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Parkinson disease among patients with diabetes mellitus

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Abstract
Background: Both diabetes mellitus (DM) & Parkinson disease (PD are common disorders. Variable neurologic consequences are common in diabetes including PD. Parkinson disease and DM have been linked through many epidemiologic studies but with conflicting conclusions that ranged from inverse association to positive association.
Aim of the study: To observe the proportion of DM among PD patients, and to study the variations in some demographic and clinical variables among them.
Patients and Method: a cross-sectional study enrolled 118 patients with PD who attended a tertiary neurology clinic over 9 months duration. The patients were divided into diabetic and nondiabetic and multivariate analysis was performed across some demographic and clinical features.
Results: This study enrolled 118 patients with PD; 29 of them was diabetic. Females was 56 (47.5%) and 62 male (52.5%) patients with a male: female ratio of 1.10. The mean PD duration was 4.9 years. Among diabetics, the male: female ratio dropped to 0.45 with statistical significance (p value = 0.007). The HY scale score medians and ranges was identical in both groups. There was a highly significant association between the early stage of Parkinson disease and diabetes duration below 10 years (p-value = 0.0001). Lower Hoehn and Yahr scale scores clustered around patients with less than 10 year diabetic history, while higher scores found in patients with more than 10 year diabetes history with a p-value of 0.0001.
Conclusion: Patients with concomitant DM and PD are predominantly females, had shorter disease duration and, had more severe clinical stage (especially when had DM for more than 10 years). However, causal relationship cannot be elucidated from our data.

Keywords: Parkinson disease, diabetes mellitus, epidemiology, clinical features

Introduction

Background

Both diabetes mellitus (DM) & Parkinson disease (PD) are common disorders with significant health & socioeconomic impacts. Variable neurologic consequences are common in diabetic patients, ranging from peripheral neuropathy [1] to Alzheimer disease [2]. Parkinson disease and DM have been linked through many epidemiologic studies but with conflicting conclusions [3, 4, 5] that ranged from inverse association to positive association.

Parkinson disease

Parkinson disease is a chronic, gradually progressive neurodegenerative disease. It is the second most common neurodegenerative disease in the world [6]. The disorder was first clearly described in 1817 by James Parkinson [7], however, it is thought that the disease was described more than 4000 years ago in the ancient Indian medical system, Ayurveda [8]. Traditionally, PD was considered a motor system disorder. However, it is now recognized to be a more complex disease with a magnitude of neuropsychiatric and non-motor clinical features [9].

Diabetes mellitus

Diabetes mellitus, on the other hand, is the most common chronic metabolic disorder with a significant public health problem worldwide with around 537 million people affected in 2021 [10]. It has scored the 9th global cause of death and the 8th global cause of disability-adjusted life years in 2019 [11]. It is a chronic disease that requires long-term medical attention to limit

the development of its devastating complications and to manage them when they do occur. The 2 main types of diabetes are type 1 and type 2. Other recognized types include secondary diabetes, gestational diabetes in addition to 5 diabetes subtypes: severe autoimmune diabetes (SAID), latent autoimmune diabetes in adults (LADA), severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), mild obesity-related diabetes (MOD), and, mild age-related diabetes (MARD). To be diagnosed with type 2 diabetes, the patient should meet the American Diabetes Association (ADA) criteria [12] (see diagnosis)

Type 2 diabetes mellitus (which is more common than type 1) consists of an array of dysfunctions characterized by hyperglycemia and resulting from the combination of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion.

Epidemiology

Parkinson's disease (PD) affects 1-2 per 1000 of the population at any time [13]. The prevalence of PD is increasing with age and it affects 1% of the population above 60 years [14]. Parkinson disease is rare before age of 50 years and reaches a prevalence of 4% in the highest age groups [15]. The annual incidence is thought to be 15 per 100,000 6. The mean age of onset is approximately 60 years while the mean age at diagnosis is 70.5 years [16]. Onset in persons younger than 40 years is relatively uncommon.

Parkinson disease is slightly more common in men with the lifetime risk of 2% in men and 1.3% in women, and the male:female ratio is estimated to be 1.46 [17,18]. No area of the world is immune to Parkinson disease [19]. In Iraq, there was 9777 cases and 299 deaths during 2016 [20].

According to the latest International Federation of Diabetes (IFD) updates, the number of people living with diabetes in 2021 is 537 million people 10 with an estimated prevalence of 9.3% [21]. The prevalence is higher in high-income (10.4%) than low-income countries (4.0%). In Iraq, around 1.4 million people have diabetes [22]. A local study including more than 5400 people in the city of Basrah, reported a 19.7% age-adjusted prevalence of diabetes in subjects aged 19 to 94 years [23, 24]. Regarding the prevalence of DM in patients with PD, figures are heterogeneous; ranging between 3.4 and 9.1% [25].

Pathology

Depletion of the neurotransmitter dopamine is the main neurochemical abnormality in PD. The substantia nigra pars compacta (SNc) is the principal source of dopaminergic neurons. These project mainly to the putamen and caudate. The extent of dopamine depletion in these structures correlates with neuronal loss in the SNc. The pathological changes of PD include cell loss in a specific distribution (mainly in the substantia nigra), the presence of Lewy bodies in surviving cells, and an undamaged striatum (putamen and caudate). Cell loss in excess of 50% of normal levels is required for clinical symptoms to develop and as much as 80% of dopamine may be lost in the striatum by the time that clinical symptoms emerge [26]. The gut microbiome and vitamin D levels may also play a role in the pathogenesis of PD [27, 28 29, 30].

With regard to diabetes, Type 1 diabetes mellitus (T1DM) comprises several diseases of the pancreatic ß cells which lead to an absolute insulin deficiency. This is usually considered to be the result of an autoimmune destruction of the pancreatic ß cells (type 1A). Some patients with T1DM with no evidence of ß cell autoimmunity have underlying defects in insulin secretion often from inherited defects in pancreatic ß cell glucose sensing and from other genetic or acquired diseases. On the other hand, type 2 diabetes mellitus (T2DM) is characterized by insulin resistance resulting from defects in the action of insulin on its target tissues (muscle, liver, and fat), but complicated by varying and usually progressive failure of beta cells' insulin secretary capacity. Most patients with T2DM in the US and Europe are overweight or obese, however in India and China, most T2DM patients have a lean body mass index (BMI), albeit with increased visceral and hepatic fat [31]. Although controversial, some evidence exists that coronavirus disease 2019 (COVID-19) may lead to the development of type 1 and type 2 diabetes. It has been theorized, for example, that diabetes arises when severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, binds "to angiotensin-converting enzyme 2 (ACE2) receptors in key metabolic organs and tissues, including pancreatic beta cells and kidneys [32]. The CoviDiab registry was established by an international group of diabetes researchers to gather data on COVID-19-related diabetes [33].

Common pathogenic mechanisms of both diabetes and PD

Several overlapping disease mechanisms have been identified including the following

Insulin resistance

Recent studies have found that insulin resistance is present in the brain in neurodegenerative diseases such as Alzheimer's disease (AD) [34], and PD [35, 36]. In addition to the known effects of systemic insulin resistance on the brain, local brain insulin resistance may act via protein deposition and aggregation, and failure of clearance mechanisms, independent of systemic insulin resistance [34].

Insulin dysregulation

Insulin receptors are expressed in the basal ganglia [37] and in the substantia nigra [38]. Animal studies have shown that insulin resistance may cause reduced expression of surface dopamine transporters in the striatum [39], reduced dopamine turnover, and reduced insulin-dependent dopamine release in the striatum [40]. A functional brain imaging study on 63 elderly subjects found that insulin resistance was increased in the brains of PD patients [35].

Amyloid aggregation

Amyloid aggregates are found in both T2DM and PD. In PD, α-synuclein aggregates into Lewy bodies, the pathological hallmark of PD. In T2DM, isl*et al*myloid polypeptide (IAPP) aggregation in pancreatic cells leads to cellular dysfunction and death [41]. A recent study found cross-reactivity between IAPP and α-synuclein and demonstrated that IAPP in T2DM can promote synuclein aggregation [42].

Microglial activation

Prolonged microglial activation may have deleterious effects on PD progression. Patients with PD have been shown to have high concentrations of inflammatory mediators such as interleukin (IL)-1, IL-6 and tumor-necrosis factor (TNF) in

the brain and increased microglial activation was found on PET imaging [43]. Insulin resistance has an effect on microglial activation and neuro-inflammation probably by the formation of advanced glycation end-products (AGEs) [37], including in regions of the brain such as the substantia nigra leading to oxidative stress, inflammation and neuronal cell death [44].

Insulin resistance impairs synaptic plasticity in PD

Insulin promotes NMDA-mediated neurotransmission by directly activating glutamate NMDA receptors and increasing the extra-synaptic transport of GluA1 AMPA receptors in neurons involved in increasing synaptic strength and regulating LTP 45. A study on streptozotocin-induced diabetic rats found that NMDA and AMPA receptor expression was reduced 46, impairing synaptic transmission.

Clinical features

The clinical features of PD can be categorized into motor, nonmotor, and premotor symptoms. Motor symptoms include cardinal motor symptoms (tremor, rigidity, bradykinesia, and postural instability) and secondary motor symptoms diminished arm swing, decreased blink rate, masked facies (hypomimia), decreased voice volume (hypophonia), and difficulty turning over in bed). The severity of motor symptoms appears to be an independent predictor of mortality in patients with PD [47].

Nonmotor symptoms are symptoms other than those involved in movement, such as tremor, rigidity, and bradykinesia. The impact from nonmotor symptoms

They include neuropsychiatric symptoms (depression, apathy, impulse control disorders, anxiety, psychosis, hallucinations, mood disorders, apathy, and abulia), cognitive symptoms (executive dysfunction, memory loss, and dementia), dysautonomic symptoms (orthostatic hypotension, constipation, urinary incontinence, sexual dysfunction, altered cardiac reflexes, olfactory dysfunction, gastrointestinal dysfunction, and sweating), sleep disorders (insomnia, somnolence, excessive daytime sleepiness, restless legs syndrome, sleep attacks, periodic limb movements of sleep, and rapid eye movement (REM) sleep behavior disorder), and sensory abnormalities (pain, numbness, fatigue, and olfactory impairment).

Premotor symptoms are defined as symptoms that predate motor symptoms of Parkinson disease and include constipation, anosmia, REM sleep behavior disorder, and depression. Some investigators categorized PD into a number of clinical subtypes [48]. The major subtypes are 1) Tremor-dominant PD, 2) Akinetic-rigid PD, and 3) Postural instability and gait difficulty subtype. Comparison studies suggested that tremor-dominant subtype was associated with slower progression and less neuropsychological impairment than the other two groups [49, 50].

Symptoms of T1DM include excessive excretion of urine (polyuria), thirst (polydipsia), constant hunger, weight loss, vision changes, and fatigue. These symptoms may occur suddenly. Symptoms of T2DM may be similar to those of type 1 diabetes, but are often less marked. As a result, the disease may be diagnosed several years after onset, after complications have already arisen [51].

Diagnosis

The diagnosis of PD remains a clinical one. However, diagnostic criteria are available. The most commonly used diagnostic criteria are the UK Parkinson Disease Society Brain Bank Diagnostic Criteria [52]. Recently, the International Parkinson and Movement Disorder Society (MDS) has released a new Clinical Diagnostic Criteria for Parkinson's disease (MDS-PD Criteria) [53]. The MDS criteria were designed for research use, but they also can be used as a general guide to clinical diagnosis of PD consequent to Lewy body pathology.

With regard to diabetes, the American Diabetes Association (ADA) criteria [12] is commonly used for diagnosis. They include:

Fasting plasma glucose level of 126 mg/dL or higher, 2 hour plasma glucose level of 200 mg/dL, or a random plasma glucose level of 200 mg/dL or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

Treatment

There are three therapeutic strategies for of PD. Neuroprotective or disease-modifying therapies: due to the protracted preclinical stage of PD is theoretically regarded an excellent candidate for neuroprotective therapeutic strategies. However, most studies are disappointing. Yet, rasagilin, a MAO-B inhibitor is a promising agent [54].

Symptomatic treatment of PD

Levodopa is still the gold standard of this strategy. Other agents commonly used include dopamine agonists, monoamine oxidase-B (MAO-B) inhibitors, COMT-inhibitors, amantadine and anticholinergics or combinations of these. All these agents Anticholinergic agents are commonly used to manage PD tremors and rigidity, but not for bradykinesia.

Surgical treatment of PD

Palliative surgical approaches (stereotactic thalamotomy, pallidotomy) have been replaced by deep brain stimulation (DBS) using implanted pulse generators implanted in thalamus, subthalamic nucleus, or globus pallidus internus.

The treatment of diabetes is more rapidly evolving. However, the main treatment strategies can be broadly categorized into direct insulin-replacement and indirect induction of insulin secretion and insulin-sensitizing agents with variable mechanisms.

Worth to mention, the dopamine agonist bromocriptine improves glycemic control in T2DM subjects [55] and was recently approved for adjunctive treatment of diabetes [56]

Aim of study

- To observe the proportion of DM among PD patients.
- To study the variations in some demographic features among them.
- To compare the variations in clinical severity scores (namely Hoen abd Yahr scale) beteween the two groups.

Patients and Methods

- **Study design:** cross-sectional study
- **Sample size:** 118 patients
- **Setting place and timetables:** we collected 118 patients who attended and registered at the movement disorders clinic and the outpatient clinic at Saad Al Witry hospital for neurosciences across the study duration (from 1st April 2021 and 1st January 2022).

- **Study population:** all the study population were 18 years or older, had normal neuroimaging and exclusively fulfilled the UK Parkinson Disease Society Brain Bank Diagnostic Criteria [52]. The diagnosis was made by senior neurologists with full history and clinical examination and the neuroimaging was reviewed by a senior radiologist. In addition to demographic data of age, sex and ethnicity, PD duration (defined since the time of diagnosis), age at PD diagnosis, and Hoehn and Yahr scale were registered for all patients. Comorbid DM diagnosis and duration were also registered to all patients. With regard to DM, diagnosis were registered according to patients reports and supported by applying the American Diabetes Association (ADA) criteria for DM diagnosis [12].

UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria 82

- **Step 1: Diagnosis of Parkinsonian Syndrome**
  Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) and at least one of the following: (Muscular rigidity, 4-6Hz resting tremor, Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction)
- **Step 2: Exclusion Criteria for Parkinson Disease**
  (History of repeated strokes with stepwise progression of parkinsonian features. History of repeated head injury. History of definite encephalitis. Oculogyric crises. Neuroleptic treatment at onset of symptoms. More than one affected relative. Sustained remission. Strictly unilateral features after 3 years. Supranuclear gaze palsy. Cerebellar signs. Early severe autonomic involvement. Early severe dementia with disturbances of memory, language, and praxis. Babinski sign. Presence of a cerebral tumor or communicating hydrocephalus on CT scan. Negative response to large doses of levodopa (if malabsorption excluded). MPTP exposure)
- **Step 3: Supportive Prospective Positive Criteria for Parkinson Disease**
  Three or more required for diagnosis of definite Parkinson disease (Unilateral onset. Resting tremor present, Progressive disorder, Persistent asymmetry affecting the side of onset most, excellent response (70-100%) to levodopa, severe levodopa-induced chorea, Levodopa response for 5 years or more, Clinical course of 10 years or more).

Hoehn and Yahr scale 83

- Unilateral involvement only usually with minimal or no functional disability
- Bilateral or midline involvement without impairment of balance
- **Bilateral disease:** mild to moderate disability with impaired postural reflexes; physically independent
- Severely disabling disease still able to walk or stand unassisted
- Confinement to bed or wheelchair unless aided

The American Diabetes Association (ADA) criteria

- Fasting plasma glucose level of 126 mg/dL or
- higher, 2 hour plasma glucose level of 200 mg/dL, or
- a random plasma glucose level of 200 mg/dL
- or higher in a patient with classic symptoms of hyperglycemia
- or hyperglycemic crisis

We excluded patients who had atypical or secondary parkinsonian syndromes, including those with abnormal neuroimaging, those who had PD onset before DM diagnosis or had the two diseases with less than one year between diagnoses (to minimize reverse causality); and, patients less than 18 years old.

Patients' ages were grouped into 4 (30-45 years, 46-64 years, 65-74 years, and more than 74 years). Parkinson disease duration were divided into 2 groups (less or equal to 5 years, and more than 5 years). Diabetes duration were divided into 2 groups (less than 10 years and more than 10 years).

Statistical analysis

The data were coded and each questionnaire assigned with a serial identifying number then entered by the researcher into the computer using Statistical Package for Social Sciences (SPSS) version 26 with the help of a specialist statistician. Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values). The significance of the difference in different percentages (qualitative data) was tested using the Pearson Chi-square test. Statistical significance was considered whenever the P-value was equal to or less than 0.05.

Results

Our study included 118 patients with confirmed PD. Of them, 56 (47.5%) female and 62 (52.5%) male patients with a male: female ratio of 1.10. Patients had different age groups, 5 patients were 30-45-year-old, 59 patients were from 46-64 years, 44 patients were from 65-74 years and older than 74 years were 10, with a mean age of 63.2 years and standard deviation 8.3 years. The mean age at PD onset was 58.34 years. About 69.5% of the patients had confirmed Parkinson disease since less than 5 years while chronic Parkinson disease patients were 30.5%. The mean duration of Parkinson disease was 4.9 years.

The majority of the study population [92 patients (78%)] were Arabs followed by 19 (16.1%) Kurdish and 7 (5.9%) Turkmen respectively. One-fourth of the study population was diabetics (Table 1).

Table 1: Some Demographic characteristics of participants (N=118)

Demographic characteristics		Number (N = 118)	%
Age	30-45 years old	5	4.2
	46-64 years old	59	50.0
	65-74 years old	44	37.3
	> 74 years old	10	8.5

Mean ± SD	63.25 ± 8.3		
Mean age at PD onset ± SD	58.34 ± 8.3		
Sex	Female	56	47.5
	Male	62	52.5
Ethnicity	Arab	92	78.0
	Kurd	19	16.1
	Turkmen	7	5.9
PD duration	≤ 5 years	82	69.5
	> 5 years	36	30.5
Mean ± SD	4.9±3.1		
Diabetes Mellitus		29	24.6

Of those who had DM, 20 patients (16.9%) had DM for less than 10 years and 9 patients (7.6%) were diabetic since more than 10 years ago (Figure 1).

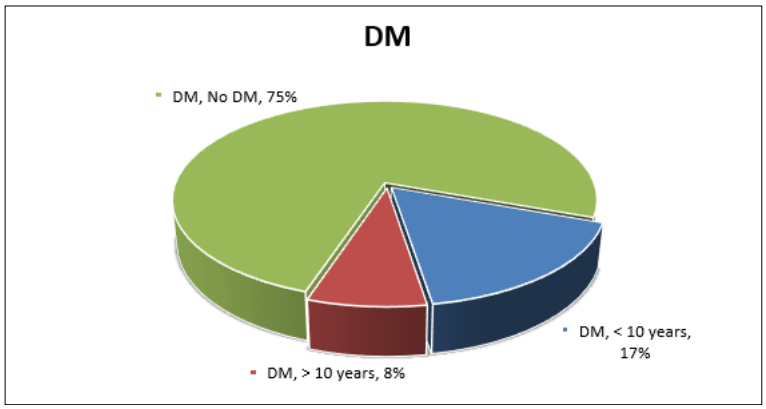

Fig 1: Pie chart show DM duration in Parkinson disease patients

Table 2 reveal that there is a strong relationship between the duration of Parkinson disease and sex; males were predominant in chronic Parkinson disease duration compared to females as p-value was less than 0.05. however, there were no statistically significant association between the PD duration and age, ethnicity or diabetes status (p-values were all more than 0.05).

Table 2: The effect of Parkinson disease duration on patients' variables (n= 118)

Variable		**Parkinson disease duration**		**P-value**
		≤ 5 years n=82 (100%)	**>5 years n=36 (100%)**	
Age Group	30-45 years old	4 (4.9%)	1 (2.8%)	0.195
	46-64 years old	43 (52.4%)	16 (44.4%)	
	65-74 years old	31 (37.8%)	13 (36.1%)	
	> 74 years old	4 (4.9%)	6 (16.7%)	
Sex	Female	46 (56.1%)	10 (27.8%)	0.005
	Male	36 (43.9%)	26 (72.2%)	
Ethnicity	Arab	64 (78.0%)	28 (77.8%)	0.718
	Kurd	14 (17.1%)	5 (13.9%)	
	Turkmen	4 (4.9%)	3 (8.3%)	
DM	No	62 (75.6%)	27 (75%)	0.944
	Yes	20 (24.4%)	9 (25%)	

The mean age did not show statistically significant difference among diabetic and non-diabetic patients. However, the male: female ratio dropped from 1.10 among the total study population to 0.45 among the diabetic patients, with statistical significance (p value = 0.007). In addition, the mean disease duration was shorter in DM group, and it did show statistical significance (p value= 0.035). However, diabetic patients had statistically insignificant higher mean age at disease onset. The HY scale score medians and ranges were identical (table 3).

Table 3: Characteristics of patients with PD alone and PD with DM

		PD non-DM n=89	**PD + DM n=29**	**P value**
Age (mean±SD)		62.3±8.40	66.03±7.55	0.261
Sex (male)		53	9	0.007
Age at PD onset		57.29	61.58	0.324
PD duration		5.04±2.91	4.45±3.76	0.035
PD duration (<5years)		62	20	0.558
HY scale	1	33	14	0.069
	2	27	5	
	3	14	2	
	4	15	8	
HY median score (range)		2 (1-4)	2 (1-4)	

Among 29 patients who had DM, there was statistically significant association between early Parkinson disease (PD duration <5 years) and early diabetes (DM duration < 10 years) with a p-value of 0.0001. Similarly, there was a statistically significant association between Hoehn and Yahr scale diabetes duration as lower scores clustered around patients with early diabetes, while higher scores found in patients with more durable disease (DM duration > 10 years) with a p-value of 0.0001 (Table 4).

Table 4: The effect of diabetes duration on patients' variables (n= 29)

Variable		Diabetes duration		P-value
		< 10 years n=20 (100%)	> 10 years n=9 (100%)	
Sex	Female	16 (80%)	4 (44.4%)	0.056
	Male	4 (20%)	5 (55.5%)	
Age Group	46-64 years old	11 (55%)	3 (33.3%)	0.006
	65-74 years old	9 (45%)	2 (22.2%)	
	> 74 years old	0 (0%)	4 (44.4%)	
Parkinson disease duration	< 5 years	19 (95%)	1 (11.1%)	0.0001
	> 5 years	1 (5%)	8 (88.9%)	
Hoehn and Yahr scale	1	14 (70%)	0 (0%)	0.0001
	2	4 (20%)	1 (11.1%)	
	3	2 (10%)	0 (0%)	
	4	0 (0%)	8 (88.9%)	

Discussion

This cross-sectional study, that performed to address the effect of DM on PD, involved 118 PD patients; 29 of them was diabetic (24.9%), 62 males (52.5%) and 56 females (47.5%). The male:female ratio was 1.10:1 for the total study population, but it dropped to 0.45:1 in DM group. The mean age of patients was 63.2 years without difference between diabetics and non-diabetics. Parkinson disease duration mean was longer in non-diabetic group (5.04 years) as compared to DM group (4.45 years). Most patients with PD had mild disease and scored 1 in modified Hoehn and Yahr scale (37.3%, n=44) without significant difference between diabetics and non-diabetics. However, inside the DM group, higher scores clustered in patients with DM for more than 10 years.

Gang Hu *et al*, conducted a prospective study with over 18 years follow-up 84. Of those who had PD (n=633), only 3.7% had T2DM (n=24). In another prospective study with over 9 years follow-up, conducted by Xu *et al*, out of 1565 patients who had PD, 172 patients was found to be diabetic prior to PD diagnosis (10.9%) 56. However, in many studies, including ours, the proportion of diabetics among PD patients ranged between as low as 4% to as high as 29.2%, [60] [63] [65] [74] [85] [86]. This disparity may be related to sampling bias. However, the above-mentioned reports, including ours, may support the notion of true association between PD and diabetes.

According to Tysnes and Storstein review, PD affects men slightly more than women 6. This difference has recently been attributed, using a neuromelanin imaging study, to a bigger substantia nigra in women. They attributed this possibly secondary to estrogen effects via optimizing iron metabolism [87,88]. Our finding of higher female preponderance in diabetic patients with PD can be attributed to sampling issues as the study is a clinic-based cross-sectional one. However, insulin resistance and estrogen deficiency do occur concomitantly [89], leading to the possible "double-hit" phenomenon in affected ladies and might explain such reversed male to female ratios.

Consistent with Bohnen *et al*, we found no significant mean age difference between diabetic and non-diabetic groups [64]. However, Erro *et al* found that PD in context of T2DM occurred in younger patients and they attributed that to genetic factors [90]. On the contrary, Chung *et al* found that PD patients with DM were older at the onset of PD symptoms [69].

The mean PD duration ranged in most similar studies from 18 months up to 7 years as far as our knowledge. None of them found any mean PD duration difference across DM vs non-DM groups [64, 66, 36]. Unique to this study, we found that diabetics had shorter mean disease duration. This can be attributed, among other factors, to survival effect where diabetics with PD might have higher mortality and pass away before reaching such long disease durations.

The risk of having PD in diabetics was found to be limited to those with diabetes for more than 10 years in a large retrospective study conducted by Xu *et al* [56]. This may explain our finding of significant older age of PD ons*et al*mong diabetics, and consequently, shorter disease duration.

Parkinson disease progression was found to be fastened in patients with concomitant DM. Mohamed Ibrahim *et al*. conducted a study of 72 PD patients (21 with concomitant T2DM) reported that those with concomitant T2DM developed motor complications on average 12 months earlier, independent of medication or other disease factors [67]. In their study, they relayed on MDS-UPDRS.

Skorvanek *et al* conducted a cross sectional study to clarify the reliability of HY score in reflecting PD severity. They concluded that PD severity levels, as defined by HY stages, reflect differences in all aspects of disease measured by the MDS-UPDRS; with scores for all 4 parts increase significantly with every HY stage. Furthermore; the study found that all MDS-UPDRS sub-scores increased significantly only in the first 15 years of the disease, reaching a relative plateau afterward [91]. In addition, and despite that HY scale being mostly driven by motor symptoms, especially postural instability and mobility; it is considered the reference standard for disability and impairment measures 83 and objective motor performance 92. It also correlates well with neuroimaging studies of dopaminergic loss [93], and carries prognostic significance [94].

Cereda *et al*. conducted a case-control study and concluded that patients with T2DM who subsequently developed PD scored higher on PD severity scales including the motor component of the Unified Parkinson Disease Rating Scale (UPDRS) and Hoehn and Yahr stage 66. In their study about PD and DM, Pagano *et al*, chose patients with HY scale as low as 2, so that, no meaningful comparison can be elicited across HY scores [68]. On the other hand, Petrou *et al*. conducted their study among patients with full range HY scores but they found no score difference between DM and non-DM PD groups [36]. In our study, HY scores did not changed among diabetics when compared to non-diabetics. However, higher scores clustered among those with DM duration more than 10 years, stressing again the concept of increasing risk is proportional to DM exposure duration.

The critique of the Hoehn and Yahr scale (HY) prepared by the Movement Disorder Society Task Force for Rating Scales for Parkinson's disease (PD) recommends using the original version of the scale rather than the modified HY scale. In addition, they recommend using medians and ranges rather than median and standard deviations [83]. In this regard, our results showed identical medians and ranges in both study groups.

The present study has several strengths, including face-to-face clinic interview. Most of patients had file records which offer more

reliability about time frames and clinical stage rather than depending on patients' or physicians' memory. Clinical scores were recorded by interviewers and imaging studies were reviewed by senior radiologist. The study design did exclude the issue of reverse association as we excluded those who had PD diagnosis became first. Finally, it is the first study to address such association in the Iraqi population.

The following limitations might be considered when interpreting our conclusions: First, we might miss some cases of asymptomatic diabetes as we did not perform fasting glucose of glycosylated hemoglobin measurements to those patients who denied having diabetes at base line. In addition, and although we registered the duration of diabetes; we did not have data on severity of diabetes, glucose control, or the drugs used to treat diabetes. Furthermore, we did not measure UPDRS among patients and did not tested treatment types and response. Besides, we cannot exclude a shared environmental or a genetic background of diabetes and PD.

Conflict of Interest

Not available

Financial Support

Not available

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