Possible Correlation Between Type 2 Diabetes Mellitus and Parkinson's Disease

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Abstract

The relationship between type 2 diabetes mellitus (T2DM) and Parkinson's disease (PD) has garnered increasing attention, with mounting evidence suggesting a potential correlation, although the exact nature of the association remains unclear. Several lines of evidence point towards a shared pathophysiological mechanism contributing to the development of both conditions. One key link involves insulin resistance and impaired glucose metabolism. Studies have consistently demonstrated a higher prevalence of T2DM in individuals with PD compared to the general population. This association may be explained by the observation that insulin resistance, a hallmark of T2DM, can negatively impact dopaminergic neuronal function and survival. Insulin signaling pathways are crucial for neuronal health, and their disruption can contribute to dopaminergic cell loss and the development of PD pathology. Furthermore, hyperglycemia associated with T2DM can induce oxidative stress and inflammation, both of which are implicated in the pathogenesis of PD. Mitochondrial dysfunction, another common feature in both diseases, provides another potential explanation for the observed correlation. Impaired mitochondrial function leads to decreased energy production and increased oxidative stress, contributing to neuronal damage in PD. Similarly, mitochondrial dysfunction is implicated in the pathogenesis of insulin resistance in T2DM. Shared genetic susceptibility may also play a role, with some genes associated with increased risk of both T2DM and PD. However, the directionality of the relationship remains a subject of debate. It is unclear whether T2DM increases the risk of developing PD, or if preclinical PD affects glucose metabolism, leading to the development of T2DM. Furthermore, confounding factors like age, obesity, and lifestyle factors need to be carefully considered when investigating this association. Further research, including longitudinal studies with large sample sizes and carefully controlled for confounding variables, is needed to fully elucidate the nature and strength of the correlation between T2DM and PD, ultimately contributing to improved prevention and treatment strategies for both diseases. Understanding the shared pathophysiological pathways could lead to the identification of novel therapeutic targets for both conditions.

Keywords: Diabetes Mellitus, Parkinson's Disease

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Introduction

Worldwide, PD is the second most prevalent neurodegenerative illness [1]. Between 2015 and 2040, its frequency is projected to more than quadruple because to rising life expectancy and an aging global population [2, 3]. The pathological hallmarks of Parkinson's disease (PD) can be found in both central and peripheral tissues, and the disease progresses through the neurological system. Nigrostriatal dopaminergic neurons degenerate as a defining feature of PD. Chronic systemic inflammation, abnormal protein buildup, and lysosomal and mitochondrial dysfunction are all disease processes that have been found to overlap [4].

The chronic illness known as type 2 diabetes mellitus (T2DM) is marked by the dysregulation of glucose metabolism and chronic systemic inflammation caused by the inability of pancreatic β-cells to release sufficient insulin to overcome systemic insulin resistance. Similar metabolic dysregulation may occur in the brain during the early stages of Parkinson's disease, according to studies [5]. Between 1980 and 2014, the worldwide prevalence of type 2 diabetes doubled, and it has already surpassed the forecasts provided for 2030 by the International Diabetes Federation and the World Health Organization in 2000 [6]. Type 1 diabetes (T1DM) differs from type 2 diabetes (T2DM) in that it is an autoimmune illness that causes the pancreatic β cells to be destroyed [7]. The link between PD and autoimmune illnesses, such as type 1 diabetes, has only been explored in a small number of publications [8–10], although this review does not go into greater detail on T1DM.

The common therapeutic approaches to type 2 diabetes and Parkinson's disease [4, 13, 16, 17] and the relationship between the two diseases [4, 11–15] have both been covered in prior review papers. This study updates previous discussions on the epidemiological link between type 2 diabetes and Parkinson's disease, the commonalities in the pathophysiology of the two diseases, and the methods used to treat both conditions.

PARKINSON'S DISEASE AND TYPE 2 DIABETES MELLITUS: A CONNECTION

An increased risk of PD is linked to T2DM.

Sandyk was the first to report a link between type 2 diabetes and Parkinson's disease in 1993. He found that those with both conditions had poorer motor symptoms and a lower response to therapy [18]. Although a more current estimate indicates that only approximately 20% of PD patients had obviously impaired glucose metabolism, a significant prevalence of poor glucose tolerance tests was found in the same study (50-80%) [19].

The correlation between type 2 diabetes and Parkinson's disease has been the subject of a great deal of research in the years that followed. The results of various prospective cohort studies show that type 2 diabetes is linked to a higher risk of Parkinson's disease [20-22]. For instance, one US prospective study indicated that type 2 diabetics were 40% more likely to acquire PD [21], and a big Finnish study indicated that individuals with T2DM had an 85% greater chance of developing PD [20]. Patients with type 2 diabetes mellitus had a 28% increased chance of developing PD, according to a 2016 meta-analysis that compiled effect estimates from seven cohort studies that looked at the general population [23].

There is evidence between type 2 diabetes and an increased risk of Parkinson's disease (PD), according to observational studies that have used various research approaches. An elevated risk of PD of 32% was found to be connected with type 2 diabetes, according to a comprehensive study that used routinely collected health record data in the UK [24]. The same holds true for Taiwan, where a retrospective study indicated a 23% higher risk of PD in T2DM patients [25], and Denmark, where a case-control study indicated a 36% higher risk of PD in T2DM patients [26]. Although multiple studies have shown that type 2 diabetes raises the chance of acquiring Parkinson's disease, the actual risk of developing the disease in persons with type 2 diabetes seems to be less than 1%, notwithstanding these connections. One study found that out of 2,017,115 people with type 2 diabetes, 14,252 (or 0.7% of the total) also had PD [24].

Because of the potential for bias and confounding in observational research, it is unclear if the correlation between type 2 diabetes and Parkinson's disease reflects a real causal relationship between the two diseases. Patients with type 2 diabetes may be at increased risk for developing PD due to the use of oral anti-hyperglycemic medications, which could obscure any links between the two conditions. There is some evidence from a variety of trials that GLP-1 agonists, metformin, and thiazolidinediones may lower the incidence of PD in type 2 diabetic individuals [27–31]. Other vascular risk factors or a high body mass index (BMI) are examples of confounders that may skew impact estimates because of their connections with type 2 diabetes and Parkinson's disease [20, 32, 33].

Several more factors can also contribute to bias in observational research. There may be bias in enhanced medical surveillance due to the higher likelihood of patients with T2DM having increased interaction with healthcare providers [22]. Reverse causality is another potential source of bias; for example, a correlation between PD and an increased likelihood of type 2 diabetes diagnosis. The hypoglycemic state is regulated by insulin receptors in the substantia nigra, which are implicated in food behavior promotion. Consequently, glycaemic regulation may be affected by dopaminergic neuronal loss [22]. When the first symptoms of Parkinson's disease (PD) manifest, it is well-known that a significant number of dopaminergic neurons have already died out. Thus, even in prospective studies with lengthy follow-up periods, it is challenging to reduce the impact of reverse causation [22].

Longer follow-up periods in prospective cohort studies increase the likelihood of participant dropout and bias due to attrition. The consequence will be a loss of precision without biassing the effect estimate if the probability of loss to follow-up does not relate to exposure, in this example diabetes.

The effect estimate could be skewed in either direction, though, if diabetes is linked to a higher or lower likelihood of staying under follow-up, which is a possible association.

There has not always been a favorable link between type 2 diabetes and Parkinson's disease, but that is generally what the research mentioned above have found. Recent cross-sectional research using the NEDICES database found no evidence of a connection between type 2 diabetes and Parkinson's disease [34]. Patients with type 2 diabetes for more than ten years may be at increased risk for PD, according to a subanalysis [34]. On the other hand, a different US prospective cohort study failed to discover a substantial link between type 2 diabetes and the risk of Parkinson's disease [35]. A meta-analysis of fourteen case-control studies found that type 2 diabetes was linked to a lower incidence of PD (summary odds ratio 0.75) [36], further complicating matters. Type 2 diabetes was also discovered to be inversely related to PD in a recent large-scale cross-sectional investigation that relied on self-report data [37]. Nevertheless, in addition to the aforementioned biases in cohort studies, there may be additional design difficulties in cross-sectional and retrospective case-control studies that impact results.

When it comes to type 2 diabetes and Parkinson's disease, various groups have discussed how pooled impact estimates from cohort studies and case-control studies differ. From the prospective cohort studies, a meta-analysis of four investigations found a pooled risk ratio for PD in diabetic patients of 1.37; from the case-control studies, an inverse connection (pooled odds ratio of 0.56) between diabetes and PD was described [32]. After that, researchers analyzed data from nine case-control studies and four cohort studies, finding pooled effect estimates of 0.72 and 1.31, respectively, [38]. Even later, the same occurrence was found in the aforementioned meta-analyses as well as in separate analyses of seven cohort studies (RR1.37) and fourteen case-control studies (OR0.75) [23, 36]. Differences in impact sizes across studies are usual, but a stark reversal in direction calls for more investigation.

Survival bias, an issue in studies using a retrospective case-control design, may account for the discrepancy between case-control and cohort studies. The inverse association between type 2 diabetes and peripheral vascular disease (PD) in these contexts has received little attention up until now, but it may be due to the higher mid-life mortality rate among diabetic patients [36].

This possibility was investigated by selecting the case-control studies that were part of the meta-analyses conducted by Cereda et al., 2011, Noyce et al., 2012, and Lu et al., 2014. Each study's odds ratio for PD risk was plotted against the mean age of participants (Fig. 1). research with the oldest participants had the highest odds ratio for PD, whereas research with the youngest participants had the lowest. Since most people have diabetes in their mid-to late-life years and PD in their late-to-old-age years, this may suggest that the risk of PD grows with the length of time that people are exposed to type 2 diabetes. The low incidence of PD in mid-life and premature mortality in people with T2DM before they acquire PD could potentially explain, in part, the inverse correlation in studies with youngest mean age. Evidence suggests that the risk of early death is higher for people diagnosed with type 2 diabetes before the age of 45 compared to those diagnosed after the age of 45 [39]. In addition, comorbidities including nephropathy and cardiovascular disease, which raise the risk of early mortality, are more common in younger people diagnosed with type 2 diabetes [40, 41].

Hyperglycemia accelerates the course of Parkinson's disease.

Research has shown that type 2 diabetes worsens the PD phenotype, including cognitive impairment [42–45], axial motor symptoms (gait abnormalities and postural instability), and the initial report by Sandyk [18].

Among PD severity measures, such as the motor component of the Unified Parkinson Disease Rating Scale (UPDRS) and the Hoehn and Yahr stage, a case-control study found that individuals with type 2 diabetes who went on to develop PD had higher scores [46]. Patients with both PD and type 2 diabetes mellitus (T2DM) were found to have motor issues an average of 12 months sooner, regardless of medication or other disease variables, according to another case-control study of 72 patients with PD [47]. Results from cognitive tests administered at the bedside, striatal dopamine transporter availability measured by 18F-FP-CIT PET imaging, cortical thickness measured by MRI, and disease severity evaluated in a retrospective cohort study of PD patients were considered. All four outcomes were significantly impacted negatively by the presence of T2DM, according to the investigators [33]. Also lending credence to the idea that the disease progresses more rapidly in type 2 diabetics is a prospective cohort study that discovered reduced binding of the striatal dopamine transporter and accelerated deterioration in motor and cognitive function in these patients [48]. Some research suggests that the more severe phenotype may be mediated by microvascular illness rather than striatal dopamine or even cholinergic deficiencies, so these traits are not always caused by dopamine depletion [43, 44].

Research on structural PD alterations in patients with concomitant type 2 diabetes has made use of magnetic resonance imaging (MRI). Cortical atrophy is more pronounced in PD patients with type 2 diabetes compared to those without the disease, according to a cross-sectional research [49]. Perhaps indicating a more rapid deterioration in executive function, these results were most pronounced in the prefrontal cortex of the brain [49]. Cortical thinning in the right inferior temporal cortex was shown to be substantially more common in PD patients with type 2 diabetes compared to those without the disease, according to a separate study [33]. These findings and the clinical variables that correlate with them require further replication. Several neurodegenerative illnesses are characterized by an increase in cerebrospinal fluid tau, a fluid biomarker that indicates the death of neurons. Therefore, it is a general indicator of how bad a neurodegenerative process is. Compared to PD patients without type 2 diabetes, those with the disease exhibited elevated tau CSF levels, according to a recent cross-sectional study that used data from the Parkinson's Progression Markers Initiative [48]. In other neurodegenerative disorders, researchers have found that patients with mild cognitive impairment who also have type 2 diabetes had a greater quantity of tau protein in their cerebrospinal fluid (CSF) [50].

Type 2 diabetes mellitus and parkinson's disease share mechanisms in pathophysiology.

Common pathogenic pathways of insulin resistance in the brain and throughout the body

There is mounting epidemiological data linking PD with T2DM, and there is also mounting experimental evidence suggesting that the disease processes and pathways may overlap. One of the hallmarks of type 2 diabetes for quite some time now is systemic insulin resistance. Neurodegenerative disorders, including Alzheimer's disease (AD) and other dementias [51], and Parkinson's disease (PD) [52], are associated with insulin resistance in the brain, according to recent investigations. Insulin resistance, whether systemic or local, may contribute to brain disease. Possible mechanisms by which systemic insulin resistance manifests include hyperglycemia and its complications [10], microvascular illness, chronic inflammation, and blood brain barrier dysfunction; comorbidities like hypertension, dyslipidaemia, and renal impairment [51] can exacerbate these issues. Protein aggregation, localized insulin resistance in the brain, and impaired clearance pathways can all operate independently of systemic insulin resistance [51, 53].

Type 2 diabetes and Parkinson's disease may share a same etiology: insulin dysregulation.

Both the basal ganglia [4] and the substantia nigra [59] express insulin receptors; these are the regions of the brain that Parkinson's disease patients often experience the greatest damage to. Insulin resistance may lead to decreased insulin-dependent dopamine release in the striatum [62], decreased dopamine turnover [61], and decreased expression of surface dopamine transporters in the striatum [60], according to studies conducted in animal models. One of the most popular animal models for Parkinson's disease is MPTP-treated rats, which generate parkinsonism through oxidative stress in dopaminergic neurons, leading to mitochondrial malfunction and cell death [63]. The observation that mice treated with MPTP show concurrent elevations in the production of pro-inflammatory cytokines and α-synuclein in both the pancreas and the midbrain suggests the possibility of organ-specific connections between PD and type 2 diabetes [64].

So far, human volunteers have only been used in a small number of mechanistic research. Insulin receptor mRNA levels were shown to be lower in postmortem human brains with PD compared to control brains in a 1996 study [65]. This was likely linked to neuronal death in the substantia nigra. These results, however, are not easily interpretable owing to methodological shortcomings and a limited sample size. On the other hand, insulin resistance was observed to be increased in the brains of PD patients, according to a functional brain imaging study that included 63 aged adults [52]. To deepen our understanding, future human studies should investigate the shared pathogenesis of insulin dysregulation and PD.

Amyloid aggregation occurs in PD and T2DM

Misfolded proteins can accumulate to create amyloid aggregates; this is a hallmark of both type 2 diabetes and Parkinson's disease. Cellular malfunction and mortality are caused by the aggregation of islet amyloid polypeptide (IAPP) in pancreatic β cells in type 2 diabetes [66, 67]. Lewy bodies, the pathogenic characteristic of PD, are formed when α-synuclein aggregates into oligomeric and then fibrillar structures, as previously mentioned [68].

According to a recent study, there is cross-reactivity between IAPP and α-synuclein, and it was shown that IAPP in type 2 diabetes can lead to α-synuclein aggregation [69]. Pancreatic proximity ligation tests provided further proof of protein-protein interaction [70]. Pancreatic β-cells in most individuals with PD or T2DM contained aggregates of phosphorylated α-synuclein, and deposits of α-synuclein were found to be co-localized and interact with IAPP. A different research found that the insulin degrading enzyme (IDE) can attach to α-synuclein oligomers and thereby prevent α-synuclein aggregation [53]. Insulin resistance can potentially increase the risk of PD or worsen the disease in type 2 diabetic patients by inhibiting IDE and leading to the development of α-synuclein fibrils [53].

In a separate study, researchers used co-immunoprecipitation studies to determine that α-synuclein interacts with Kir6.2 to decrease insulin secretion. Kir6.2 is a subunit of the ATP-sensitive potassium channel in pancreatic beta cells [71]. There may be a role for neuronal Kir6.2 in Parkinson's disease [72], as it is implicated in the downregulation of dopamine release in the brain. The PI3K/Akt pathway, which is implicated in increasing α-synuclein production, IDE aggregation and inactivation, and GSK3β activation, was shown in another work conducted in an MPTP animal model [73]. A research that looked at PD brains after death found that α-synuclein and GSK3β levels were higher, and that tau hyperphosphorylation was also higher in PD patients [74].

Inflammation throughout the body and activation of microglia raise the danger of type 2 diabetes and Parkinson's disease.

In the brain and spinal cord live immune cells called microglia, which are mononuclear and phagocytic. By releasing neuroprotective substances, they aid in synaptic repair and are typically implicated in the elimination of injured neurons [75]. Both inflammatory and anti-inflammatory phenotypes of microglia activation are possible. As an illustration, microglia can be induced to activate their inflammatory response and release pro-inflammatory cytokines such TNFα, interleukin (IL) 1β, and IL6, which in turn drive neuroinflammation, when exposed to lipopolysaccharide [76]. Increased microglial activation was detected on PET imaging in a study of fourteen PD patients [77]. Research has demonstrated that individuals with Parkinson's disease (PD) have elevated levels of inflammatory mediators including IL1β, IL6, and TNFα in their brains, which is a result of microglial activation and the subsequent release of inflammatory cytokines [78].

Prolonged microglial activation may have detrimental effects on PD progression [80], whereas initial microglial activation is typically linked with neuroprotection [79]. The NFκB and PI3K/Akt pathways, which govern microglial activation and the production of inflammatory mediators, are impacted by insulin resistance, which in turn affects neuroinflammation [76] (Fig. 2). Furthermore, it has been observed that inflammatory cytokines like TNFα can cause IRS1 to become inactive, which therefore prevents the activation of downstream mediators, creating a vicious loop [57]. Advanced glycation end-products (AGEs) can be formed in several parts of the brain, including the substantia nigra, in individuals with type 2 diabetes due to insulin resistance [4]. The interaction between AGEs and their receptor, RAGE, triggers subsequent pathways that cause oxidative stress, inflammation, and the death of neurons [81]. Lewy bodies include AGEs in addition to α-synuclein, which is an intriguing finding [16]. In multiple ways, glycated α-synuclein can exacerbate the course of PD. The production of α-synuclein oligomers and the induction of cross-links by glycation enhances the aggregation of α-synuclein. These smaller aggregations of α-synuclein seem to be more harmful than bigger ones [81]. In addition, the process of glycation prevents the normal clearance of α-synuclein, which is controlled by ubiquitin, proteasomes, and lysosomes, leading to the buildup of α-synuclein [16]. The glycation agent methylglyoxal (MGO) hinders the ubiquitin-proteasome system, which is responsible for breaking down α-synuclein. This leads to an increase in the buildup of α-synuclein, which could exacerbate the progression of Parkinson's disease [81].

The role of oxidative stress and mitochondrial dysfunction in the development of type 2 diabetes and Parkinson's disease was

When mitochondrial proteins aren't working properly, it leads to more oxidative stress and cell death. By targeting complex I, the initial enzyme in the mitochondrial respiratory chain route, MPTP causes neuronal death and neurodegeneration in animal models of Parkinson's disease [13]. Type 2 diabetes and Parkinson's disease may overlap symptoms of mitochondrial dysfunction [82]. Excessive oxidative stress is associated with impaired insulin signaling in PD [84, 85], and a new study demonstrated that prolonged insulin resistance in diabetic db/ db mice can lead to mitochondrial breakdown and degeneration of dopaminergic neurons [86]. The PI3K/Akt pathway is involved in the inhibition of FOXO1 by IRS1 and IRS2, according to studies conducted in rodent models [85, 87]. This leads to dysfunctional ATP synthesis, fatty acid oxidation, ROS formation, and oxidative stress. It is probable that mitochondrial dysfunction and oxidative stress play a significant role in the etiology of PD and may be relevant to the association with type 2 diabetes, but the precise process by which these factors contribute to PD is still unknown.

Insulin resistance impairs synaptic plasticity in PD

When dopamine levels drop in Parkinson's disease, synaptic plasticity occurs, leading to an increase in the expression of factors that inhibit movement and a decrease in the expression of factors that promote movement [88]. Synaptic remodeling has a role in both the development and storage of memories, as do the two primary components of synaptic plasticity, long-term depression (LTD) and long-term potentiation (LTP) [89]. For long-term memory consolidation, dendritic regeneration, neuronal shape reconfiguration, and synaptic plasticity via actin aggregation, the activation of mTORC1 and mTORC2 must occur simultaneously [90].

Through direct activation of glutamate NMDA receptors [57] and an increase in the extra-synaptic trafficking of GluA1 AMPA receptors in neurons [91], which is important in boosting synaptic strength and regulating LTP [92], insulin increases NMDA-mediated neurotransmission. Synaptic transmission was reported to be impaired in streptozotocin-induced diabetic rats due to a decrease in NMDA and AMPA receptor expression [93].

The common pathophysiological processes linking T2DM and PD offer new avenues for research into the use of T2DM therapeutic approaches repurposed for use in PD.

References:

[1]. Tysnes OB, Storstein A (2017) Epidemiology of Parkinson's disease, J Neural Transm 124, 901–905. [DOI] [PubMed] [Google Scholar]

[2]. Dorsey ER, Elbaz A, Nichols E, Abd-Allah F, Abdelalim A, Adsuar JC, Ansha MG, Brayne C, Choi JYJ, Collado-Mateo D, Dahodwala N, Do HP, Edessa D, Endres M, (2018) Global, regional, and national burden of Parkinson's disease, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016, Lancet Neurol 17, 939–953. [DOI] [PMC free article] [PubMed] [Google Scholar]

[3]. Marras C, Beck JC, Bower JH, Roberts E, Ritz B, Ross GW, Abbott RD, Savica R, Van Den Eeden SK, Willis AW, Tanner CM (2018) Prevalence of Parkinson's disease across North America, NPJ Parkinsons Dis 4, 21. [DOI] [PMC free article] [PubMed] [Google Scholar]

[4]. Athauda D, Foltynie T (2016) Insulin resistance and Parkinson's disease: A new target for disease modification?, Prog Neurobiol 145-146, 98–120. [DOI] [PubMed] [Google Scholar]

[5]. Dunn L, Allen GFG, Mamais A, Ling H, Li A, Duberley KE, Hargreaves IP, Pope S, Holton JL, Lees A, Heales SJ, Bandopadhyay R (2014) Dysregulation of glucose metabolism is an early event in sporadic Parkinson's disease, Neurobiol Aging 35, 1111–1115. [DOI] [PMC free article] [PubMed] [Google Scholar]

[6]. Zheng Y, Ley SH, Hu FB (2018) Global aetiology and epidemiology of type 2 diabetes mellitus and its complications, Nat Rev Endocrinol 14, 88–98. [DOI] [PubMed] [Google Scholar]

[7]. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ (2010) Chapter 1: Epidemiology of type 1 diabetes, Endocrinol Metab Clin North Am 39, 481–497. [DOI] [PMC free article] [PubMed] [Google Scholar]

[8]. Witoelar A, Jansen IE, Wang Y, Desikan RS, Gibbs JR, Blauwendraat C, Thompson WK, Hernandez DG, Djurovic S, Weale M (2017) Genome-wide pleiotropy between Parkinson disease and autoimmune diseases, JAMA Neurol 74, 780–792. [DOI] [PMC free article] [PubMed] [Google Scholar]

[9]. Rugbjerg K, Friis S, Ritz B, Schernhammer ES, Korbo L, Olsen JH (2009) Autoimmune disease and risk for Parkinson disease, Neurology 73, 1462–1468. [DOI] [PMC free article] [PubMed] [Google Scholar]

[10]. Li X, Sundquist J, Sundquist K (2012) Subsequent risks of Parkinson disease in patients with autoimmune and related disorders: A nationwide epidemiological study from Sweden, Neurodegener DIs 10, 277–284. [DOI] [PubMed] [Google Scholar]

[11]. Santiago JA, Potashkin JA (2013) Shared dysregulated pathways lead to Parkinson’s disease and diabetes, Trends Mol Med 9, 176–186. [DOI] [PubMed] [Google Scholar]

[12]. Hölscher C (2014) Drugs developed for treatment of diabetes show protective effects in Alzheimer’s and Parkinson’s diseases, Acta Physiol Sin 66, 497–510. [PubMed] [Google Scholar]

[13]. Aviles-Olmos I, Limousin P, Lees A, Foltynie T (2013) Parkinson’s disease, insulin resistance and novel agents of neuroprotection, Brain 136, 374–384. [DOI] [PubMed] [Google Scholar]

[14]. Craft S, Watson GS (2004) Insulin and neurodegenerative disease: Shared and specific mechanisms, Lancet Neurol 3, 169–178. [DOI] [PubMed] [Google Scholar]

[15]. Biosa A, Outeiro TF, Bubacco L, Bisaglia M (2018) Diabetes mellitus as a risk factor for Parkinson’s disease: A molecular point of view, Mol Neurobiol 55, 8754–8763. [DOI] [PubMed] [Google Scholar]

[16]. Konig A, Miranda HV, Outeiro TF (2018) Alpha-synuclein glycation and the action of anti-diabetic agents in Parkinson’s disease, J Parkinsons Dis 8, 33–43. [DOI] [PMC free article] [PubMed] [Google Scholar]

[17]. Palleria C, Leporini C, Maida F, Succurro E, De Sarro G, Arturi F, Russo E (2016) Potential effects of current drug therapies on cognitive impairment in patients with type 2 diabetes, Front Neuroendocrinol 42, 76–92. [DOI] [PubMed] [Google Scholar]

[18]. Sandyk R (1993) The relationship between diabetes mellitus and Parkinson’s disease, Int J Neurosci 69, 125–130. [DOI] [PubMed] [Google Scholar]

[19]. Marques A, Dutheil F, Durand E, Rieu I, Mulliez A, Fantini ML, Boirie Y, Durif F (2018) Glucose dysregulation in Parkinson’s disease: Too much glucose or not enough insulin?, Parkinsonism Relat Disord 5, 122–127. [DOI] [PubMed] [Google Scholar]

[20]. Hu G, Jousilahti P, Bidel S, Antikainen R, Tuomilehto J (2007) Type 2 diabetes and the risk of Parkinson’s disease, Diabetes Care 30, 842–347. [DOI] [PubMed] [Google Scholar]

[21]. Xu Q, Park Y, Huang X, Hollenbeck A, Blair A, Schatzkin A, Chen H (2011) Diabetes and risk of Parkinson’s disease, Diabetes Care 34, 910–915. [DOI] [PMC free article] [PubMed] [Google Scholar]

[22]. Driver JA, Smith A, Buring JE, Gaziano JM, Kurth T, Logroscino G (2008) Prospective cohort study of type 2 diabetes and the risk of Parkinson’s disease, Diabetes Care 31, 2003–2005. [DOI] [PMC free article] [PubMed] [Google Scholar]

[23]. Yue X, Li H, Yan H, Zhang P, Chang L, Li T (2016) Risk of Parkinson disease in diabetes mellitus, Medicine (Baltimore) 95, e3549. [DOI] [PMC free article] [PubMed] [Google Scholar]

[24]. De Pablo-Fernandez E, Goldacre R, Pakpoor J, Noyce AJ, Warner TT (2018) Association between diabetes and subsequent Parkinson disease, Neurology 91, e139–142. [DOI] [PubMed] [Google Scholar]

[25]. Yang YW, Hsieh TF, Li CI, Liu CS, Lin WY, Chiang JH, Li TC, Lin CC (2017) Increased risk of Parkinson disease with diabetes mellitus in a population-based study, Medicine (Baltimore) 96, e5921. [DOI] [PMC free article] [PubMed] [Google Scholar]

[26]. Schernhammer E, Hansen J, Rugbjerg K, Wermuth L, Ritz B (2011) Diabetes and the risk of developing Parkinson's disease in Denmark, Diabetes Care 34, 1102–1108. [DOI] [PMC free article] [PubMed] [Google Scholar]

[27]. Lu M, Su C, Qiao C, Bian Y, Ding J, Hu G (2016) Metformin prevents dopaminergic neuron death in MPTP/P-induced mouse model of Parkinson's disease via autophagy and mitochondrial ROS clearance, Int J Neuropsychopharmacol 19, pyw047. [DOI] [PMC free article] [PubMed] [Google Scholar]

[28]. Hunter RL, Dragicevic N, Seifert K, Choi DY, Liu M, Kim HC, Cass WA, Sullivan PG, Bing G (2007) Inflammation induces mitochondrial dysfunction and dopaminergic neurodegeneration in the nigrostriatal system, J Neurochem 100, 1375–1386. [DOI] [PubMed] [Google Scholar]

[29]. Athauda D, Foltynie T (2017) Protective effects of the GLP-1 mimetic exendin-4 in Parkinson's disease, Neuropharmacology 136, 260–270. [DOI] [PubMed] [Google Scholar]

[30]. Brauer R, Bhaskaran K, Chaturvedi N, Dexter DT, Smeeth L, Douglas I (2015) Glitazone treatment and incidence of Parkinson's disease among people with diabetes: A retrospective cohort study, PLOS Med 12, e1001854. [DOI] [PMC free article] [PubMed] [Google Scholar]

[31]. Brakedal B, Flønes I, Reiter SF, Torkildsen Ø, Dölle C, Assmus J, Haugarvoll K, Tzoulis C (2017) Glitazone use associated with reduced risk of Parkinson's disease, Mov Disord 32, 1594–1599. [DOI] [PMC free article] [PubMed] [Google Scholar]

[32]. Cereda E, Barichella M, Pedrolli C, Klersy C, Cassani E, Caccialanza R, Pezzoli G (2011) Diabetes and risk of Parkinson's disease: A systematic review and meta-analysis, Diabetes Care 34, 2614–2623. [DOI] [PMC free article] [PubMed] [Google Scholar]

[33]. Chung SJ, Jeon S, Yoo HS, Kim G, Oh JS, Kim JS, Evans AC, Sohn YH, Lee PH (2018) Detrimental effect of type 2 diabetes mellitus in a large case series of Parkinson's disease, Parkinsonism Relat Disord 64, 54–59. [DOI] [PubMed] [Google Scholar]

[34]. De Pablo-Fernandez E, Sierra-Hidalgo F, Benito-León J, Bermejo-Pareja F (2017) Association between Parkinson's disease and diabetes: Data from NEDICES study, Acta Neurol Scand 136, 732–736. [DOI] [PubMed] [Google Scholar]

[35]. Palacios N, Gao X, Mccullough ML, Jacobs EJ, Patel A V, Mayo T, Schwarzschild MA, Ascherio A (2011) Obesity, diabetes, and risk of Parkinson's disease, Mov Disord 26, 2253–2259. [DOI] [PMC free article] [PubMed] [Google Scholar]

[36]. Lu L, Fu DL, Li HQ, Liu AJ, Li JH, Zheng GQ (2014) Diabetes and risk of Parkinson's disease: An updated meta-analysis of case-control studies, PLoS One 9, e85781. [DOI] [PMC free article] [PubMed] [Google Scholar]

[37]. Heilbron K, Noyce AJ, Fontanillas P, Alipanahi B, Nalls MA, Cannon P (2019) The Parkinson's phenome-traits associated with Parkinson's disease in a broadly phenotyped cohort, NPJ Parkinsons Dis 5, 4. [DOI] [PMC free article] [PubMed] [Google Scholar]

[38]. Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, Schrag A (2012) Meta-analysis of early nonmotor features and risk factors for Parkinson disease, Ann Neurol 72, 893–901. [DOI] [PMC free article] [PubMed] [Google Scholar]

[39]. Hui Y, Wang J, An Y, Gong Q, Li H, Zhang B, Shuai Y, Chen Y, Hu Y, Li G (2019) Premature death and risk of cardiovascular disease in young-onset diabetes: A 23-year follow-up of the Da Qing Diabetes Study, Endocrine 65, 46–52. [DOI] [PubMed] [Google Scholar]

[40]. Saydah SH, Siegel KR, Imperatore G, Mercado C, Gregg EW (2019) The cardiometabolic risk profile of young adults with diabetes in the U.S, Diabetes Care 42, 1895–1902. [DOI] [PubMed] [Google Scholar]

[41]. Gregg EW, Zhuo X, Cheng YJ, Albright AL, Narayan KMV, Thompson TJ (2014) Trends in lifetime risk and years of life lost due to diabetes in the USA, 1985-2011: A modelling study, Lancet Diabetes Endocrinol 2, 867–874. [DOI] [PubMed] [Google Scholar]

[42]. Bosco D, Plastino M, Cristiano D, Colica C, Ermio C, De Bartolo M, Mungari P, Fonte G, Consoli D, Consoli A, Fava A (2012) Dementia is associated with Insulin Resistance in patients with Parkinson's Disease, J Neurol Sci 315, 39–43. [DOI] [PubMed] [Google Scholar]

[43]. Kotagal V, Albin RL, Müller MLTM, Koeppe RA, Frey KA, Bohnen NI (2013) Diabetes is associated with postural instability and gait difficulty in Parkinson disease, Parkinsonism Relat Disord 19, 522–526. [DOI] [PMC free article] [PubMed] [Google Scholar]

[44]. Bohnen MI, Kotagal V, Muller MLTM, Koeppe RA, Scott PJ, Albin RL, Frey KA, Petrou M (2014) Diabetes mellitus is independently associated with more severe cognitive impairment in Parkinson disease, Parkinsonism Relat Disord 20, 1394–1398. [DOI] [PMC free article] [PubMed] [Google Scholar]

[45]. Giuntini M, Baldacci F, Del Prete E, Bonuccelli U, Ceravolo R (2014) Diabetes is associated with postural and cognitive domains in Parkinson's disease. Results from a single-center study, Parkinsonism Relat Disord 20, 671–672. [DOI] [PubMed] [Google Scholar]

[46]. Cereda E, Barichella M, Cassani E, Caccialanza R, Pezzoli G (2012) Clinical features of Parkinson disease when onset of diabetes came first: A case-control study, Neurology 78, 1507–1511. [DOI] [PubMed] [Google Scholar]

[47]. Mohamed Ibrahim N, Ramli R, Koya Kutty S, Shah SA (2018) Earlier onset of motor complications in Parkinson's patients with comorbid diabetes mellitus, Mov Disord 33, 1967–1968. [DOI] [PubMed] [Google Scholar]

[48]. Pagano G, Polychronis S, Wilson H, Giordano B, Ferrara N, Niccolini F, Politis M (2018) Diabetes mellitus and Parkinson disease, Neurology 90, e1654–e1662. [DOI] [PubMed] [Google Scholar]

[49]. Petrou M, Davatzikos C, Hsieh M, Albin R, Kotagal V, Müller M, Koeppe RA, Herman WH, Frey KA, Bohnen NI (2016) Diabetes, gray matter loss and cognition in the setting of Parkinson Disease, Acad Radiol 23, 577–581. [DOI] [PMC free article] [PubMed] [Google Scholar]

[50]. Moran C, Beare R, Phan TG, Bruce DG, Callisaya ML, Srikanth V (2015) Type 2 diabetes mellitus and biomarkers of neurodegeneration, Neurology 85, 1123–1130. [DOI] [PMC free article] [PubMed] [Google Scholar]

[51]. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, Craft S, Gandy S, Buettner C, Stoeckel LE, Holtzman DM, Nathan DM (2018) Brain insulin resistance in type 2 diabetes and Alzheimer disease: Concepts and conundrums, Nat Rev Neurol 14, 168–181. [DOI] [PMC free article] [PubMed] [Google Scholar]

[52]. Morris JK, Vidoni ED, Perea RD, Rada R, Johnson DK, Lyons K, Pahwa R, Burns JM, Honea RA (2014) Insulin resistance and gray matter volume in neurodegenerative disease, Neuroscience 270, 139–147. [DOI] [PMC free article] [PubMed] [Google Scholar]

[53]. Sharma AN, Ligade SS, Sharma JN, Shukla P, Elased KM, Lucot JB (2015) GLP-1 receptor agonist liraglutide reverses long-term atypical antipsychotic treatment associated behavioral depression and metabolic abnormalities in rats, Metab Brain Dis 30, 519–527. [DOI] [PubMed] [Google Scholar]

[54]. Yao WD, Gainetdinov RR, Arbuckle MI, Sotnikova TD, Cyr M, Beaulieu JM, Torres GE, Grant SGN, Caron MG (2004) Identification of PSD-95 as a regulator of dopamine-mediated synaptic and behavioral plasticity, Neuron 41, 625–638. [DOI] [PubMed] [Google Scholar]

[55]. Zhao WQ, Chen H, Quon MJ, Alkon DL (2004) Insulin and the insulin receptor in experimental models of learning and memory, Eur J Pharmacol 490, 71–81. [DOI] [PubMed] [Google Scholar]

[56]. Brunet A, Bonni A, Zigmond MJ, Lin MZ, Juo P, Hu LS, Anderson MJ, Arden KC, Blenis J, Greenberg ME (1999) Akt promotes cell survival by phosphorylating and inhibiting a forkhead transcription factor, Cell 96, 857–868. [DOI] [PubMed] [Google Scholar]

[57]. Hariharan M (2012) Effects of insulin on synapse formation and function; A possible role for insulin resistance. Dalhousie University Department of Biochemistry and Molecular Biology Available from: http://www.dt.co.kr/contents.html?article_no=2012071302010531749001

[58]. Wan Q, Xiong ZG, Man HY, Ackerley CA, Braunton J, Lu WY, Becker LE, MacDonald JF, Wang YT (1997) Recruitment of functional GABA(A) receptors to postsynaptic domains by insulin, Nature 388, 686–690. [DOI] [PubMed] [Google Scholar]

[59]. Unger JW, Livingston JN, Moss AM (1991) Insulin receptors in the central nervous system: Localization, signalling mechanisms and functional aspects, Prog Neurobiol 36, 343–362. [DOI] [PubMed] [Google Scholar]

[60]. Jones KT, Woods C, Zhen J, Antonio T, Carr K, Reith MEA (2017) Effects of diet and insulin on dopamine transporter activity and expression in rat caudate-putamen, nucleus accumbens and midbrain, J Neurochem 140, 728–740. [DOI] [PMC free article] [PubMed] [Google Scholar]

[61]. Baladi MG, Horton RE, Owens WA, Daws LC, France CP (2015) Eating high fat chow decreases dopamine clearance in adolescent and adult Male rats but selectively enhances the locomotor stimulating effects of cocaine in adolescents, Int J Neuropsychopharmacol 18, 1–11. [DOI] [PMC free article] [PubMed] [Google Scholar]

[62]. Stouffer MA, Woods CA, Patel JC, Lee CR, Witkovsky P, Bao L, Machold RP, Jones KT, De Vaca SC, Reith MEA, Carr KD, Rice ME (2015) Insulin enhances striatal dopamine release by activating cholinergic interneurons and thereby signals reward, Nat Commun 6, 8543. [DOI] [PMC free article] [PubMed] [Google Scholar]

[63]. Li Y, Perry T, Kindy MS, Harvey BK, Tweedie D, Holloway HW, Powers K, Shen H, Egan JM, Sambamurti K, Brossi A, Lahiri DK, Mattson MP, Hoffer BJ, Wang Y, Greig NH (2009) GLP-1 receptor stimulation preserves primary cortical and dopaminergic neurons in cellular and rodent models of stroke and Parkinsonism, Proc Natl Acad Sci U S A 106, 1285–1290. [DOI] [PMC free article] [PubMed] [Google Scholar]

[64]. Wang L, Zhai YQ, Xu LL, Qiao C, Sun XL, Ding JH, Lu M, Hu G (2014) Metabolic inflammation exacerbates dopaminergic neuronal degeneration in response to acute MPTP challenge in type 2 diabetes mice, Exp Neurol 251, 22–29. [DOI] [PubMed] [Google Scholar]

[65]. Takahashi M, Yamada T, Tooyama I, Moroo I, Kimura H, Yamamoto T, Okada H (1996) Insulin receptor mRNA in the substantia nigra in Parkinson's disease, Neurosci Lett 204, 201–204. [DOI] [PubMed] [Google Scholar]

[66]. Jaikaran ETAS, Nilsson MR, Clark A (2004) Pancreatic beta-cell granule peptides form heteromolecular complexes which inhibit islet amyloid polypeptide fibril formation, Biochem J 377, 709–716. [DOI] [PMC free article] [PubMed] [Google Scholar]

[67]. Wang H, Raleigh DP (2014) The ability of insulin to inhibit the formation of amyloid by pro-islet amyloid polypeptide processing intermediates is significantly reduced in the presence of sulfated glycosaminoglycans, Biochemistry 53, 2605–2614. [DOI] [PMC free article] [PubMed] [Google Scholar]

[68]. Spillantini MG, Schmidt ML, Lee VMY, Trojanowski JQ, Jakes R, Goedert M (1997) α-synuclein in Lewy bodies, Nature 388, 839–840. [DOI] [PubMed] [Google Scholar]

[69]. Horvath I, Wittung-Stafshede P (2016) Cross-talk between amyloidogenic proteins in type-2 diabetes and Parkinson's disease, Proc Natl Acad Sci U S A 113, 12473–12477. [DOI] [PMC free article] [PubMed] [Google Scholar]

[70]. Martinez-Valbuena I, Amat-Villegas I, Valenti-Azcarate R, Del Mar Carmona-Abellan M, Marcilla I, Tuñon M-T, Luquin MR (2018) Interaction of amyloidogenic proteins in pancreatic β cells from subjects with synucleinopathies, Acta Neuropathol 135, 877–886. [DOI] [PubMed] [Google Scholar]

[71]. Vidal-Martinez G, Yang B, Vargas-Medrano J, Perez RG (2018) Could α-synuclein modulation of insulin and dopamine identify a novel link between parkinson's disease and diabetes as well as potential therapies? Front Mol Neurosci 11, 465. [DOI] [PMC free article] [PubMed] [Google Scholar]

[72]. Patel J, Witkovsky P, Coetzee W, Rice ME (2011) Subsecond regulation of striatal dopamine release by pre-synaptic KATP channels, J Neurochem 119, 721–736. [DOI] [PMC free article] [PubMed] [Google Scholar]

[73]. Duka T, Duka V, Joyce JN, Sidhu A (2009) α-synuclein contributes to GSK-3β-catalysed Tau phosphorylation in Parkinson's disease models, J Fed Am Soc Exp Biol 23, 2820–2830. [DOI] [PMC free article] [PubMed] [Google Scholar]

[74]. Wills J, Jones J, Haggerty T, Duka V, Joyce JN, Sidhu A (2010) Elevated tauopathy and alpha-synuclein pathology in postmortem Parkinson's disease brains with and without dementia, Exp Neurol 225, 210–218. [DOI] [PMC free article] [PubMed] [Google Scholar]

[75]. Imamura K, Hishikawa N, Sawada M, Nagatsu T, Yoshida M, Hashizume Y (2003) Distribution of major histocompatibility complex class II-positive microglia and cytokines profile of Parkinson's disease brains, Acta Neuropathol 106, 518–526. [DOI] [PubMed] [Google Scholar]

[76]. Kim DS, Choi H, Wang Y, Luo Y, Hoffer BJ, Greig NH (2017) A new treatment strategy for Parkinson's disease through the gut-brain axis: The glucagon-like peptide-1 receptor pathway, Cell Transplant 26, 1560–1571. [DOI] [PMC free article] [PubMed] [Google Scholar]

[77]. Bartels AL, Willemsen ATM, Doorduin J, de Vries EFJ, Dierckx RA, Leenders KL (2010) [11C]-PK11195 PET: Quantification of neuroinflammation and a monitor of anti-inflammatory treatment in Parkinson's disease?, Parkinsonism Relat Disord 16, 57–59. [DOI] [PubMed] [Google Scholar]

[78]. Chen H, O'Reilly EJ, Schwarzschild MA, Ascherio A (2008) Peripheral inflammatory biomarkers and risk of Parkinson's disease, Am J Epidemiol 167, 90–95. [DOI] [PubMed] [Google Scholar]

[79]. Chen Z, Jalabi W, Hu W, Park HJ, Gale JT, Kidd GJ, Bernatowicz R, Gossman ZC, Chen JT, Dutta R, Trapp BD (2014) Microglial displacement of inhibitory synapses provides neuroprotection in the adult brain, Nat Commun 5, 4486. [DOI] [PMC free article] [PubMed] [Google Scholar]

[80]. Sekiyama K, Sugama S, Fujita M, Sekigawa A, Takamatsu Y, Waragai M, Takenouchi T, Hashimoto M (2012) Neuroinflammation in Parkinson's disease and related disorders: A lesson from genetically manipulated mouse models of α-synucleinopathies, Parkinsons Dis 2012, 271732. [DOI] [PMC free article] [PubMed] [Google Scholar]

[81]. Vicente Miranda H, El-Agnaf OMA, Outeiro TF (2016) Glycation in Parkinson's disease and Alzheimer's disease, Mov Disord 31, 782–790. [DOI] [PubMed] [Google Scholar]

[82]. Schapira AH (2008) Mitochondria in the aetiology and pathogenesis of Parkinson's disease, Lancet Neurol 7, 97–109. [DOI] [PubMed] [Google Scholar]

[83]. Kleinridders A, Cai W, Cappellucci L, Ghazarian A, Collins WR, Vienberg SG, Pothos EN, Kahn CR (2015) Insulin resistance in brain alters dopamine turnover and causes behavioral disorders, Proc Natl Acad Sci U S A 112, 3463–3468. [DOI] [PMC free article] [PubMed] [Google Scholar]

[84]. Wang S, Zhang C, Sheng X, Zhang X, Wang B, Zhang G (2014) Peripheral expression of MAPK pathways in Alzheimer's and Parkinson's diseases, J Clin Neurosci 21, 810–814. [DOI] [PubMed] [Google Scholar]

[85]. Guo S, Copps KD, Dong X, Park S, Cheng Z, Pocai A, Rossetti L, Sajan M, Farese RV, White MF (2009) The Irs1 branch of the insulin signaling cascade plays a dominant role in hepatic nutrient homeostasis, Mol Cell Biol 29, 5070–5083. [DOI] [PMC free article] [PubMed] [Google Scholar]

[86]. Khang R, Park C, Shin JH (2015) Dysregulation of parkin in the substantia nigra of db/db and high-fat diet mice, Neuroscience 294, 182–192. [DOI] [PubMed] [Google Scholar]

[87]. Dong XC, Copps KD, Guo S, Li Y, Kollipara R, Depinho A, White MF (2008) Inactivation of hepatic Foxo1 by insulin signaling is required for adaptive nutrient homeostasis and endocrine growth regulation, Cell Metab 8, 65–76. [DOI] [PMC free article] [PubMed] [Google Scholar]

[88]. Zhai S, Tanimura A, Graves SM, Shen W, Surmeier DJ (2018) Striatal synapses, circuits, and Parkinson's disease, Curr Opin Neurobiol 48, 9–16. [DOI] [PMC free article] [PubMed] [Google Scholar]

[89]. Calabresi P, Mercuri NB, Di Filippo M (2009) Synaptic plasticity, dopamine and Parkinson's disease: One step ahead, Brain 132, 285–287. [DOI] [PubMed] [Google Scholar]

[90]. Thomanetz V, Angliker N, Cloëtta D, Lustenberger RM, Schweighauser M, Oliveri F, Suzuki N, Rüegg MA (2013) Ablation of the mTORC2 component rictor in brain or Purkinje cells affects size and neuron morphology, J Cell Biol 201, 293–308. [DOI] [PMC free article] [PubMed] [Google Scholar]

[91]. Passafaro M, Piãch V, Sheng M (2001) Subunit-specific temporal and spatial patterns of AMPA receptor exocytosis in hippocampal neurons, Nat Neurosci 4, 917–926. [DOI] [PubMed] [Google Scholar]

[92]. Grillo CA, Piroli GG, Lawrence RC, Wrighten SA, Green AJ, Wilson SP, Mott DD, Reagan LP (2015) Hippocampal insulin resistance impairs spatial learning and synaptic plasticity, Diabetes 64, 3927–3936. [DOI] [PMC free article] [PubMed] [Google Scholar]

[93]. Di Luca M, Ruts L, Gardoni F, Cattabeni F, Biessels GJ, Gispen WH (1999) NMDA receptor subunits are modified transcriptionally and post- translationally in the brain of streptozotocin-diabetic rats, Diabetologia 42, 693–701. [DOI] [PubMed] [Google Scholar]