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Is insulin resistance associated with fatigue, the severity of the disease and motor disability in idiopathic Parkinson's disease?

İdiopatik Parkinson hastalığında insülin direnci yorgunluk, hastalık şiddeti ve motor yetersizlik ile ilişkili midir?

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Abstract

Aim: Abnormal glucose metabolism is known to potentially correlate abnormal mitochondrial function and neurodegenerative processes. The purpose of the study was to determine the association of insulin resistance on fatigue, the severity of the disease and motor disability in patients with idiopathic Parkinson's disease (IPD).

Methods: A total of 50 patients diagnosed with IPD by a neurologist from university hospital were enrolled to study. Demographic characteristics (age, gender, height, weight and body mass index (BMI) were recorded. Patients were allocated into two groups by insulin resistance (IR), named insulin resistance (+) as group 1 (IR+) (n=30 (10 female, 20 male), age=66 years, height=169 cm, weight=75 kg, BMI=26.6 kg/m^2 (median)) and insulin resistance (-) as group 2 (IR-) (n=20 (8 female, 12 male), age=63.5 years, height=168 cm, weight=75 kg, BMI=26.95 kg/m^2 (median)). The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) test was used for assessment of insulin resistance. The disease severity was assessed by the Modified Hoehn and Yahr Scale, motor disability was assessed by Movement Disorders Society-revised Unified PD Rating Scale (MDS-UPDRS) and fatigue was rated by Fatigue Severity Scale (FSS).

Results: MDS-UPDRS scores were statistically significantly different between the groups of IPD patients with IR (+) and IR (-) (P=0.034). Modified Hoehn - Yahr (P=0.300) and FSS (P=0.147) scores were not statistically significantly different between the same groups.

Conclusion: This study suggests that IR may have a role for disease severity in patients with IPD. In patients with IPD, insulin resistance should be questioned and considered in the treatment and rehabilitation program.

Keywords: Idiopathic Parkinson's disease, Insulin resistance, Fatigue, Motor disability

Öz

Amaç: Anormal glukoz metabolizmasının, anormal mitokondriyal fonksiyon ve nörodejeneratif süreçler ile potansiyel olarak ilişkili olduğu bilinmektedir. Çalışmanın amacı idiopatik Parkinson hastalığı (İPH) olan hastalarda insulin direnci ile yorgunluk, hastalık şiddeti ve motor yetersizlik ile ilişkisini incelemektir.

Yöntemler: Çalışmaya üniversite hastanesine başvuran ve nörolog tarafından İPH tanısı alan toplam 50 hasta alındı. Hastaların demografik özellikleri (yaş, cinsiyet, boy, kilo, vücut kitle indeksi (VKİ) kaydedildi. Hastalar insulin direnci (IR) olup olmamasına göre iki gruba ayrıldı. İnsülin direnci olan grup, grup 1 (IR+) (n=30 (10 kadın, 20 erkek, yaş= 66, boy=169 cm, kilo=75 kg, VKI=26,6 kg/m2 (medyan)), insulin direnci olmayan grup, grup 2 (IR-) (n=20 (8 kadın, 12 erkek, yaş=63,5, boy=168 cm, kilo=75 kg, VKI=26,95 kg/m2 (medyan)). İnsülin direncinin değerlendirilmesi için Homeostatic Model of Assessment-Insulin Resistance (HOMA-IR) testi yapıldı. Hastalık şiddeti Modified Hoehn-Yahr skalası ile, motor yetersizlik Birleşik Parkinson Hastalığı Derecelendirme Ölçeği (MDS-UPDRS) skalası ile, yorgunluk ise Yorgunluk Etki Ölçeği ile değerlendirildi.

Bulgular: MDS-UPDRS skorları IR (+) ve IR (-) olan İPH hasta grupları arasında istatistiksel olarak anlamlı farklılık gösterdi (P=0,034). Modifiye Hoehn - Yahr (P=0,300) ve FSS (P=0,147) skorları açısından gruplar arasında istatistiksel olarak anlamlı farklılık bulunmadı.

Sonuç: Bu çalışma, İPH hastalarında IR'nin hastalık şiddeti için bir rolü olabileceğini düşündürmektedir. İPH'li hastalarda insülin direnci sorgulanmalı ve tedavi ve rehabilitasyon programında düşünülmelidir.

Anahtar kelimeler: İdiopatik Parkinson hastalığı, İnsülin direnci, Yorgunluk, Motor yetersizlik

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Introduction

Idiopathic Parkinson's disease (IPD) is the most common age-related movement disorder associated with neurodegenerative disease. IPD is characterized by bradykinesia, resting tremor, rigidity and motor symptoms of postural instability at the advanced stage. Also nowadays it is known that psychiatric disorders including dementia, depression and anxiety, autonomic disorders such as sleep disturbances, orthostatic hypotension, abnormal thermoregulation and urinary problems, blurry vision caused by impaired accommodation, olfactory disorders, dysphasia, craniofacial disorders such as sialorrhea and non-motor symptoms like fatigue may also occur before and during the disease. Non-motor symptoms as well as motor symptoms contribute to the morbidity associated with disease. Fatigue is a non-motor symptom that occurs in nearly 50% of IPD sufferers [1].

Alterations in endocrine functions and low-grade systemic inflammation are the main drivers of insulin resistance. Several research studies in epidemiology, molecular genetics and cell biology have identified relations between Parkinson's disease and insulin resistance. Recent studies have showed common cellular pathways that potentially relate neurodegenerative processes with abnormal mitochondrial function and abnormal glucose metabolism. This evidence defining that peroxisome proliferator activated receptor gamma coactivator 1-α, a key regulator of enzymes involved in mitochondrial respiration and insulin resistance, is potentially very important in the pathogenesis of neurodegeneration in Parkinson's disease [2]. These biological systems have also been linked to fatigue symptoms. Importantly, inflammation is associated with substantial changes in the biosynthesis of monoamines including dopamine, noradrenaline and serotonin which are involved in the pathophysiology of fatigue symptoms. We know that in PD, dopaminergic midbrain neurons degenerate, cause to cerebral dopamine decrease.

Review of the relevant literature clearly shows that there is a need to identify the exact role of these pathways and to what extent insulin resistance plays a role in the development of fatigue, the severity of the disease and motor disability in IPD.

The mechanism underlying fatigue development in insulin resistance is considered to involve endocrine/metabolic and inflammatory processes [3]. Therefore, the association of fatigue with insulin resistance in IPD patients is examined in the current study with the aim to support this consideration.

Materials and methods

Study design and subjects

A cross-sectional observational study enrolled patients diagnosed with IPD who were being followed at the Neurology outpatient clinics at SANKO University Research and Practice Hospital. The patients were consecutively included in the study by the same Neurologist.

IPD diagnosis was confirmed using the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [4].

As a result of the power analysis with 80% effect size with 0.05 error margin, total sample size was determined as 42 patients.

A total of 50 patients (32 males, 18 females) without a diagnosis of dementia or any neurological and/or systemic disorders that could cause fatigue were enrolled in the study. Individuals with a psychiatric illness that could interfere with the ability to accurately understand and complete the questionnaire were excluded as were those being treated with neuroleptic drugs and antidepressants (Figure 1). Demographic characteristics of all participants were recorded. Age, gender, marital status, education level, known comorbidities, duration of IPD, initial motor symptoms, anti-Parkinson medications taken and clinical findings were recorded through face-to-face communication with patients.

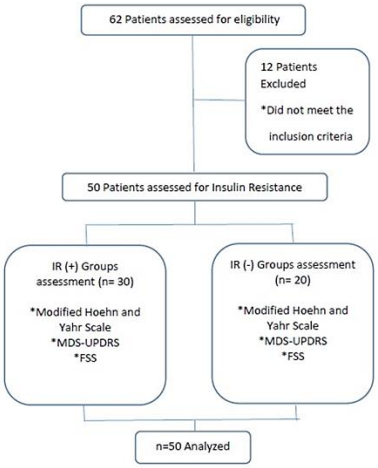

Figure 1: Flowchart of the study

Metabolic analysis

The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) test was performed for measurement of insulin resistance. The body weight, height and body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) were recorded for all patients. Blood samples were obtained and centrifuged at room temperature for 5 minutes at 3000 RPM. Extracted sera were kept in ice bags and transferred to deep freezers for storage at -80°C on the same day. Blood samples obtained after 8-10 hours of fasting were used for HOMA-IR test. For this test, fasting blood glucose and fasting insulin values were multiplied and the product was divided by 405. A cut-off value of 2.5 was chosen for the test. Insulin resistance was considered positive if the test result was greater than 2.5 [5].

Enrolled patients were divided into two groups, according to their insulin resistance: Group 1; IR(+): 30 IPD patients with insulin resistance by HOMA-IR test, Group 2; IR(-): 20 IPD patients without insulin resistance by HOMA-IR test.

Clinical assessment

The disease severity was assessed by the Modified Hoehn and Yahr Scale. The Hoehn and Yahr scale is used to describe the severity Parkinson disease. The scale was originally described in 1967 and had 5 stages, 1 to 5. It has since been modified with the addition of stages 1.5 and 2.5 to account for the intermediate course of Parkinson disease [6]. 1 means: Unilateral involvement only and symptoms are mild. 5 means: Wheelchair bound or bedridden unless aided.

Motor disability was assessed with Movement Disorders Society-revised Unified PD Rating Scale (MDS-UPDRS) [7]. The scale is considered to be the gold standard since it provides comprehensive information in many directions between the

clinical measures used in the evaluation. Scale includes 4 parts, respectively; Part I: Nonmotor Aspects of Experiences of Daily Living, Part II: Motor Experiences of Daily Living, Part III: Motor Examination, Part IV: Motor Complications. The sum of the scores of the first 3 parts gives a total score. Low scores reflect less disability.

Fatigue assessment

Fatigue was rated using the Fatigue Severity Scale (FSS). The FSS, which was published in 1989 by Krupp, has 9 items. For each question, the patient is asked to choose a number from 1 to 7 that indicates how much the patient agrees with each statement, where 1 indicates strong disagreement and 7 indicates strong agreement. A score of 4 or higher generally indicates severe fatigue [8].

The study was approved by the SANKO University Ethics Committee for Clinical Research Trials (2018/04;14. 19.04.2018) and conducted in accordance with the principles set forth in the Declaration of Helsinki. All participants gave their written informed consent before their participation in the study and were free to withdraw at any time.

Statistical analysis

IBM SPSS 24 package program was used for statistical analyses (SPSS Inc., Chicago, IL, USA). Descriptive statistics were given as median (minimum–maximum), number and percentage. Normality of data was evaluated with Shapiro-Wilk test. Mann-Whitney U test was used for comparing of two groups' MDS-UPDRS, Modified Hoehn-Yahr and FSS values. For all analyses $P<0.05$ was considered statistically significant.

Results

Demographic features

In this study 50 IPD patients, 30 (60%) were insulin resistance-positive (IR+) of whom 10 (33.3%) were females and 20 (66.7%) were males, the remaining 20 patients (40%) did not show insulin resistance (IR-), of whom 8 (40%) were females, 12 (60%) were males. Table 1 shows the demographic characteristics of groups. There was no statistically significant difference between the two groups with respect to body weight, height or age distribution.

Table 1: Demographics of the study groups

Variables	Group IR+ (n=30) Median (min-max)	Group IR- (n=20) Median (min-max)	*P*-value
Age (years)	66 (42-82)	63,5 (37-85)	0.165
Height (cm)	169 (156-185)	168 (150-176)	0.105
Weight (kg)	75 (63-95)	75 (59-85)	0.371
BMI (kg/m^2)	26.6 (20.8-31.7)	26.9 (20.7-35.6)	0.751
HOMA-IR	5.8 (2.5-23.6)	2.1 (1.1-2.4)f	<0.001

BMI: Body Mass Index, IR(+) with Insulin Resistance, IR(-) without Insulin Resistance, HOMA-IR: The Homeostatic Model Assessment of Insulin Resistance

Clinical and metabolic features

Analysis of the results showed that MDS-UPDRS scores were statistically significantly different between IR (+) and IR (-) groups ($P=0.034$). However, Modified Hoehn - Yahr ($P=0.300$) and FSS ($P=0.147$) scores were not statistically significantly different between the groups (Table 2).

Table 2: Clinical characteristics of the groups

Variables/Test	Group IR(+) (n=30) Median (min-max)	Group IR(-) (n=20) Median (min-max)	*P*-value
MDS-UPDRS	40 (18-59)	38 (12-73)	0.034
Modified Hoehn - Yahr	2.1 (1-5)	2.2 (1-5)	0.300
FSS	6 (1-7)	5.1 (1-7)	0.147

MDS-UPDRS: Movement Disorders Society-revised Unified PD Rating Scale, FSS: Fatigue Severity Scale, IR(+) with Insulin Resistance, IR(-) without Insulin Resistance

Discussion

In this study, we investigated association of insulin resistance on fatigue, the severity of the disease and motor disability in 50 patients with Idiopathic Parkinson's Disease. The results of this study showed that IPD patients with IR (+) (group 1) had higher motor disability which was assessed by MDS-UPDRS, than the IR (-) (group 2). Both group showed no significant difference in fatigue symptoms and disease severity.

The incidence of IR is 25% in healthy individuals, 60-75% in individuals with impaired glucose tolerance and 60-75% in patients with Type 2 diabetes [9]. In our study 30 patients (60%) insulin resistance was positive (IR+), the remaining 20 patients (40%) had negative insulin resistance (IR-).

Fatigue is a non-motor symptom of Parkinson's disease with a prevalence as high as 58% among affected patients [10]. More than 50% of patients with Parkinson's disease consider fatigue as one of the most disabling symptoms of PD but the causative mechanisms underlying fatigue have not been fully elucidated [11]. While peripheral mechanisms are partly involved in the pathophysiology of fatigue that occurs in CNS disorders, central abnormalities play a more significant role. Immune system dysregulation, impaired nerve conduction, neuroendocrine/neurotransmitter dysregulation, autonomic nervous system (ANS) involvement and energy depletion have all been implicated in the pathogenesis [12].

Proposed physiological mechanisms of fatigue associated with IPD include the role of circulating proinflammatory cytokines, impaired functioning of nigrostriatal and extrastriatal dopaminergic pathways and nondopaminergic (particularly serotonergic) pathways and involvement of the autonomic nervous system [13,14].

Based on this information, we investigated the relationship between fatigue in patients with IPD who did not have insulin resistance and had insulin resistance. In our current study, showed no significant difference in fatigue between IR (+) and IR (-) patients with IPD. However, this is the first study for literature which has specifically examined the relationship between fatigue and insulin resistance in IPD.

Recent studies have demonstrated that insulin has multiple functions in the brain and aberrant insulin signaling may have a role in the development of Alzheimer's disease and IPD. Insulin performs a variety of biological effects through its interaction with the insulin receptor, a transmembranous glycoprotein receptor tyrosine kinase. Downstream intracellular substrates of activated insulin receptor activate the PI3kinase/Akt pathway, thereby affect cellular functions. Additionally, mammalian target of rapamycin (mTOR) which is involved in the activation of PI3K/Akt via insulin induction is an important molecular junction of aging, diabetes and neurodegenerative diseases. It has been shown that the lifespan extension due to caloric limitation may be based on to suppression of mTOR, a cellular sensor of the nutrient environment of the organism. Although its interest to human lifespan remains unclear, the effect of caloric limitation-starvation on aging has been observed in a range of species from yeast to mammals [15]. Therefore, it is of great interest to determine whether therapeutically progressing

insulin resistance may affect disease severity and longevity in patients with IPD.

Bosso et al. [16] investigated that relationship between dementia and insulin resistance in patients with IPD. In this study, they showed that patients with dementia have higher prevalence of abnormal glucose metabolism, mainly IR, than nondemented patients. In other study, Schelp et al. [17] showed that there was a role of body composition, ageing and insulin resistance on amnestic dementia impairment in Parkinson's disease. Nakatsuji et al. [18] studied correlation of insulin resistance and motor function in spinal bulbar muscular atrophy (SBMA). In this study, they showed that insulin resistance is intensified in SBMA patients. Moreover, the degree of insulin resistance was strongly correlated with the severity of motor dysfunction in SBMA.

Although there were studies that showed the correlation of IR and motor disability in several neurodegenerative diseases, studies investigating the relationship between IPD patients and IR have not examined the relationship between disease severity and motor disability. In our study we investigated relationship with insulin resistance and motor disability. We found a significant difference in MDS-UPDRS scores between IR(+) and IR(-) patients. Increased insulin resistance has been associated with greater motor disability in IPD patients thoughtful of the idea of IR's effects on molecular pathways.

In literature, there were studies that investigating the relationship between IR and neurodegenerative disorders. Ruiz-Arguelles et al. [19] showed that insulin resistance in patients with Multiple Sclerosis is associated to the severity of the disease. But there was no significant difference on severity of disease between groups.

Fatigue is an important symptom that affects quality of life in patients with IPD, also characterization and assessment of fatigue would be helpful for proper diagnosis and management of fatigue. Therapeutic strategies for fatigue can only be developed after precise identification of its pathophysiology.

The limitation of this study is first the small number of patients. Also the effect of the drugs causing fatigue cannot be completely excluded in the neuropathy, cardiac and pulmonary system for reasons of association yet. Data obtained from the study examining the effect of insulin resistance on the development of fatigue indicated the need to elucidate the pathophysiology of fatigue as well as the need to demonstrate the association between fatigue and insulin resistance at the molecular level in IPD. Another limitation includes the lack of consideration of gender differences. Further studies can be planned by eliminating the effect of gender on insulin resistance. In addition, the effects of body mass index on insulin resistance should be considered in future studies.

In conclusion, in this study, a significant difference was found between insulin resistant and non-insulin resistant groups with respect to MDS-UPDRS scores. It has been recognized that increased insulin resistance results in greater motor disability through molecular mechanisms in patients with IPD.

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