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# Correlation of high glycemic index diets with the occurrence of Parkinson's disease and involvement of glycation end products: A case-control study

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## *Abstract*

*Objective:* This study aimed to determine the correlation of glycemic load (GL) and glycemic index (GI) with Parkinson's disease (PD) in terms of the serum levels of methylglyoxal (MGO), oligomeric α-synuclein (α-syn), and DJ-1. *Methods:* In this case-control study (40 PD and 40 healthy individuals) dietary intake of the participants was assessed for a 4-day period (24-hour dietary recall questionnaire and three-day food record). Serum levels of MGO, oligomeric α-syn, and DJ-1 were measured by ELISA. Adjusted odds ratios (ORs) for PD were estimated according to quantiles of dietary factors and serum factors. *Results:* Serum levels of oligomeric α-syn ($p = 0.003$) and DJ-1 ($p < 0.001$) were significantly higher in the patients compared to the healthy participants. The participants with PD had higher GI levels ($p = 0.02$) compared to healthy individuals. A positive correlation emerged between the risks of PD and GI (OR: 10.05; [95%CI: 1.94, 51.95] for the highest vs. the lowest quintile, p for trend 0·028). In the patients, level of GI, but not GL, correlated with MGO [β (95% CI): 0.27 (0.02, 1.98); $p = 0.04$], oligomeric α-syn [β (95% CI): 0.34 (0.01, 0.17); $p = 0.03$], and DJ-1 [β (95% CI):0.39 (0.04, 0.30); $p = 0.01$] positively and significantly. Moreover, serum levels of MGO, oligomeric α-syn, and DJ-1 were associated with each other significantly and positively ($p < 0.05$). *Conclusions:* It can be concluded that high GI diets are positively correlated with PD, more possibly by the increased α-syn oligomerization and advanced glycated end products (AGEs) formation.

*Keywords:* alpha-synuclein, DJ-1, glycemic index, glycemic load, methylglyoxal, Parkinson's disease

## INTRODUCTION

Parkinson's disease (PD) is one of the most common neurodegenerative diseases. Its prevalence increases with aging and it is estimated that about 1% of people over the age of 60 years old are affected by the disease.[1,2] Despite many uncertainties on the pathologic mechanisms, the oligomerization of α-synuclein (α-syn), which is a presynaptic protein, and formation of Lewy bodies in the cytoplasm of nerve cells are known as major hallmarks of PD. The formation of the advanced glycated end products (AGEs) is a possible factor that may contribute to PD.[3,4] AGEs can be originated from glucose, glyceraldehyde or from α-dicarbonyls such as methylglyoxal (MGO). Accordingly, it can be said that MGO, as a potent source of AGEs, can be involved in the pathogenesis of age-related diseases such as PD.[5] In this regard, some studies suggested that diets that rapidly deliver sugar into blood, called high glycemic index (GI) diet, may be associated with age-related diseases via increasing MGO levels and subsequent generation of AGEs in the brain.[6] In PD, it is suggested that excessive levels of MGO can react with lysine residues of α-syn, exacerbate the oligomerization of α-syn, and impair oligomeric α-syn clearance through the modification of oligomeric α-syn into cross-linked and non-degradable forms.[7] Altogether, it is speculated that high GI carbohydrate may contribute to the occurrence or progression of PD by increasing MGO levels and subsequently glycation and oligomerization of α-syn.[6]

DJ-1 is another protein involved in PD pathogenesis that can protect nerve cells against the toxicities of MGO and oligomeric α-syn. In other words, it can protect α-syn monomers from oligomerization.[8] Furthermore, DJ-1, as an anti-MGO enzyme, is able either to act as glutathione-independent methylglyoxalase that makes MGO

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in the non-toxic form or to act as an antioxidant that modulates MGO-related oxidative stress.[9,10]

Although previous studies have suggested a potential role for glycation in the pathogenesis of PD, less is known about the association of GI and GL with serum levels of MGO, oligomeric α-syn, DJ-1, and the subsequent PD occurrence. Thus, the current study aimed to assess any possible correlation among GL, GI, PD, and serum levels of MGO, oligomeric α-syn, and DJ-1.

## METHODS

*Study population*

This cross-sectional study included 40 patients with PD (27 men and 13 women) aged over 18 years old who were diagnosed using the United Kingdom PD Society Brain Bank criteria.[11] The control group included 40 age- and sex-matched healthy people. The participants with PD were selected by convenience sampling from an outpatient neurology clinic, and the control group's participants were recruited from healthy people attending routine health surveillances. This study was approved by the Ethical Committee of the Tabriz University of Medical Sciences, Tabriz, Iran. Thereafter, written informed consent was obtained from all the participants at the beginning of the study. The exclusion criteria included the followings: having parkinsonism or other major neurological disorders such as Alzheimer's disease and Huntington disease, having diabetes mellitus or thyroid disorders, the history of PD-related surgery, receiving hypoglycaemic drugs and corticosteroids or specific diets such as a low-sugar diet.

*Anthropometric assessments*

The weight was measured by a digital scale while the participants were wearing light clothes and no shoes. The subjects' height was measured using a stadiometer at head level, without any shoes. To calculate body mass index (BMI), weight in kilograms was divided by height in square meters.

*Dietary intake assessments*

The subjects' dietary intake was assessed using 24-hour dietary recall and three-day food record (2 weekdays and 1 weekend) methods. For obtaining more accurate food data recording, this process was followed by a phone call and GI of each food was obtained from international tables.[12] For those foods that were not included in international table, GI values were estimated by similar components foods. Finally, the total GI of dietary intake was calculated by the following formula: $\Sigma$ (GI$^a$ × available carbohydrate$^a$) / total available carbohydrate.[13] Available carbohydrate$^a$ was also calculated by subtracting the content of fiber$^a$ from total carbohydrate$^a$. Nutritionist IV software (version 4.1) was then used to obtain the amounts of nutritional intake of carbohydrate and fibre. Finally, an average of four days' GI values was calculated for each one of the subjects. Dietary GL was calculated by multiplying the dietary GI by total daily carbohydrate intake.

*Biochemical assessment*

Five ml of venous blood was obtained from each participant. Afterward, serum samples were collected by centrifuging the blood at 2000-3000 RPM for 20 minutes and then stored at -70°C until analysis. The measurement of oligomeric α-syn, DJ-1, and MGO levels was carried out using the commercially available ELISA kits (Shanghai Crystal Day Biotech Co., Ltd).

*Statistical analysis*

SPSS software version22 (IBMSPSS statistics, Chicago, IL) was used for the analysis. Subsequently, Independent sample t-test, Mann-Whitney test, and chi-squared test were used to calculate intergroup differences. Thereafter, linear logistic regression models were used to estimate the correlation between the studied variables. Age, sex, and educational levels were considered as confounder factors, which were then taken into account in the correlational analysis. Spearman's correlations were used to test the correlation between serum factors. The differences were considered to be statistically significant at p-value < 0.05.

## RESULTS

*Demographic characteristics, GI, and GL of the participants*

As shown in Table 1, 70% of the PD subjects of the patient's group and 75% of the subjects of the control group were men. There were no significant differences in terms of the educational levels, age, height, dietary GL, and total carbohydrate intake between the PD and control groups. In the PD group, means of weight ($p < 0.001$) and BMI ($p = 0.001$) were significantly lower and the mean of GI was significantly higher ($p = 0.019$) when compared to the control group.

**Table 1: Demographic Characteristics and nutritional status of the studied groups**

| Characteristics | Patients (n = 40) | Control (n = 40) | *p* |
|---|---|---|---|
| Gender n (%) | | | |
| Male | 28 (70%) | 30 (75%) | 0.619 |
| Female | 12(30%) | 10 (25%) | |
| Age (Yr) mean ± SD | 61 ± 9.30 | 60.78 ± 5.91 | 0.899 |
| Education n (%) | | | 0.891 |
| Elementary or less | 30 (75%) | 33 (82.5%) | |
| Middle school | 5 (12.5%) | 2 (5%) | |
| High school | 4 (10%) | 3 (7.5%) | |
| College or more | 1 (2.5%) | 2 (5%) | |
| Weight (Kg) mean ± SD | 70.32 ± 11.91 | 82.07± 12.37 | <0.001* |
| Height (cm) mean ± SD | 167.94 ± 8.26 | 170.21 ± 9.77 | 0.286 |
| BMI ($Kg/m^2$) mean ± SD | 25.03 ± 4.30 | 28.01± 3.06 | 0.001* |
| GL median (min-max) | 158.56 (61.31-332.44) | 157.56 (99.01-386.26) | 0.617 |
| GI mean ± SD | 62.00 ± 4.61 | 59.58± 4.41 | 0.019* |
| Total carbohydrate median (min-max) | 260.62 (126.88-565.96) | 262.01(164.30-554.27) | 0.603 |
| Duration of disease (Yr) median (min-max) | 4 (1-10) | | |

Abbreviations: **BMI**, Body mass index; **GL**, Glycemic Loud; **GI,** Glycemic index
*Difference is significant at the <0.05 levels (2-tailed)

*Levels of serum parameters*

As shown in Figure 1, the serum levels of oligomeric α-syn (p = 0.003) and DJ-1 (p < 0.001) were significantly higher in the patient group. Moreover, the serum level of MGO was higher in the PD group, but this difference was not significant (p = 0.07).

*Odds ratio of PD according to studied factors*

Table 2 shows ORs for PD according to dietary factors after adjusting the factors related to age, sex, and educational levels. A direct relationship has emerged between PD and dietary GI (OR: 10.05; [95% CI: 1.94, 51.95] for the highest vs. the lowest quintile, p for trend 0.028). No significant correlations were found among dietary GL and total carbohydrate and PD. Besides, serum levels of MGO (OR: 1.04 [95% CI: 1.00, 1.08]; p = 0.04), oligomeric α-syn [OR: 1.94 (95% CI: 1.17, 3.22); p = 0.01], DJ-1 [OR: 2.41 (95% CI: 1.45, 4.00); p = 0.001], and BMI [β (95% CI):0.80 (0.70, 0.92), p = 0.002] were shown to be significantly associated with PD (Table 3).

*Correlation of serum parameters with GI and GL in patients*

As shown in Table 4, serum MGO [OR: 0.27 (95% CI: 0.02, 1.98); p = 0.04], oligomeric α-syn [OR: 0.34 (95% CI:0.01, 0.17), p = 0.03], and DJ-1 [OR: 0.39 (95% CI:0.04, 0.30), p = 0.001] were shown to be significantly correlated with GI levels, but not GL, in the patient's group by considering age, sex, and educational levels as confounder factors.

*Correlation of serum levels of oligomeric α-syn, DJ-1, and MGO with each other in patients*

As shown in Figure 2, the serum levels of MGO have been indicated to be positively correlated with serum levels of oligomeric α-syn (r = 0.603, p < 0.001). A similar positive correlation was also observed between serum levels of MGO and DJ-1 (r = 0.652, p < 0.001) and between serum levels of DJ-1 and oligomeric α-syn (r = 0.727, p < 0.001) in the patients.

## DISCUSSION

The key finding of this study was that the dietary GI, which is an index summarizing

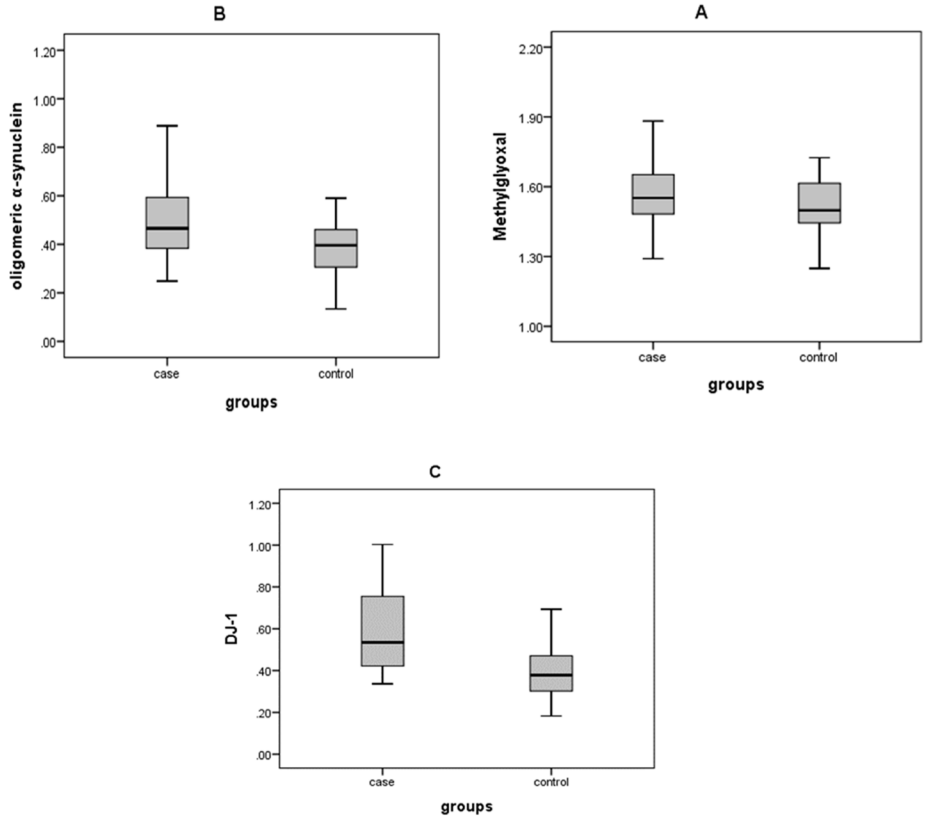


Figure 1. (A) Serum levels of methylglyoxal (MGO) in PD and control groups [1.55 (1.29 - 1.96) vs. 1.49 (1.25 - 1.72) respectively, p = 0.07], (B) Serum levels of oligomeric α-synuclein (α-syn) in PD and control groups [0.46 (0.25- 0.89) vs. 0.39 (0.15 - 0.58) respectively, p = 0.003], (C) Serum levels of DJ-1 in PD and control groups [0.53 (0.34 - 1.00) vs. 0.37 (0.18 - 0.88) respectively, p < 0.001]. The values have been changed to logarithm. (minimum, maximum and median levels for each group is shown).

**Table 2: Overall OR for PD according to quintiles of daily average of glycaemic load, glycaemic index, total carbohydrates (Adjusted for age, sex and education level)**

| **All subjects (40/40 cases/controls)** | **Quintiles** | | | | | |
|---|---|---|---|---|---|---|
| | **Q1** | **Q2** | **Q3** | **Q4** | **Q5** | |
| | **OR** | **OR (95% CI)** | **OR (95% CI)** | **OR (95% CI)** | **OR (95% CI)** | **$P_{trend}$** |
| GL | | | | | | |
| Actual range of value | <126.07 | 126.07-147.65 | 147.66-169.79 | 169.80-194.37 | 197.37< | |
| Cases/controls | 7/9 | 8/8 | 8/8 | 7/9 | 10/6 | |
| OR | 1.00 | 1.60 (0.36, 6.94) | 1.71 (0.37, 7.84) | 1.39 (0.30, 6.53) | 2.96 (0.62, 14.16) | 0.726 |
| GI | | | | | | |
| Actual range of value | <57.52 | 57.52-58.93 | 58.94-61.84 | 61.85-65.23 | 65.23< | |
| Cases/controls | 4/12 | 5/11 | 10/6 | 9/7 | 12/4 | |
| OR | 1.00 | 1.11 (0.21, 5.51) | 5.09 (1.06, 24.42) | 4.35 (0.92, 20.39) | 10.05 (1.94, 51.95) | 0.028* |
| Total carbohydrates (g/day) | | | | | | |
| Actual range of value | <205.07 | 205.07-243.11 | 243.12-283.07 | 283.08-320.63 | 320.63< | |
| Cases/controls | 9/7 | 10/6 | 6/10 | 6/10 | 9/7 | |
| OR | 1.00 | 1.36 (0.319, 5.81) | 0.51 (0.11, 2.25) | 0.50 (0.11, 2.26) | 1.13 (0.24, 5.14) | 0.541 |

**PD**, Parkinson Disease; **GL**, Glycemic Loud; **GI**, Glycemic index; **OR**, Odd ratio
Data were adjusted for age, sex and educational level.

**Table 3: Odds ratio of PD according to studied factors**

| | OR | (95% CI) | P |
|---|---|---|---|
| MGO | 1.04 | 1.00-1.08 | 0.04 |
| Oligomeric a-syn | 1.94 | 1.17-3.22 | 0.01 |
| DJ-1 | 2.41 | 1.45-4.00 | 0.001 |
| Sex | 1.44 | 0.54-3.83 | 0.46 |
| Age | 1.00 | 0.95-1.06 | 0.90 |
| BMI | 0.80 | 0.70-0.92 | 0.002 |

**MGO**, Methylglyoxal; **α-syn**, α-synuclein; **OR**, Odd ratio; **BMI**, Body mass index; **PD**, Parkinson's disease

the glycemic impact of foods, was shown to be correlated with PD that may be associated with higher glycosylation and oligomerization of α-syn. Conversely, we have observed no correlation between GL and PD. This finding is somewhat difficult to explain. As some studies have stated, GL of dietary intake might provide little information on dietary total carbohydrate content.[14,15] Only one previous study performed by Murakami *et al*. evaluated the relationship of dietary GI and GL with PD.[14] Although our results are in line with their findings about GL, they are in contrast with GI. This variance could be due to the difference in methods of data collection. Murakami *et al*. have used the diet history questionnaire (DHQ) to collect food intake information. While our study used a 24-hour dietary recall questionnaire as well as three-day food record. Although, the protective effect of a low-GI diet on neurodegenerative diseases like Alzheimer's disease has been reported in the previous studies[16], the exact mechanism is unknown yet. Altogether, it can be said that the diet with higher GI causes the enhanced protein oligomerization, inflammation, and oxidative stress associated with PD, via increasing MGO levels.[6]

In this study, for the first time up to the best of our knowledge, we demonstrated a correlation between serum levels of MGO and PD. In this line, Beeri *et al*. in their study showed a correlation between higher serum levels of MGO and cognitive decline in the elderly.[17] Chu *et al*. have also suggested which MGO may be related to diabetes-related neurodegeneration.[18] No study on the levels of MGO in PD patients was found. Previous studies have suggested that under chronic glycative stress conditions such as diabetes or having diets with high GI, MGO levels increase. These elevated levels of MGO may be involved in the pathogenesis of age-related diseases like PD.[6] Several mechanisms have been proposed to explain why MGO is associated with PD. For example, MGO can affect α-syn proteins and stabilize them by glycation at the N-terminal region; therefore, it aggravates their oligomerization.[7] Moreover, it can cause neuroinflammation, oxidative stress, and mitochondrial dysfunction associated with PD.[19] Accordingly, some studies identified diabetes, as a risk factor for PD via elevating MGO levels.[20,21] Hence, some of the glycemia regulators drugs, which were approved for the treatment of diabetes, have been proposed as promising for the treatment of PD.[22] Correspondingly, glucagon-like peptide 1 (GLP-1), due to its effects on the regulation of the levels of glucose, protein aggregation, and neuronal function, has been considered as a common treatment for diabetes and PD.[22,23]

In the current study, oligomeric α-syn was found to be positively correlated with PD. Oligomerization of α-syn is known as a

**Table 4: Association of GL and GI with serum levels of MGO, oligomeric α-syn and DJ-1 in patients**

| Characteristics | GI | | GL | |
|---|---|---|---|---|
| | OR (95% CI) | p | OR (95% CI) | p |
| **MGO** | 0.27 (0.020, 1.98) | 0.04 | 0.03 (-0.10, 0.12) | 0.882 |
| **oligomeric α-syn** | 0.34 (0.01, 0.17) | 0.03 | 0.07 (-0.01, 0.01) | 0.70 |
| **DJ-1** | 0.39 (0.04, 0.30) | 0.001 | 0.05 (-0.01, 0.01) | 0.80 |

**MGO**, Methylglyoxal; **α-syn**, α-synuclein; **GI**, Glycemic Index; **GL**, Glycemic Load; **OR**, Odd ratio
Data were adjusted for age, sex and educational level.

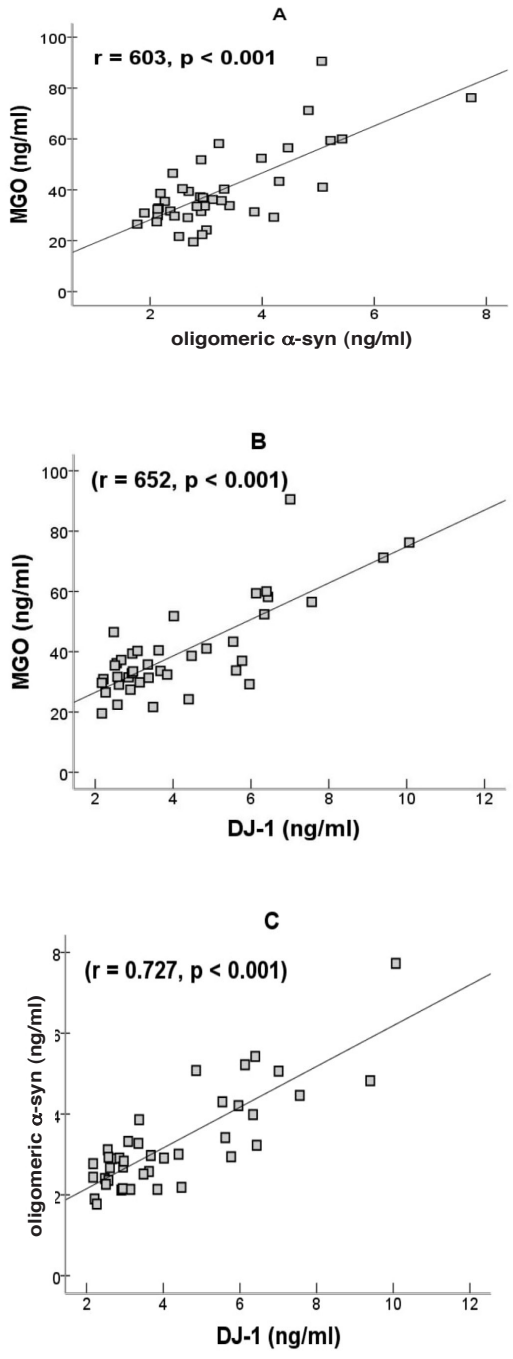


Figure 2. Correlations between serum levels of methylglyoxal (MGO), oligomeric a-synuclein (α-syn) and DJ-1 in patients. (A) There was a positive correlation between serum levels of MGO and oligomeric α-syn ($r = 0.603$, $p < 0.001$). (B) MGO also positively correlated with DJ-1 ($r = 0.652$, $p<0.001$). (C) a significant positive correlation was between serum levels of oligomeric oligomeric α-syn and DJ-1 ($r = 0.727$, $p < 0.001$).

characteristic of PD. The elevated levels of oligomeric α-syn in CSF, saliva, basal tears, and plasma of PD patients were indicated in prior studies.[24-27] However, Emelyanov *et al.* found no significant difference in plasma levels of oligomeric α-syn between 17 drug-naïve PD patients and 18 control groups.[28] Recent studies have suggested that the soluble oligomeric form of α-syn toxicity is more in PD pathogeneses compared to mature amyloid fibrils. According to this hypothesis, oligomeric α-syn-induced toxicity causes neuronal death related to PD through mitochondrial dysfunction, altering membrane permeability, and producing high levels of reactive oxygen species.[29] These findings have led to the current most accepted hypothesis stating that the formation of Lewy body in the neurons of PD patients may be a defence response as a sequester that isolates toxic oligomeric α-syn.[30]

This study has also evaluated DJ-1 serum levels. In this regard, we found that DJ-1 is correlated with PD directly and significantly. In this line, Waragai *et al*. in their study reported high levels of DJ-1 in the CSF and plasma in PD patients.[31,32] An *et al*. reported no significant difference in terms of the serum levels of DJ-1 between PD patients and the adjusted control group.[33] These different results could be due to the fact that the control group's subjects of their study were selected from patients with cerebral infarction. Given that some animal studies have reported the up-regulation of DJ-1 as an antioxidant in ischemic post-condition[34], this can be considered as a factor that disrupts their outcomes. DJ-1 is a multifunctional protein that can prevent PD in different pathways. For example, it can protect α-syn from oligomerization by its chaperone activity. Moreover, as a methylglyoxalase, it can make MGO in the non-toxic form. Furthermore, as an antioxidant, DJ-1 can moderate oxidative stress associated with PD.[8,9,31,35] Therefore, the up-regulation of DJ-1 in PD patients may be a defensive response against PD.

Our results show a significant positive correlation among serum levels of MGO, oligomeric α-syn, DJ-1, and GI in the patients. However, this relationship was not significant about GL. In high GI diets similar to that of diabetes condition, there is an increase in MGO levels due to high glucose metabolism.[6] In this line, Adolphe *et al*. in their study suggested that the intake of carbohydrates with high GI increases postprandial MGO serum levels.[36] So, the correlation between GI and MGO seems reasonable. Furthermore, regarding the correlation

between GI and oligomeric α-syn, it can be said that high GI diets set up a vicious cycle of higher glycation and oligomerization of α-syn, which consequently causes glycation-induced protease resistance leading to further oligomeric α-syn accumulation.[7] Therefore, this correlation is acceptable. The mechanisms by which dietary GI is correlated with DJ-1 may be indirect once, via increasing glycosylation of α-syn, inflammation, and oxidative stress associated with PD[6], which can stimulate overexpression of DJ-1, as a deglycase, antioxidant, and anti-inflammatory agent.[37,38] No studies on these possible relationships were found. Furthermore, we found positive correlations of serum levels of MGO, oligomeric α-syn, and DJ-1 with each other in the included patients. To the best of our knowledge, the relationship among these three factors has not been assessed in previous studies. Although the interactions among these factors have not been completely elucidated, it seems that excessive levels of MGO could lead to the accelerated oligomerization of α-syn. Consequently, an increase in DJ-1 levels could be expected to modulating the increased levels of MGO (as a methyglyoxalase) and oligomeric α-syn toxicity (as a chaperon).[8,9]

Our study has several limitations, including a small sample size. In addition, due to some PD-related disorders, such as mood, thinking and sensory disorder[14], the use of a retrospective food questionnaire is less reliable. Thus, this study used a 24-hour dietary recall questionnaire as well as a three-day food record to collect dietary habits by assuming that the dietary habits of our samples remained constant over time. This may increase the probability of error.

In conclusion, our study provided preliminary evidence that diet with high GI is correlated with PD. In addition, diet with high GI is positively correlated with serum levels of MGO, oligomeric α-syn, and DJ-1. Thus, it can be concluded that a diet with high GI may increase the α-syn oligomerization and AGEs formations by increasing MGO levels. Subsequently, the elevated levels of DJ-1 are expected for modulating this condition. Future large cohort studies in this regard can offer preventive or curative treatments based on the causes of disease, not only its symptoms.

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## DISCLOSURE

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Conflict of interest: None

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