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Serum Level of S100B Protein as a Biomarker of Therapeutic Adherence in Parkinson's Disease Patients

Mustafa Raheem Oglah[*,1], Ali A. Kasim[2] and Bahaa A. Hassan[3]

[1]Department of Clinical Pharmacy, College of Pharmacy, University of Baghdad, Baghdad, Iraq.
[2]Department of Clinical Laboratory Sciences, College of Pharmacy, University of Baghdad, Baghdad, Iraq.
[3] Ministry of Health and Environments, Department of Neurology, Saad Al-Witry Neuroscience Hospital, Baghdad, Iraq
[*]**Corresponding author**
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Abstract

Pharmacological management of Parkinson's disease (PD) is complex and may negatively impact patients' adherence to therapy. Several objective and subjective approaches are used to assess therapeutic adherence. Measurement of biological markers, that are well correlated with the effect of the medications, and that are distributed into easily accessible body fluids would be feasible approach for measuring therapeutic adherence for these medications. S100B protein has been proposed to be involved in the pathophysiology of PD. The study aims to measure the serum S100B level in PD patients and to assess its potentials to be used as a biomarker to predict therapeutic adherence in PD patients. Sixty-eight adult outpatients, of both genders, who were already diagnosed with PD, receiving different anti-Parkinson medications, were enrolled in this cross-sectional study. Hoehn and Yahr scale was used to determine the stage of disease; while, therapeutic adherence to treatment was assessed using the Arabic version of Morisky Medication Adherence Scale (MMAS-8). Serum S100B level was measured by enzyme-linked immune sorbent assay. Serum S100B level of participants was 10.55 (13.3) ng/l, and there was no significant difference between medians of S100B protein according to disease stages, P =0.975. Serum S100B level in patients with poor therapeutic adherence [14.2 (13.2) ng/l] was significantly higher than that in patients with good therapeutic adherence [3.14 (3.34)]; P = 0.008. Furthermore, serum S100B level with the MMAS-8; (r= -0.414, P = 0.001). Finally, at a cut-off point 3.57 ng/l and above, serum S100B level was shown to have good potential [area under the curve (AUC)= 0.715], as biomarker of therapeutic adherence with 70.6% sensitivity and 70.6%, specificity; P = 0.008. In conclusion, serum S100B level in PD patients is negatively correlated with therapeutic adherence level and has good potentials as biomarker of therapeutic adherence in PD patients to anti-Parkinson medications.
Keywords: Parkinson's disease, Neurodegeneration, Therapeutic adherence, S100B, MMAS-8.

مستوى بروتين S100B في المصل كعلامة حيوية للالتزام العلاجي في مرض باركنسون

مصطفى رحيم[١]، علي عبد الحسين قاسم[٢]و بهاء عبد الأمير حسن[٣]

[١]فرع الصيدلة السريرية، كلية الصيدلة، جامعة بغداد، بغداد، العراق.
[٢]فرع العلوم المختبرية السريرية، كلية الصيدلة، جامعة بغداد، بغداد، العراق.
[٣] وزرارة الصحة ، فرع العلوم العصبية، مستشفى الدكتور سعد الوتري للعلوم العصبية، بغداد، العراق.

الخلاصة

إن تنظيم العلاج الدوائي لداء باركنسون عملية معقدة وقد تؤثر سلباً على التزام المرضى بالعلاج. هناك عدة مناهج تطبيقية ونفسية مستخدمة لتقييم الالتزام العلاجي. إن قياس العلامات البيولوجية، المنتشرة سوائل الجسم والتي يسهل الوصول إليها، والتي ترتبط ارتباطاً وثيقاً بتأثير الأدوية ممكن أن يكون منهجاً وطريقاً عملياً لقياس الالتزام العلاجي للمرضى بهذه الأدوية. لقد اقتُرحَت بعض الدراسات أن بروتين (S100B) يشارك في الفسلجة المرضية الخاصة بداء باركنسون. تهدف الدراسة إلى قياس مستوى بروتين (S100B) في مصل الدم في مرضى باركنسون وتقييم إمكانياته كمؤشر حيوي للتنبؤ بالالتزام العلاجي في مرضى داء باركنسون. ضمت هذه الدراسة ٦٨ مريضا بالغاً، من كلا الجنسين، الذين تم تشخيصهم مسبقاً بداء باركنسون، ويتلقون أدوية مختلفة مضادة للمرض، في هذه الدراسة المستعرضة. تم استخدام مقياس هوين وبار (Hoehn & Yahr) لتحديد مرحلة تقدم المرض؛ في حين تم تقييم الالتزام العلاجي باستخدام النسخة العربية من مقياس موريسكي للالتزام الدوائي، وتم قياس مستوى بروتين (S100B) في المصل باستخدام المقايسة الامتصاصية المناعية للأنزيم المرتبط. كان متوسط مستوى بروتين (S100B) في مصل للمشاركين ١٠,٥٥ (١٣,٣) نانوجرام / لتر، ولم يكن هناك فرق كبير بين متوسطات بروتين (S100B) وفقًا لمراحل المرض، P = 0.975. كان مستوى المصل (S100B) في المرضى الذين يعانون من ضعف الالتزام العلاجي [١٤,٢ (١٣,٢) نانوجرام / لتر] أعلى بكثير من ذلك في المرضى الذين لديهم التزام علاجي جيد [٣,١٤ (٣,٣٤)]؛ P = 0.008. علاوة على ذلك فان مستوى البروتين (S100B) في المصل يرتبط عكسيا مع نتائج مؤشر

موريسكي للالتزام الدوائي (r= -0.414, P = 0.001). أخيرًا، عند تركيز ٣,٥٧ نانوجرام / لتر فما فوق، تبين أن مستوى المصل (S100B) لديه إمكانات جيدة لاستخدامه كعلامة حيوية للالتزام العلاجي [المنطقة الواقعة تحت المنحنى (AUC) = 0.715]، بحساسية ٧٠,٦٪ وتخصصية ٧٠,٦٪؛ P = 0.008. بهذا يمكن الاستنتاج ان مستوى بروتين (S100B) في مصل الدم لدى مرضى داء باركنسون يرتبط سلبًا بمستوى الالتزام العلاجي وان له إمكانات جيدة كعلامة حيوية للالتزام العلاجي في هؤلاء المرضى.

الكلمات المفتاحية: داء باركنسون، الانحلال العصبي، الالتزام العلاجي، بروتين S100B، مقياس موريسكي .

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative condition primarily affecting the central nervous system. It is characterized by a gradual decline in dopamine-producing neurons in a specific area of the brain, the substantia nigra, resulting in various motor and non-motor symptoms[1].

The exact cause of PD remains not entirely comprehended, but it is likely influenced by a combination of genetic and environmental factors. Although no cure exists for the disease, there are available medications and therapies that can help manage the symptoms and enhance the quality of life for individuals living with PD[1-5].

On a global scale, PD is relatively common in older populations. The incident rate increases in individuals aged over 65 years, and it increases in individuals over 80 years. The overall age-standardized prevalence rate was 106.28/100,000 in 2019. Nevertheless, these prevalence rates may vary significantly across different countries and regions[6].

In 2019, the age-standardized prevalence, death, and disability-adjusted-life-years (DALY) rates of PD in Iraq were 74.2, 5.7, and 85.6 cases per 100,000 of the population; respectively[7].

Pharmacological management of PD is complex. It consists of medications to manage motor symptoms like Levodopa-Carbidopa preparations, Dopamine agonists, Monoamine Oxidase-B inhibitors, and anti-cholinergics. And medications for non-motor symptoms like tricyclic antidepressants (TCAs), Selective serotonin reuptake inhibitors (SSRIs), and selective serotonin norepinephrine reuptake inhibitors (SNRIs). The complexity and diversity of medications may negatively impact patients' adherence to therapy[8]. Motor and nonmotor symptoms of PD require tailored therapy, which can include multiple drugs and dosing schedules; hence, development of adverse effects are more likely to occur in PD patients[9]. Furthermore, as PD is more prevalent in elderly individuals who usually suffer other comorbidities, they often receive several pharmacotherapeutic classes that complicate dosing and titration schedules of anti-Parkinson medications [10]. Suboptimal therapeutic adherence is common in PD patients and is associated with poor symptoms management, clinical outcomes, and higher healthcare financial costs. Moreover, it can result in diagnostic uncertainty[11]. Poor therapeutic adherence among PD patients has been reported to range between 10% and 74%[11-14]. The variability in this regard can be attributed to the differences in methodological approaches, as there is "gold standard" approaches to study therapeutic adherence[15].

Several objective and subjective approaches are used to assess therapeutic adherence. In the objective approaches, therapeutic adherence is assessed based on prescription refill records, residual pill counts, and electronic pill-boxes reports. On the other hand, subjective approaches are based on patient self-reports, family members or care-givers interviews and reports, and questionnaires [14].

Measurement Of biological markers, that are well correlated with the effect of the medications, and that are distributed into easily accessible body fluids, such as blood or urine would be feasible approach for measuring therapeutic adherence for these medications. Currently, only few biomarkers are used to measure objective therapeutic adherence and evaluate the medication success[16]. An excellent example in this regard is the measurement of serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) to monitor therapeutic adherence for medications used in heart failure patients[17].

Protein S100B is a calcium-binding protein that belongs to the S100 proteins family. It is widely expressed in the brain, mostly by astrocytes, and to a lesser extent by neural-progenitor cells, developing oligodendrocytes, and dendritic cells[18]. Physiologically S100B is involved in calcium homeostasis, cell proliferation, energy metabolism, motility, and cytoskeletal control intracellularly, and can interact in a Ca2+-sensitive manner with more than 20 different proteins[19]. S100B is connected with the receptor for Advanced Glycation End-products (RAGE), so it functions as a damage-associated molecular pattern (DAMP) protein, and is thought to be an indication of brain injury that can be released extracellularly[19-22].S100B has been proposed to be involved in the pathophysiology of PD[23].

The study aims to measure the serum S100B level in PD patients and to study its association with the therapeutic adherence, and to assess its potentials to be used as a biomarker to predict therapeutic adherence in PD patients.

Patients and Methods

This cross-sectional study was carried out in the movement disorders consultancy clinic in Dr. Saad Al-Witry Neuroscience Hospital in Baghdad, Iraq; under the supervision of consultant neurologist from December 2021until November 2022.

The study has been approved by the ethical committee of the College of Pharmacy, University of Baghdad, the Iraqi Ministry of Health/ Department of Research and Development, and the health authorities in Dr. Saad Al-Witry Neuroscience Hospital. Written consent was taken from each patient after thorough explanation of the aims of the study and ensuring him/her about the confidentiality of the collected data which would be anonymous and would not be used for any purpose other than the current study.

Sixty-eight adult outpatients, of both genders, who were already diagnosed with PD for at least one year, and receiving different antiparkinson medications for at least one year were enrolled in the study. Patients undergoing deep brain stimulation or patients with any other neurological or non-neurological diseases, migraine, receiving antipsychotics or benzodiazepines, previous head trauma or subarachnoid hemorrhage, and pregnant women were excluded from the study.

Hoehn and Yahr scale was used to determine the stage of disease; the scale categorizes PD progression into five stages[24]. Therapeutic adherence to treatment was assessed using a subjective approach using the Arabic version of Morisky Medication Adherence Scale (MMAS-8)[25]. The scale involves eight items that identify barriers to and behaviors associated with adherence to medications, with yes or no responses for items 1 to 7, and a 5-point Likert-scale response for the last item. Total scores ranged from 0 to 8, scores of less than 6 reflecting poor adherence, and scores of 6 to 8 reflect moderate to good adherence.[26] The responses to MMAS-8 were reported by the enrolled patients themselves.

Patients who met the inclusion criteria and accepted to participate in the study were interviewed separately. Sociodemographic and medical data were collected and recorded on a data collection sheet, designed for the purpose of the study. A blood sample (5ml) was collected from each participant then serum was separated and used for the measurement of S100B protein by enzyme-linked immune sorbent assay (ELISA), the human specific ELISA kit was purchased from (Shanghai YL Biotech Co. Ltd, Catalogue number YLA1268HU ; China).

Statistical analysis

Data were analyzed using SPSS software for Windows version 26.0. Shapiro-Wilk test was employed to determine whether data were normally distributed. Categorical variables were presented as number and percentage; while, continuous variables were presented as median [interquartile range (IQR)]. Chi-square was used to study the association of categorical variables. Spearman rank test was used to study the correlation of variables. Receiver operating characteristic curve was employed to study the diagnostic potentials of serum S100B protein level as biomarker of PD patients' therapeutic adherence A P-value <0.05 was considered statistically significant.

Results

The mean participants' age was (55±11.7) years. As shown in Table 1; more than half of the participants aged 56 years and more; 60.3% of participants were males and 39.7% were females. Furthermore 25% of them had normal weight, while 55.9% were overweight and 19.1% were obese; most of the participants (91.2 %) were married at the time of the study. Moreover, 42.6% of participants had primary school degree, 27.9% have secondary school degree, and 29.5% had higher degrees. Finally, 38.2% of participants are living in rural areas; while the remaining, 61.8 %, are living in cities.

Table 1. The sociodemographic characteristics of the participants

Variable	Category	Number	Percent
Age (year)	<56 year	33	48.5
	≥ 56 years	35	51.5
Gender	Male	41	60.3
	Female	27	39.7
Weight status	Normal weight	17	25.0
	Overweight	38	55.9
	Obese	13	19.1
Marital status	Married	62	91.2
	Unmarried	6	8.8
Education	Primary	29	42.6
	Secondary	19	27.9
	University	20	29.5
Zone of residence	Rural area	26	38.2
	Urban area	42	61.8

According to Hoehn and Yahr disease staging scale implemented in this study, most of the participants were in stage 2 (41.2%) and stage 3 (35.3%) of the disease; while 10.3% of participants were in both stages 1 and 4, and the remaining 2.9% were in stage 5; Table 2.

Table 2. Participants distribution based on the disease stage

Stage of the disease	Number	Percent
Stage 1	7	10.3
Stage 2	28	41.2
Stage 3	24	35.3
Stage 4	7	10.3
Stage 5	2	2.9

As shown in Table 3; 1.47% of patients have good, 23.53% have moderate, while 75 % have poor therapeutic adherence.

Table 3. Therapeutic adherence level of participants

Adherence level	MMAS-8	Number of patients	Percentage
Good	8	1	1.47
Moderate	7	2	2.94
	6	14	20.59
Poor	5	10	14.71
	4	12	17.65
	3	8	11.77
	2	17	25
	1	3	4.4
	0	1	1.47

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Patients in stage 1 had the lowest adherence score, while these in stage 5 had the highest score; as shown in Table 4. Even though the difference among medians MMAS-8 according to disease stage was not significant (P= 0.304).

Table 4. Adherence score per disease stage

Disease stage	Number	Median MMAS-8 (IQR)	P- value
Stage 1	7	2.75 (1.25)	0.353
Stage 2	28	4.87(3.06)	
Stage 3	24	4.37(3.37)	
Stage 4	7	4.75(2.25)	
Stage 5	2	5(0)	

As shown in Table 5, the therapeutic adherence level was significantly associated with age (P=0.032). There was significant negative correlation between MMAS-8 and age, (rho= -0.32, P = 0.008). Whereas, there was no significant association between the therapeutic adherence level with each of gender, weight status, marital status, education level, and zone of residence; P-value more than 0.05 for all of these variables.

Table 5. Association between the medication adherence level and sociodemographic characteristics of participants

Variable	Category	Adherence level				P-value
		Poor		Moderate to good		
		Number	Percent	Number	Percent	
Age	<56 year	21	41.2%	12	70.6%	0.032*
	≥ 56 year	30	58.8%	5	29.4%	
Gender	Male	29	56.9%	12	70.6%	0.317
	Female	22	43.1%	5	29.4%	
Weight status	Normal weight	14	27.5%	3	17.6%	0.410
	Over weight	29	56.9%	9	52.9%	
	Obese	8	15.7%	5	29.4%	

Continued table 5.

Marital status	Married	46	90.2%	16	94.1%	0.622
	Unmarried	5	9.8%	1	5.9%	
Education	Primary	23	45.1%	6	35.3%	0.470
	Secondary	15	29.4%	4	23.5%	
	University	13	25.5%	7	41.2%	
Residence	Rural area	19	37.3%	7	41.2%	0.7٧٣
	Urban area	32	62.7%	10	58.8%%	

Where: * refers to significant difference (P< 0.05)

There was no significant correlation between MMAS-8 and stage of the disease (rho= 0.062, P-value =0.614). Serum S100B protein level of participants was 10.55 (13.3) ng/l. As shown in Table 6, there was no significant difference between medians of S100B protein according to disease stages. P =0.975

Table 6. Serum S100B protein level per disease stage

Disease stage	Number	Serum S100B protein level (ng/l) [Median (IQR)]	P-value
Stage 1	7	2.951 (13.63)	0.975
Stage 2	28	7.81(12.85)	
Stage 3	24	13.79(13.23)	
Stage 4	7	7.76(14.68)	
Stage 5	2	7.88(2.36)	

As shown in Table 7, the median of S100B protein in patients with poor therapeutic adherence, 14.2 (13.2) ng/l, was significantly higher than that in patients with good therapeutic adherence, 3.14 (3.34); P = 0.008.

Table 7. Serum S100B protein level of participants per therapeutic adherence level

Adherence level	Number	Serum S100B ng/l [Median (IQR)]	P-value
Poor	51	14.2 (13.2)	0.008
Moderate to good	17	3.14 (3.34)	

There was significant negative correlation between of serum S100B level with the MMAS-8; (r= -0.414, P = 0.001). Finally, at a cut-off point 3.57 ng/l and above, serum S100B level was shown to discriminate poor adherence from intermediate to good one among 71.5% (AUC= 0.715) of cases with sensitivity equals to 70.6% and specificity equals to 70.6%, P = 0.008; as shown in Figure 1.

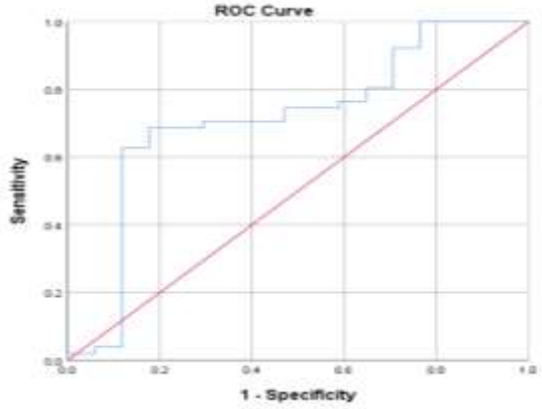

Figure 1. Receiver operating characteristic curve of serum S100B protein as diagnostic biomarker of PD patients' therapeutic adherence

Discussion

The mean age of patients was (55 ±11.7) year and 51.5% were at the age of 56 year or older. This occurs in accordance with the fact that Parkinson's disease is an age-related condition; the incidence and prevalence of the disease both increase as the percentage of older people in the population increases[6].

Over 60% of the enrolled subjects were males. This finding agrees with the literature, which points to a higher prevalence of the disease in males[27]. Moreover, Moisan et al. showed that the male to female ratio in PD patients increases with age[28].

As for weight, 25% of patients had normal weight while 55.9% were overweight and 19.1% were obese. In a meta-analysis, Chen et al. has reported that obesity and overweight were found to be risk factors for PD in cohort studies but not in case-control studies[29]. An international, multicenter, cohort study that aimed to identify biomarkers of PD progression found that obesity is related to an increased risk of functional dependency and rapid motor progression in patients with early PD[30].

Most of participants (91%) were married this eliminates the effect of being single on the quality of life and therapeutic adherence rate. Rana et al. proposed that being married represents physical and emotional support for PD patients, and improves depression and pain in these patients[31]. On the other hand, Valldeoriola et al. showed that having a spouse or life partner was associated with higher therapeutic adherence in PD patients on different anti-Parkinson medications[32].

In the present study, 38.2% of participants were living in rural areas; while the remaining, 61.8 %, were living in cities. This finding is in alignment with other studies that reported higher frequency of PD patients in urban areas in Iraq. A cross sectional survey study conducted in an outpatient clinic in Kurdistan at the north of Iraq found that (54.3%) of PD patients were living in urban areas and (45.7%) living in rural area[33]. Similarly, higher frequency of PD patients were reported in urban areas compared to rural ones, in another cross-sectional community-based study in Al-kadhiymia district in Baghdad, the capital of Iraq[34].

Finally, the participants in the present study were at different educational level.

As for disease stage; 51.5% of participants were at early stages of the disease (stages one and two), while 48.5% in stage 3 and above. This implies that both early and late stages of PD are nearly equally represented by the study.

The study showed that (75%) of participants had scores below 6. This finding is further solidified by the very low percentage of participants with high adherence level and considerably low percentage of these with moderate adherence.

The problem of poor therapeutic adherence is quite common among PD patients on different anti-Parkinson medications. Different studies have reported suboptimal adherence in PD patients to range from 10% to 74% [11-14]. The variability in this regard may be attributed to the differences in the type of study populations or study methodology. Hughes et al. stated that there is no method to be considered as the "gold standard" approaches to study therapeutic adherence[15].

The most widely used methodological approaches for the evaluation of therapeutic adherence are (a) the objective approach; in which the adherence is assessed based on prescription refill records, residual pill counts, and electronic pill-boxes reports and (b) subjective approach; in which the adherence is assessed based on patient self-reports, family members or care-givers interviews and reports, and questionnaires[14]. Suboptimal adherence in PD is associated increased clinical and financial burden of the disease; it results in reduced medication effects in controlling the symptoms, poor prognosis, and increases the overall treatment costs due to unnecessary medication adjustments by using higher doses or introducing further medications[35].

Unfortunately, there was no previous study measuring the therapeutic adherence of Iraqi PD patients to their prescribed medications in order to compare the results of the present study.

Generally, adherence of Iraqi patients to the prescribed long-term therapies varies widely. Abdul-Jabbar et al al. has measured the low adherence rate of patients on maintenance hemodialysis to different medications in Baghdad to be 6%[36]. Alalaqi et al. has reported that 18.2% of patients of cardiovascular diseases in Misan, at the south of Iraq, exhibited poor adherence[37]. Baiee et al. has reported that 51.2% of hypertensive diabetic patients in Babylon, at the middle of Iraq, had poor adherence to hypoglycemic and blood pressure lowering medications[38]. Whereas, Allela et al. showed that 72% of diabetic patients in Duhok, at the north of Iraq, have low adherence rate to hypoglycemic medications[39].

In the present study, PD patients in stage 1 had the lowest adherence score, while these in stage 5 had the highest score; despite the difference in therapeutic adherence among participants based on the disease stage was statistically none significant. Straka et al. found that poor therapeutic adherence in PD patients, receiving at least three daily doses of anti-Parkinson medications, was associated with higher PD duration, lower quality of life, and severity of non-motor symptoms and their frequency[40]; these factors can be translated as advanced disease stage. Moreover, the therapeutic adherence level was significantly associated with age, where PD patients aged below 56 years had higher adherence scores. Whereas, there was no significant association between the therapeutic adherence level with each of gender, weight status, marital status, education level, and zone of residence. Aggarwal et al. reported that there was no association of sociodemographic factors, living environment, family type, and educational level on therapeutic adherence to anti-Parkinson medications in PD patients[41]. Furthermore, Radojevic et al. did not find an association between therapeutic adherence to anti-Parkinson medication in PD patients with age, gender, and educational level [14].

The association of age with therapeutic adherence that is reported in the present study, and the disagreement with Aggarwal et al.and Radojevic et al.in this regard may be attributed the differences in methodological approaches and sample size.

The decline of PD patients' therapeutic adherence with advanced age may be attributed to the progression characteristics of PD and the cognitive decline, psychosis, and depression. Moreover, the complexity of therapeutic management with disease progression, and increased number of medications and the costs of

required treatments may participate in decreasing the therapeutic adherence. All these factors contribute to lower medication adherence. However, in the present study therapeutic adherence score was not correlated with disease stage. Most of the participants in the present study were at stages 2 and 3, with relatively moderate number of participants in stages 1 and 4 and low number of participants in stage 5. The non-uniform distribution of participants, based on the stages of the disease, may mask the relationship of therapeutic adherence and disease stage.

Sathe et al. found that S100B protein level was elevated in substantia nigra of deceased PD patients in comparison with control tissue; and that S100B level in CSF was elevated in PD patients in comparison with healthy individuals. Moreover, knock-down of S100B gene was associated with neuroprotection, reduced microglial inflammation and decreased expression Of receptors of the inflammatory mediators, TNF-α and advanced glycation end products. Sathe et al. proposed that S100B protein is involved in the pathophysiology of PD, and targeting S100B can represent a promising potential treatment approach for this disease[23]. Nevertheless, some studies revealed no significant difference in serum S100B level between PD patients and healthy individuals[23, 42].

Serum level S100B was shown to be positively associated with intensity of motor symptoms of PD patients[42]. Carvalho et al. reported that the overnight elevation of serum S100B level was associated with elevated disease severity and poor sleep of patients with moderately advanced PD[43].

In the present study, serum S100B was not associated with PD stage that disagrees with the aforementioned studies. This may be attributed to the difference in methodological approaches among studies, and the relatively low number of participants at some stages of PD in the present study.

Finally, the present study showed that S100B level was associated with therapeutic adherence of participants. Higher S100B level was reported in PD patients with poor adherence. Moreover, serum S100B level, at cut-off value (3.57 ng/l), provided a good discrimination value (AUC 0.715) between poor and intermediate to good therapeutic adherence of PD patients, with (70.6%) sensitivity and (70.6%) specificity; (P = 0.008).

To the best of the researcher's knowledge, no previous study has been conducted to investigate the association of serum S100B level with the therapeutic adherence level in PD patients, not even in patients of other diseases.

The lower serum level of S100B in PD patients with intermediate to good therapeutic adherence compared these with poor adherence may be related to the effect of anti-Parkinson medications on the expression, degradation and/or clearance of S100B protein; these topics needs further investigations.

Therapeutic non-adherence represents crucial medication-related problems among patients with long-term conditions; it usually results in low quality of life, higher social and medical load, along with increased health care costs. However, the problem of therapeutic non-adherence is often underestimated by the health care givers[8, 44]. As mentioned earlier poor adherence to anti-Parkinson medications was found to be considerably varied among different cohorts[11-14]. The non-adherence rate increases as the number of medications increases[12].

Measurement of therapeutic adherence whether by subjective or objective approaches, or even by measurement of the medication level in blood (i.e., therapeutic drug monitoring), has certain pitfalls and can be subjected to bias. A significant challenge to the measurement of therapeutic adherence is that the topic is not standardized; as well as the currently available measures can produce varied results[45]. Generally, several factors have been reported to affect therapeutic adherence including disease-, patient-, and medication-related factors. Additionally, measurement of therapeutic adherence in different populations may be subjected to various social, cultural and economic factors[41].

Measurement of biological markers, that are well correlated with the effect of the medications, and that are distributed into easily accessible body fluids, such as blood or urine would be feasible approach for measuring therapeutic adherence for these medications. Currently, only few biomarkers are used to measure objective therapeutic adherence and evaluate the medication success[16]. An excellent example in this regard is the measurement of serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) to monitor therapeutic adherence for medications used in heart failure patients[17]. Although this biomarker is used in both research and clinical practice, its cut-off values are under debate and need to be standardized[46].

Serum S100B can be good candidate to measure therapeutic adherence to anti-Parkinson medications as it is involved in the pathogenesis of PD. Further study is required to establish the effect of individual anti-Parkinson medications on serum S100B level.

The major limitations for assessment of biomarkers to estimate the therapeutic adherence includes cost, sample collection issues, drug and/or food interactions with measurement of the biomarker or with the physiological effects of the pharmacotherapies, and longtime intervals between measurements can results in lack of monitoring of adherence for substantial periods of treatment[47].

Limitations

This present study has certain limitations that may have impacted the results, to be noted. Being a cross-sectional study, a causal relationship of risk factors or serum S100B levels with therapeutic adherence to anti-Parkinson medications cannot be established. Therapeutic adherence was measured using a self-reporting subjective questionnaire; such approach can be affected by social desirability response bias, recall bias or white coat bias. The studied sample size was relatively small, and some PD stages were represented by very low number of patients, limiting the statistical power. Furthermore, the enrolled PD patients were receiving different anti-Parkinson medications that may mask the effect of individual medication or the effect of dosing regimens on therapeutic adherence or serum S100B level.

Conclusions

The optimal therapeutic adherence rate of Iraqi PD patients to anti-Parkinson medications is only 25 %; and therapeutic adherence was significantly associated with age, where PD patients aged below 56 year had higher adherence scores.

Serum S100B level in PD patients is not associated with PD stage, however it is negatively correlated with therapeutic adherence level and is good predictive biomarker of therapeutic adherence in PD patients to anti-Parkinson medications.

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Conflicts of Interest

None.

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Ethics Statements

This study has been approved by the scientific committee of the University of Baghdad/ College of Pharmacy, the Iraqi Ministry of Health/ Department of Research and Development, and the health authority in Saad alwitry neural sciences hospital before it was conducted. Written consent was taken from each patient after thorough explanation of the aim of the study and ensuring him/her about the confidentiality of the collected data which was anonymous and was not used for any purpose other than the current study.

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: Mustafa and Ali; data collection: Mustafa and Bahaa; analysis and interpretation of results: Mustafa and Ali; draft manuscript preparation: Mustafa and Ali. All authors reviewed the results and approved the final version of the manuscript.

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