3β: Glycogen Synthase Kinase 3 Beta; NF-κB: Nuclear Factor Kappa B; CSF: Cerebrospinal

Fluid; NGF: Nerve Growth Factor; AMP: Adenosine Monophosphate; bFGF: Basic Fibroblast Growth Factor; MHC: Major Histocompatibility Complex; MHC-II: Major Histocompatibility Complex-II; HLA: Human Leukocyte Antigen; HLA-DR: Human Leukocyte Antigen-DR; IFN-α: Interferon- Alpha; NOS2: Nitric Oxide Synthase 2; COX2: Cyclooxygenase2; PAMPs: Pathogen-Associated Molecular Pattern Molecules; DAMPs: Danger-Associated Molecular Pattern Molecules; AMPK: AMP-Activated Protein Kinase; VDR: Vitamin D Receptor; CaMKKβ: Calmodulin Protein Kinase Beta.

Introduction

Since 2020, after the outbreak of COVID-19, stress has extended in a new dimension in human life. Along with the pre-existing stressors, the added burdens are suffering from COVID-19 and measures to control the spread of COVID, such as confinement-induced stress, depression, and anxiety. Stressful event causes a chain of reactions that begins in the brain and results in the production of proinflammatory cytokines while suppressing the genes involved in the production of interferons and antibodies. Moreover, cytokines induce oxidative stress after the stimulation of reduced nicotinamide adenine dinucleotide phosphate (NADPH) [1]. The essential causes of OS are either the mental stress, nutritional origin in the case of deficiencies in vitamins and trace elements, overloads in pro-oxidant factors, accidental origin (inflammation, infections, exposure to pro-oxidizing xenobiotics), and genetic origin [2]. OS has been implicated in a range of chronic neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease (PD), Huntington's disease, and Amyotrophic Lateral Sclerosis [3]. With the changing life style like more sedentary work-culture and less exposure to sunlight in new normal era, other two very important health issues, Type-2 Diabetes (T2DM) and Vitamin D deficiency (VDD) is emerging that need to be addressed. Role of OS, T2DM and VDD on pathoaetiology of PD will be discussed in detail in this review.

PD is a degenerative brain condition that spreading quickly and the illness does not just affect the elderly; it also appears before old age [4]. PD has a 10% genetic aetiology and the rest of the cases are sporadic. It is still unclear what exactly caused the disease. Genetic and epigenetic variables may play a role, crosstalk or contribute to sporadic PD [5]. The disease's early symptoms may be ignored and overlooked, and it's possible that all sufferers won't have the same signs and symptoms as others. Later in life, the disease is defined by typical motor symptoms such as postural instability, stiffness, and bradykinesia. Dopaminergic (DA) neurons of the brain's substantianigra pars compacta (SNpc), which are in charge of regulating and coordinating movement and coordination, are the source of these motor issues [6].

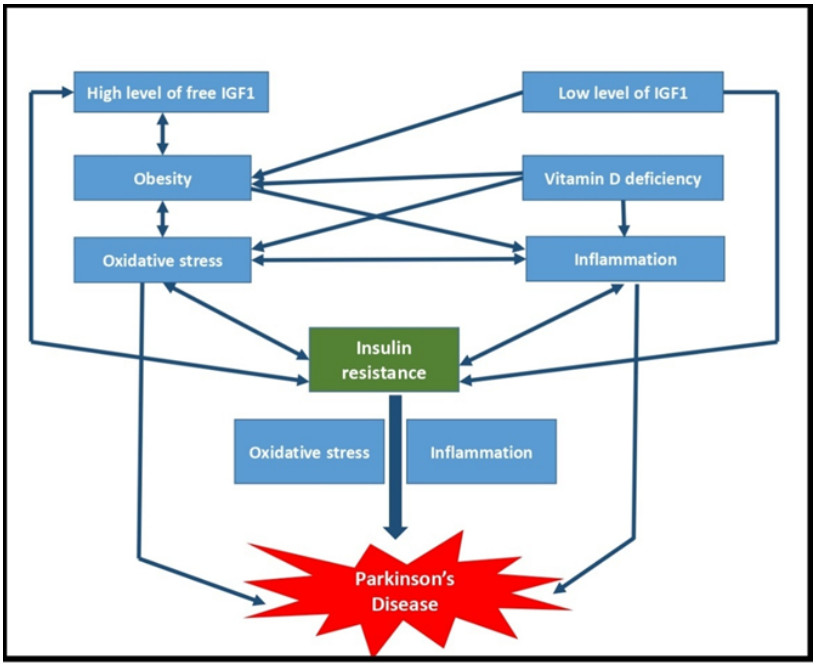

Figure 1: Schematic diagram showing the role of abnormal level of IGF1, obesity, vitamin D deficiency, oxidative stress, and inflammation and insulin resistance in Parkinson's disease.

The presence of aggregated and misfolded forms of α-synuclein and the Lewy body (the pathological hallmark of PD) in the DA neurons confirms this neurodegenerative disorder together with some other associated proteins like tau and β amyloid proteins [6]. Numerous situations and factors can cause the death of DA neurons and the main mechanism behind DA loss is OS and inflammation [7,8]. These two underlying mechanisms are also triggered by insulin resistance (IR) [9], which begin to build slowly in a person even before the onset of diabetes and is remain undetectable and is one of the causes behind PD development. There is evidence too, that people with type T2DM are more likely to develop PD [10,11]. Again, obesity a rapidly growing public health concern is a major contributing factor to IR which leads to hyperinsulinemia [12]. The high level of insulin signals to the liver produce more insulin-like growth factor 1 (IGF1) as well as reduce the insulin-like growth factor binding proteins (IGFBPs) [13]. Again due to reduced concentration of IGFBPs, there is an increase in the levels of free insulin-like growth factor 1 (F-IGF1) in the serum as IGF1 remains in the free state if it's not bound to IGFBPs [13]. IGF1 is a neurotrophic factor that aids in the protection of neurons other than maintaining glucose homeostasis [14]. As IGF1 has an almost similar molecular structure to insulin, it also shares a similar downstream pathway for their actions. Both the above and below normal levels of IGF1 are linked to IR [15] and PD [16,17], suggesting that IR might be a potent regulator in the development of PD. The probable mechanisms by which the IGF1-PI3K-Akt pathway is blamed to be the culprit for PD are inflammation and OS. Further, in addition to IR, the pathway is also negatively influenced by VDD [18], another pandemic that is increasing globally, particularly in elderly people, and aids in developing PD [19]. Vitamin D's ability to cross the blood-brain barrier (BBB) suggests its role in the brain. Vitamin D insufficiency also causes inflammation, OS [19] and IR [20] which is the key underlying regulators of PD pathogenesis. Therefore, this review article aims to comprehend the role of IGF1in IR and PD as well as the impact of inflammation and OS behind PD development in light of vitamin D deficiency Figure 1.

Discussion

Stress, Insulin Resistance and Parkinson's Disease

Stress hormones like cortisol is a potent insulin-antagonist that inhibit insulin secretion, stimulate glucagon secretion and disrupt insulin signaling pathway causing IR. Insulin resistance is one the fastest growing pandemic all around the world with a risk of causing neurodegenerative diseases other than metabolic syndromes like T2DM. IR plays a great role in causing inflammation and OS which are the root cause behind the development of PD [11]. These two factors; OS and inflammation can also interfere with the PI3K-Akt pathway that results in IR, suggesting that they influence each other. In addition to insulin, IGF1 takes charge of controlling glucose homeostasis and is also a neurotrophic growth factor having multiple functions and plays a great role in the central nervous system (CNS) growth and development [14]. IGF1's position in the CNS and its involvement in neurodegeneration are indicated by IGF1 expression in neuronal-rich cells and the presence of IGF1 receptors in the brain, as well as IGF1 can also enter the CNS through the choroid plexus [21]. IR results either due to impairment in the insulin signaling PI3K-Akt pathway or due to abnormal IGF1 levels. Elevated or reduced levels IGF1 is associated with IR and acts as an indicator for developing T2DM [15]. Due to the involvement of IGF1 in the IR, it is strongly associated with hyperinsulinemia and obesity. Obesity and overweight are other growing health concerns contributed by high nutrient content and elevated free fatty acids (FFA) can also influence IGF1 levels [13]. Circulating IGF1 and IGFBPs control the biological action of IGF1. The binding of IGF1 with its binding protein is essential for its activity and it is also studied that IGF1 can only cross the BBB if it is bound with IGFBPs [22]. The IGFBPs are synthesized by the liver and their secretion is negatively correlated with high levels of insulin [13]. FFA in obesity also trigger the pancreatic β cells to secrete insulin making the condition hyperinsulinemic [23]. On the other hand, insulin above optimal level stimulates the liver to synthesize more and more IGF1 and reduced IGFBPs, as a result, free circulating IGF1 level goes on increasing [13], and this high free IGF1 level acts as a negative feedback regulator of growth hormone (GH). Reduced and decreased GH is associated with the obesity problem [13]. Therefore, the binding of IGF1 to the IGFBPs might suggest that binding may promote and enhance IGF1 action. The free IGF1 is might be the reason behind impairment in the insulin signaling PI3K-Akt pathway. Studies have also found that free IGF-I levels are higher in obese people [24] and elevated FFA in these obese individuals can activate JNK and NFκB pathway that results in increased expressions of proinflammatory cytokines like tumor necrosis factor-α (TNF-α), interleukin-6(IL-6), interleukin-1 beta(IL-1β) and circulating monocyte chemoattractant protein 1(MCP-1). Pro-inflammatory cytokines decrease insulin sensitivity by phosphorylating insulin receptor substrate 1(IRS1) at a serine residue and dephosphorylating IRS1 at a tyrosine residue thus, downregulating the PI3K-Akt pathway [25]. Further, in obesity there is an increase in the activity of tyrosine phosphatases, an enzyme that interfere with the insulin signaling pathway and responsible for maintaining the relatively stable phosphorylation of the INSR and other proteins involved in the insulin signalling cascade. Active tyrosine phosphatases reduced the autophosphorylated form of INSR at tyrosine residue as well as dephosphorylating IRS1 which signals downstream protein of the signalling pathway [26], resulting IR and obesity.

IGF1- PI3K-Akt Signalling Pathway in Insulin Resistance and Parkinson's Disease

IGF1 actions are mediated by binding to its receptors. IGF1 shares the same insulin signaling PI3K-Akt pathway and initiates a similar cascade for maintaining the normal functions for which it is responsible. IGF1 can bind to the hybrid receptor (INSR-IGF1R) or the insulin receptor (INSR) in addition to its receptor, IGF1R [27]. The presence of INSR and IGF1R in the brain, suggests its functions in CNS [28]. The binding of IGF1 to the receptors leads to activation and phosphorylation of the IRS1/2 (insulin receptor substrate) that phosphorylates and recruits PI3K (phosphoinositide-3-kinase) which in turn phosphorylates PIP2 (phosphatidylinositol 4,5-bisphosphate) to PIP3 (phosphatidylinositol 3,4,5) allowing PDKI (phosphoinositide-dependent kinase-1) for Akt activation and phosphorylation. Akt is the main important downstream substrate of the signaling pathway that regulates a variety of physiological responses by inhibiting or stimulating specific substrates after phosphorylation [27].

The glucose transporter type 4 (GLUT4) is moved to the plasma membrane by Akt's phosphorylation of the AS160-a160kD protein, allowing the cell to take up extracellular glucose and preserve glucose homeostasis. Therefore, alterations in the IGF1 interfere with AS160 and may prevent GLUT4 from functioning normally in T2DM [29]. Hyperinsulinemia produces a negative effect on GLUT4 and shifts the insulin signaling pathway at PI3K, phosphorylating Rac by PI3K rather than PIP2, which increases the activity of NOX4 (NADPH4 oxidase 4-a powerful oxidizing enzyme). The increased activity of NOX4 increases ROS concentration which triggers casein kinase-2, which then, in turn, activates the retromer, translocating GLUT4 to the lysosomes for destruction. Thus, making the environment more oxidative and hyperglycemic . The activity of NOX4 can be increased by adipose tissues that secrete adipokines, a class of cytokines that raises ROS and also encourage macrophages to produce more pro-inflammatory cytokines, hence aggravating systemic inflammation and leading to more ROS production that impairs insulin sensitivity [30]. Akt also phosphorylates the FOXO1 (forkhead box protein O1) transcription factor that results in the translocation of FOXO1 from the nucleus to the cytoplasm, making it inactive. This inactivation causes the transcriptional stimulation of gluconeogenesis to halt [31].

In the absence of an insulin or IGF1 signal, FOXO1 goes to the nucleus and promotes the production of gluconeogenic genes such as phosphoenol pyruvate carboxykinase and glucose-6-phosphatase gene and thus increase glucose production [31]. FOXO1 inhibits the production of adipose tissue and also plays important role in apoptosis because it causes the production of death receptor ligands [32]. FOXO1 by increasing TLR4 (Toll-like receptors 4) mediated signaling in mature macrophages promotes inflammation and is tightly controlled by the PI3K-Akt pathway [33]. Activation of FOXO1 disrupts the mitochondrial electron transport chain (ETC) and NAD/NADH ratio, thus suppressing the mitochondrial biogenesis. Furthermore, studies had shown that activation of FOXO1 is activated by IR that, lowers mitochondrial content or affects mitochondrial integrity [34]. Akt also phosphorylate and inactivate another important substrate glycogen synthase kinase β (GSK3β) which is very essential for the normal functioning of the signaling pathway [28]. Activation of GSK3β is responsible for various pathological conditions and diseases [35]. Whereas, inhibition of GSK3β is seen to reduce IR and stimulate glucose transport, suggesting that it plays a great role in glucose homeostasis [36].

Downregulation of IGF1/PI3K-Akt signaling with the elevation of GSK3β activity also leads to brain disorders. Thus inactivation of GSK3β is essential for various normal functions that include glucose homeostasis, neuronal growth and development, and cell survival. An activated form of GSK3β is responsible for various abnormal conditions including PD. Activation of this kinase leads to upregulationof NF-κB pathways involving an increase in pro-inflammatory cytokines IL-6, IL-1β, and TNFα and a decrease in anti-inflammatory cytokines such as IL-10 [35], suggesting that the PI3K/Akt/GSK3β signaling pathway appears to reduce NF-κB nuclear translocation and is also the source of inflammation. Further, pro-inflammatory cytokines like IL-6 and IL-1β can alter the BBB's permeability and raise the permeability of other solutes or immune cells, which causes brain IR and neurodegeneration [37]. Pro-inflammatory cytokines can also lead to a reduction in insulin sensitivity and an increase in IR. This accelerates neurodegeneration while also causing mitochondrial damage, that in turn raises the production of ROS to sustain the inflammatory state.

Activated GSK3β takes part in increasing caspase 3 & 9, thus inducing neuronal apoptosis by impairing mitochondrial function and plays role in α-synuclein aggregation and phosphorylation. Altered insulin signalling (insulin or IGF1/PI3K/Akt signaling) is also responsible for tau and β-amyloid (Aβ) protein phosphorylation (a misfolded protein aggregate) that is observed in PD with dementia [35]. Hence, it has been well established that GSK3β dysregulation participates in a variety of cellular processes that eventually promote the pathology of neurodegenerative diseases such as PD other than hampering glucose homeostasis. Therefore, the IGF1/PI3K/AKT/ GSK3β pathway is found to regulate many important functions that influence the development of PD, and the effect of IGF-I is found to be mediated by the activation of the PI3K-Akt pathway [35]. Both high and

low levels of IGF1 are associated with PD. Supporting the notion some studies have reported increased levels of IGF-1 in serum or CSF of early PD patients [16,38] while other studies showed low plasma IGF-1 level association with poor cognitive performance in PD [17], possibly via the key underlying process of inflammation and OS (Figure 2).

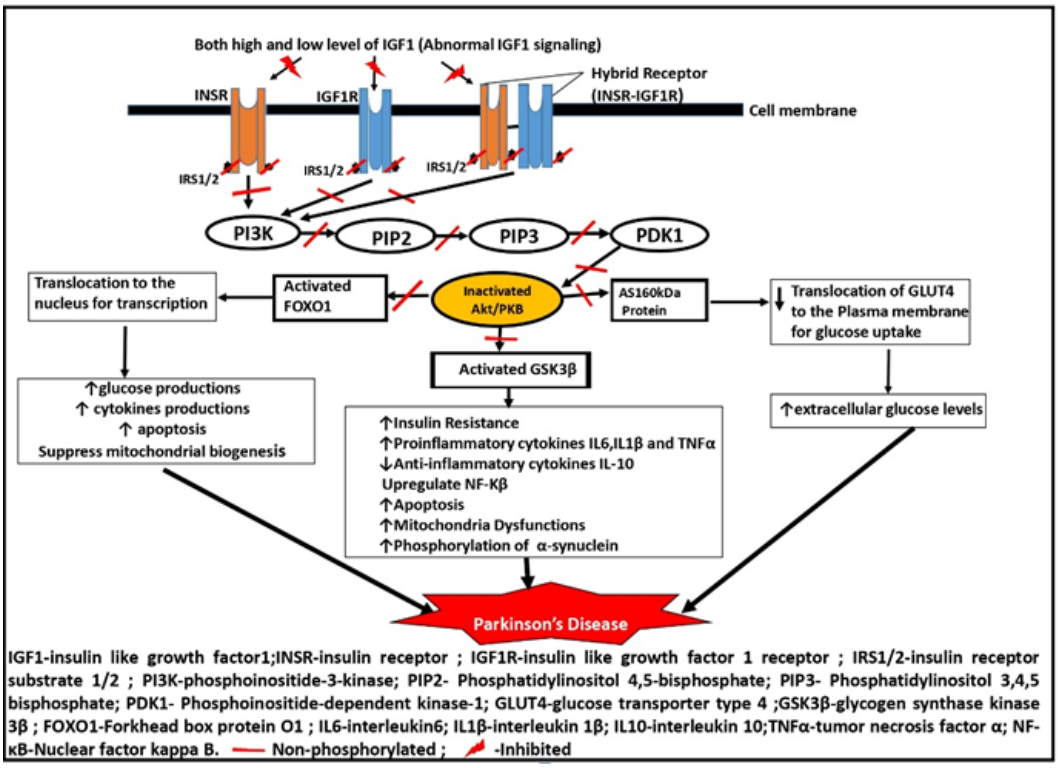

Figure 2: Role of abnormal level of IGF1 in insulin resistance and Parkinson's disease.

Oxidative Stress and Parkinson's Disease

Oxidative stress, which is associated with age-related neurodegenerative diseases PD [8], is defined as a cell having higher quantities of ROS than antioxidants [39]. The ROS molecules, which are unstable and reactive, destroy cellular molecules and are the main cause of mitochondrial malfunction, which results in the death of the neuron [8]. The fundamental function of mitochondria is the production of ATP through the process of oxidative phosphorylation at the electron transport chain. As a consequence, ROS are also produced by mitochondria. The mitochondria, which are both the generator and the sufferer of ROS, control apoptosis, calcium homeostasis, and stress response [39]. Any impairment or dysfunction in the mitochondria leads to several abnormal outcomes, triggering and initiating a cascade that leads to the death of the DA neurons, the key cause behind PD [8]. Hyperactive mitochondria due to high nutrients or hyperglycemic conditions, produce more ROS [30], making the environment more stressful and stimulating various stress pathways resulting in mitochondrial dysfunction and ultimately leading to the death of the DA neurons in the brain's SNpc to die [8,40]. Since neurons can only store a little quantity of energy and the brain has a high oxygen requirement due to the existence of numerous mitochondria to satisfy the demands of high levels of energy consumption [41], OS is a big threat to these cells or a major victim of OS. Further, due to a large number of mitochondria, there is more mitochondrial enzyme in the brain and the majority of these enzymes need iron to function [42].

Iron on the other hand can produce ROS by Fenton's reaction, enhancing OS and causing neuronal death. In 2020, a study reported high levels of iron in the substantianigra of PD patients [43]. The loss of DA neurons can happen due to dopamine itself. Dopamine undergoing auto-oxidation forms dopamine quinones and itself becomes the source of OS. This reactive dopamine quinone can make a component called neuromelanin, which can activate microglia and trigger neuroinflammation [44] and can also bind with iron and react with hydrogen peroxide (H_2O_2) forming a member of ROS- hydroxyl ions (.OH). These (.OH) causes the death of cells and lipid peroxidation in the brain. Dopamine quinones may stimulate protein ubiquitination and the formation of α-synuclein and Lewy bodies, the pathological hallmark of PD [45,46]. Furthermore, the presence of monoamine oxidase B

in the substantianigra glial cells can deaminate dopamine, forming an oxidizing agent H_2O_2 that can enter the nearby dopaminergic cells and also reacts with Fe2+ (iron) to form hydroxyl radical resulting in extra oxidative damage [47].

The other sources of ROS in the brain include low levels of antioxidants, particularly GSH (glutathione) as the amount of this antioxidant is found to be negatively correlated with aging and PD is an age-related neurodegenerative disorder. This antioxidant reduction is one of the earliest biochemical changes seen in PD. GSH depletion may have a significant effect on the resilience of dopamine neurons, particularly if they are experiencing OS [48]. Obesity is another source for generating OS apart from its direct association with IR and hyperglycemia [12].Vitamin and mineral deficiencies can also play a role in the formation of a compromised antioxidant defence in the pathogenesis of obesity [49,50] and as obesity is the driving force behind IR [18], raises the FFA level and hinders adenine nucleotide translocation in the ETC of mitochondria by the production of superoxide ion (O2•−) [51] a member of the ROS family that leads to damage and death of a cell. PD patients and mitochondrial toxin examples of the disease both exhibit persistent inhibition of mitochondrial Complex I activity [52]. Again FFA from excessive adipocytes increases ROS production by increasing the NADPH oxidase-a powerful oxidizing enzyme and also by stimulating special cytokines called adipokines and other pro-inflammatory cytokines like TNFα, IL6, IL1β, and MCP-1 causing mitochondrial dysfunction and enhancing ROS. These cytokines and oxidizing molecules in turn are responsible for IR which further aids in adding the oxidative burden [25]. The pro-inflammatory cytokines can also cross BBB and further aggravate the degeneration of the neurons [37] and at the same time damage the mitochondria and hasten neurodegeneration while also increasing ROS production [53]. Therefore, OS is one of the main actor processes in the formation and advancement of PD (Figure 3).

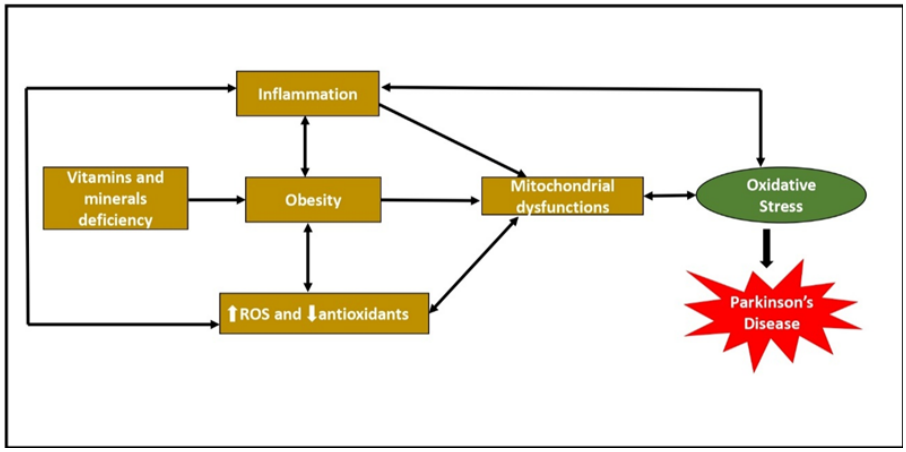

Figure 3: Oxidative stress and Parkinson's Disease.

Inflammation and Parkinson Disease

Inflammation in the CNS is a prominent and common feature in PD where nigral dopaminergic neurons are damaged along with the accumulation of α-synuclein. Additionally, neuroinflammation which is commonly recognized as a key role in the neurodegenerative process, is the aggregate name for the inflammatory responses triggered by soluble substances produced by damaged neurons in neurodegenerative disorders such as PD [9].

There are various processes through which inflammation is triggered in Parkinson's disease, such as IR, gut dysbiosis, aging, genetics, epigenetics, and mitochondrial dysfunction that may ultimately lead to the production of various cytokines by activating the T cells. Excessive/dysregulated activation of the immune cells leads to the overproduction of proinflammatory cytokines such as IL1β, IL6, TNF-α, interferon-γ (INF-γ), etc ultimately paving the path for cytokine storm. This increased level of peripheral cytokines acts on the endothelial cells of BBB causing an increase in vascular permeability and leading to the breakdown of BBB. The breakdown of BBB occurs during acute or chronic inflammation [54]. Thus CNS is no longer regarded as an immunologically privileged location. These inflammatory CNS endothelial cells boost the production of certain adhesion molecules, which draw in circulating T cells, and monocytes, and recruit more immune cells and antibodies over the barrier [55].

Microglial Activation and its Role in Parkinson's Disease: Microglia has both neuroprotective as well as neurotoxic effects in the brain. In healthy brain, resting microglia helps to maintain homeostasis and surveillance against

potential threats. It also produces nerve growth factors (NGF) & adenosine monophosphate (AMP); basic fibroblast growth factor (bFGF). There are lots of substances such as infectious agents, foreign pathogens, prions, or other pathologically-modified CNS proteins, aggregates, apoptotic cells, interferon (IFN)-γ, β-amyloid, lipopolysaccharide, and α-synuclein acting as an activating factor for microglia [56]. Activation of microglia is a key event in neuroinflammation. Significant microglial activation has been observed in post-mortem PD brains, which is demonstrated by aberrant overexpression of the major histocompatibility complex–II (MHC-II) cell surface receptor human leukocyte antigen-DR (HLA-DR) in the brain and afflicted areas (mainly in SNpc). To be recognized by CD4+ T lymphocytes, these various HLA molecules are produced by DA neurons and display the digested antigenic peptides on their surface. Although neurons typically lack major histocompatibility complex (MHC) expression, after IFN activation, substantianigra and locus coeruleus neurons have been discovered to express MHC [57]. Activated microglia secrete a wide range of inflammatory mediators such as TNFα, IL-6, nitric oxide synthase2 (NOS2), Cyclooxygenase-2 (COX2), and ROS. These molecules mediate the efficient presentation of neoantigens to CD4+ T cells via the MHC-II pathway, leading to cell proliferation, subsequent slow degeneration, and finally the death of DA neurons [58]. MHC-II expressing microglia and CD4+, CD8+ T cells were documented in the SNpc of rat models of PD [59]. Therefore, chronic microglia activation in PD could exacerbate the condition by producing an excessive amount of these pro-inflammatory and cytotoxic factors [60].

Insight of Mechanism

Activated microglia adopts an M1 inflammatory phenotype, secreting proinflammatory cytokines, ROS, and glutamate; inducing neuronal damage. Astrocytes also become reactive in this process, and like microglia, they secrete proinflammatory cytokines. Many of these cytokines act on microglial cells, exacerbating their activation, and favouring neuronal damage. The release of TNF-α by microglia induces glutamate release by astrocytes causing the death of neurons as well as degenerating and/or dead neurons which in turn trigger microglial activation by secreting pathogen-associated molecular patterns (PAMPs) and or damage-associated molecular patterns (DAMPs). Protein accumulation (e.g., α-synuclein) is another triggering factor for microglial activation. Microglia degrades and presents components of dead cells and protein aggregates to CD4+ T lymphocytes. This, in conjunction with the release of cytokines, results in the infiltration of CD4+ T cells, which release more proinflammatory cytokines, leading to greater neurodegeneration. As a consequence of this neuroinflammation, BBB becomes dysfunctional, leading to the entry of peripheral immune cells. In the periphery, gut microbiota can trigger inflammation mediated by innate immune cells [61] Figure 4.

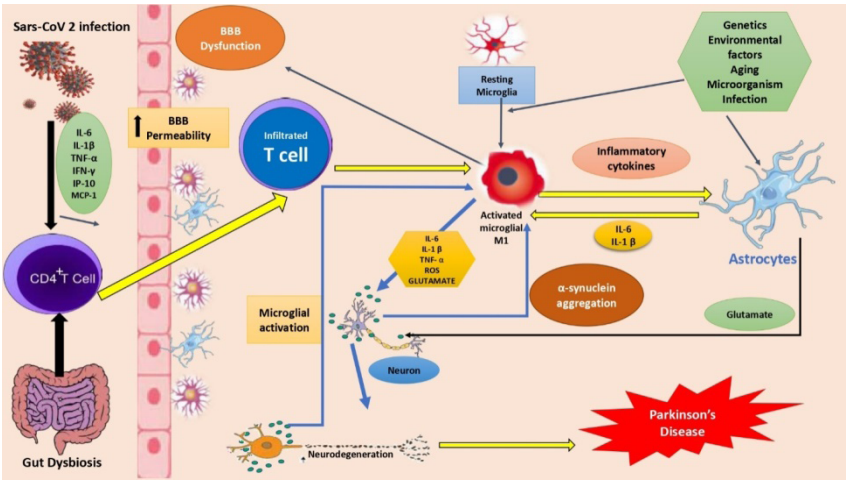

Figure 4: Inflammation and Parkinson's disease.

Role of Vitamin D Deficiency in Oxidative Stress, Inflammation, Insulin Resistance and Parkinson's Disease

Low Vitamin D is associated with poor health conditions. VDD seems to be frequent and related to pathogenesis of numerous diseases, including metabolic diseases like diabetes [62] and neurodegerative diseases like PD [19]. Vitamin D influences the nervous system and the pathophysiology of most of the neurodegenerative diseases [19]. This seco-steroid is known to have neuroprotective role. Vitamin D stimulates neurotropin production and the synthesis of Ca2+-binding proteins such as parvalbumin, inhibits the synthesis of iNOS, macrophage colony-stimulating factor and tumor necrosis

factor α (TNF-α). Furthermore, a lower concentration of vitamin D is correlated with high levels of inflammatory marker, CRP [63]. Inflammatory markers are found to be elevated in PD patients compared to control [64]. Overall the role of vitamin D appears fundamental in the prevention of brain aging, considering also its function in the production of growth factors, including nerve growth factor (NGF), ciliary neurotrophic factor (CNTF), glial cell-derived neurotrophic factor (GDNF), glial cell-line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and neurotrophin 3 (NT3) [65,66]. The relationship between abnormal insulin signalling in the central nervous system and neurodegeneration has gained attention as insulin exerts its role on neuronal plasticity, survival, oxidative stress and neuroinflammation. Both PD and diabetes mellitus are aging-associative diseases where the latter and insulin resistance not only increases the chances of developing PD but also influences the progression and prognosis of the disease [11].

The association of VDD and insulin resistance is also a ventured proposition [67]. Vitamin D supplementation have been seen clinically to reduce the level of metabolic parameters such as total cholesterol , low-density lipoprotein , triglyceride , glycated hemoglobin (HbA1c), as well as decreases insulin resistance indicator-homeostasis model assessment-estimated insulin resistance (HOMA-IR) in T2DM patients [68,69]. Vitamin D receptor (VDR), responsible for internalisation of Vitamin D and vitamin D-metabolizing enzymes were detected in various cell types like pancreatic β-cells and insulin-responsive cells such as adipocytes. Adipose tissue is a major site of vitamin D storage and an important source of adipokines and cytokines participating in the formation of systemic inflammation [20]. It is well known that obesity, especially visceral fat, is one of the major risk factors for T2DM. It has been also suggested that the potential link between diabetes and obesity is if vitamin D deficiency coexist with obesity [70]. Evidence suggests that vitamin D seems to be a regulator of numerous sequential events that are responsible for enabling the pancreatic β-cells to secrete insulin, and thereby to control of blood glucose level. Extra skeletal activities of Vitamin D include anti-inflammation along with prevention of cardiovascular risk and cancer development. Preclinical studies have shown that vitamin D seems to be a potential regulator of insulin secretion, calcium level, and survival of the pancreatic β-cells. Several studies have demonstrated that VDD contributes to impairment of glucose-mediated secretion of insulin in rat pancreatic β-cells [71,72]. It was also reported that glucose-mediated secretion of insulin seems to be restored via vitamin D supplementation [71,73]. The results of some clinical studies [74,75], but not all [76,77], have shown that vitamin D supplementation was associated with the improvement of insulin secretion.

Vitamin D was found to exert an effect on hepatic lipogenesis and gluconeogenesis. This action may be mediated via various vitamin D-regulated pathways including AMP-activated protein kinase (AMPK)-calmodulin and Akt/Notch signaling. AMPK is an enzyme regulating metabolism that is activated by phosphorylation through either the calcium/calmodulin protein kinase beta (CaMKKβ) or serine/threonine kinase 11 pathways [78].

VDD and obesity often share a cause-effect relationship. It is documented that obese children and adolescents are more prone to VDD [79]. VDD is often related to visceral adiposity which makes it a probable biomarker for visceral adiposity-related dysmetabolic state [62]. Volumetric dilution of VD is the most probable mechanism of the inverse relationship between vitamin D serum levels and BMI. Even though obese and lean subjects have similar amounts of VD, in overweight people, VD is distributed into a larger volume, making serum concentrations lower. Interestingly, 25(OH) D is distributed dominantly into the serum, muscle, fat, and liver-areas which are affected by obesity and increase due to fat deposition [80]. A common feature in obesity is a steatotic liver which results in decreased capacity for hydroxylation of prohormones into 25-hydroxy vitamin D [62]. Thus, it is unclear that VDD induces obesity or obesity causes reduced activation of vitamin D into its active bioavailable calcitriol form. However, it is reported that increasing physical activity had positive effect on the prevention and treatment of PD [81]. Figure 5 represents the relation of vitamin D deficiency and other associated factors leading to PD.

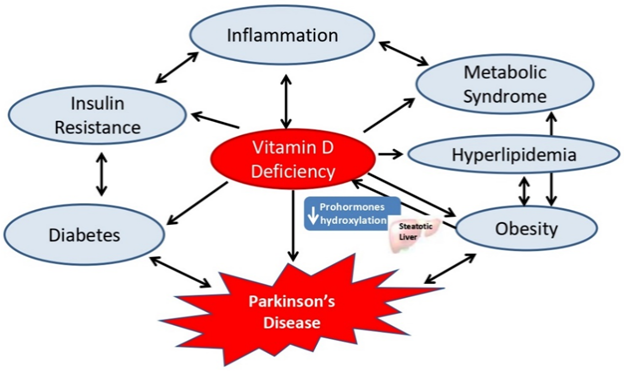

Figure 5: Vitamin D deficiency in Oxidative Stress, Inflammation, Insulin Resistance, Obesity, Hyperlipidemia, Metabolic syndrome and Parkinson's disease.

Conclusion

Along with many deaths and diseases, the COVID-19 pandemic has had a major negative impact on the social and economic conditions of the global population. The stress of

this pandemic also had a detrimental effect on the mental health of patients, caregivers, as well as healthy people. Home confinement and digitalisation restricted the outdoor activities that lead to inclination of basic health towards VDD and IR followed by OS, and inflammation. Other than genetic causes; VDD, IR followed by T2DM, OS and inflammation are the four pillars regulating the mechanisms underlying the onset and worsening of neurodegenerative diseases like PD. IGF1 have a strong connection with IR, and VDD has been linked to all of the key causes (OS, inflammation, IR, and adiposity) that lead to PD. However, polymorphic genetic profile of some individuals related to antioxidant enzyme systems, regulating blood sugar, maintaining active metabolite of Vitamin D, balancing anti/pro inflammatory cytokines has led them to more susceptible to develop a neurodegeneration and hence it need to be address far earlier before the disease onset. As the onset of PD like diseases take place years ago before a diagnosis is actually made and does not currently have a cure, lifestyle management is essential to prevent them. Stress is an unavoidable phenomenon in modern day life, so combating it with proper way in individualistic approach and addressing the modifiable factors like VDD, IR-T2DM, OS should be taken into account for leading a healthy life in older age.

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Author's contribution

FB wrote the main content of the manuscript and contributed to the Figures 1, 2 and 3 and reviewed the manuscript. RP wrote the VDD and PD part, contributed to the Figure 5 and reviewed the manuscript. SSG wrote the inflammation and PD part of the manuscript and contributed to the figure 4. BRB designed, critically reviewed and approved the manuscript.

Conflict of Interest

There is no conflict of interests stated by the authors.

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