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ORIGINAL ARTICLE

The association of low levels of nesfatin-1 and glucagon-like peptide-1 with oxidative stress in Parkinson's disease

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Abstract

Aim In Parkinson's disease (PD), oxidative stress plays a substantial role in degeneration of dopaminergic neurons at the substantia nigra. Recent reports describe nesfatin-1 and glucagon-like peptide-1 (GLP-1) as molecules with neuroprotective property that relieve oxidative stress. In this study, we aimed to determine the blood levels of nesfatin-1, GLP-1 and oxidative stress status in patients with PD.

Material and method Forty patients with PD, followed-up at the Department of Neurology of Mugla Sitki Kocman University Training and Research Hospital, were enrolled, as well as 40 age- and sex-matched participants as a control group. We determined and compared nesfatin-1, GLP-1, total antioxidant status (TAS), and total oxidant status (TOS) levels in patients with PD and control group.

Results The mean GLP-1 and nesfatin-1 values of patients with PD were lower than those of the control group, whereas their mean TOS value was higher. The mean TAS values, on the other hand, did not reveal any significant difference between the patient and the control groups.

Conclusion The lower nesfatin-1 and GLP-1 levels, in addition to higher TOS levels, in patients with PD compared to those of control group suggest that the neuroprotective effects of these molecules might be related to the oxidative processes. Further studies are required to search for the impact of abovenamed molecules on the treatment option and the likelihood that they may slow down disease progression.

Keywords Parkinson's disease · Oxidative stress · Nesfatin-1 · GLP-1

Introduction

Parkinson's disease (PD) is the second most prevalent chronic neurodegenerative disorder. Understanding the etiopathogenesis of the disease is yet exactly unidentified. However, previous studies have shown the increased oxidative stress and mitochondrial dysfunction and leading cell dysfunction and death on neuron cells in PD [1–3]. Some clinical studies are also crucial to test any potent neuroprotective agent, and there have been recent advances in the utilization of anti-inflammatory agent and plant flavonoid antioxidants to protect against specific neuronal degeneration. The decreasing of the neuroprotective events may have a role in the stimulated oxidative stress and the progress of losing of dopaminergic neurons at the substantia nigra. Oxidative stress reflects a disbalance between cellular reactive oxygen radicals and antioxidants, occurring when the net amount of oxidant exceeds the antioxidant capacity. Total oxidant status (TOS) levels demonstrate the total amount of oxidative products such as superoxide radical anions, hydrochloric acid, malonylaldehyde, and lipid peroxides [4]. Antioxidant molecules such as superoxide dismutase, glutathione peroxidase, catalase, albumin, uric acid, bilirubin, carotenoids, vitamin E, and vitamin C block these harmful reactive oxygen species. These additive antioxidant

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molecules in serum can be determined totally and practically in laboratories separately and this is called total antioxidant status (TAS) [5].

Nesfatin-1, an 82 amino acid peptide, was first identified in 2006 in the rat hypothalamus by Oh et al. [6] and derived from N-terminal fragment of NEFA/nucleobindin 2 (NUCB2), a 396 amino acid protein. Nesfatin-1 expression in the brain is at paraventricular, arcuate, and supraoptic nucleus of hypothalamus, nucleus tractus solitarii, dorsal nucleus of the vagus nerve, and pituitary gland [7, 8]. It has a number of central and peripheral effects [6]. It has to be noted that nesfatin-1 has been tested as a potential therapeutic agent in treatment of many diseases, such as infectious and autoimmune diseases. Nesfatin 1 protects dopaminergic cells against neurotoxicity via anti-apoptotic, antioxidative, and anti-inflammatory effects [7–11].

GLP-1 peptide is a peptide hormone and a growth factor, expressed by enteroendocrine cells located in the small intestine [12]. GLP-1 is also produced mainly in the brainstem and in the sequel transported to a great number of regions in the brain. Neuronal cells in nucleus tractus solitaries can produce GLP-1 and release to the hypothalamic, thalamic, and cortical areas and have a role in signaling pathways. GLP-1 analogs have determined neuroprotective effects in some diseases, such as Parkinson's disease, Alzheimer's disease, head trauma, and stroke [13]. Exendin 4, the GLP-1 analog, has been reported to protect dopaminergic neurons at the substantia nigra and to prevent the dopamine loss at the basal ganglion in animal models of PD [14].

In this study, we aimed to determine the levels of nesfatin-1 and GLP-1 that are suggested to have neuroprotective effects and also to assess the role of oxidative stress by determining TAS and TOS in PD.

Material and methods

In this study, 40 patients with PD, followed-up at the Department of Neurology of Mugla Sitki Kocman University Training and Research Hospital and presented to our outpatient clinic between December 2015 and March 2016, were enrolled, as well as 40 participants as a control group who as well presented to our outpatient clinic at the same time period. Individuals with chronic neurological or psychiatric disorders, with diabetes mellitus or those under 18 years of age were excluded from the study. Sex- and age-matched individuals established patient and control groups. Each person in the patient or control groups was informed about the study and informed subject consent forms were obtained. Previous diagnosis of the patients with PD enrolled into the study was verified using the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's disease. [15]. The third section of Unified Parkinson's disease rating scale (UPDRS) and Hoehn-Yahr (H&Y) scale were applied for clinical severity and staging of PD, respectively.

Collection and examination of blood samples

Venous blood sample of each participant was collected into biochemistry test tube following 10–12 h of fasting, and separated serums were stored at − 80 °C until analysis. TAS and TOS levels were measured by colorimetric assay according to a method developed by Erel [4].

The TOS Rel Assay Diagnostics kit (Rel Assay, Gaziantep, Turkey) was carried out as a procedure following the manufacturer's instruction. The analysis performed on the serum is based on oxidants present in the iron-mediated reactions of the sample oxidize the ferrous ion-o-dianisidine complex to the ferric ion. The oxidation of ferrous ion to ferric ion in the presence of various oxidant species in serum measured the disappearance of color, which is measured at 560 nm. Serum TOS levels (mmol H_2O_2 Eq/L) were calculated based on the given formula. The coefficients of variation values were determined less than 5%.

$$TOS = (\Delta\, AbsSample/\Delta\, AbsStandard2) \times 20(Standard2\ Value)$$
$$\Delta SampleAbsorbance = (Second\ Absorbance\ of\ Sample - First\ Absorbance\ of\ Sample)$$
$$\Delta Absorbancestandard\ 2 = (Second\ Absorbance\ of\ Std\ 2 - First\ Absorbance\ of\ Std\ 2)$$
$$Standard\ 2\ Value = 20\ \mu mol\ H_2O_2Equiv./L$$

TAS Rel Assay Diagnostics kit (Rel Assay, Gaziantep, Turkey) was used by determination of the TAS. The analysis performed in serum is based on incubation of 2,20-azino-di-(3-ethylbenzthiazoline sulfonate) (ABTS) produced by the hydroxyl radical with a peroxidase (metmyoglobin). The blood antioxidants lead to cationic neutralization and the disappearance of color, which is measured at 600 nm. The presenting of antioxidant components in the serum suppresses the oxidative reactions initiated by the hydroxyl radicals. The coefficients of variation values were determined less than 5%.

TAS levels (mmol Trolox Eq/L) within the sera were calculated based on the formula below, which was provided within the kit.

$$TAS = [(\Delta Abs\ standard\ 1) - (\Delta Abs\ serum)]/[(\Delta Abs\ standard\ 1) - (\Delta Abs\ standard\ 2)]$$

Nesfatin-1 and GLP-1 values were determined through ELISA method; using the devices BioTek Instruments (USA), ELx800, Microplate Reader, S/No. 199845 and BioTek Instruments (USA), ELx50, Microplate Washer, S/No. 196060.

Serum GLP-1 levels were determined by ELISA method. Elabscience GLP-1 ELISA kit was used. Test was conducted in accordance with the instructions of the kit insert. Optical density (OD) was measured spectrophotometrically at 450 nm ± 2 nm. Results were expressed in ng/mL.

Elabscience Nesfatin-1 ELISA kit was used to measure nesfatin-1 levels. Instructions of the kit insert were followed to perform the test. Optical density (OD) was measured spectrophotometrically at 450 nm ± 2 nm. Results were expressed in pg/mL.

Statistical analysis

The Welch *t* tests were used to assess the difference between patient with PD and control group in terms of their age, nesfatin-1, GLP-1, TAS, and TOS levels. Summary statistics of the compared values were presented as mean ± standard deviation. To determine whether there was any significant association between sex of the participants and groups, Chi-square was used. In order to compare the patient with PD with a disease duration of more than 5 years and those with less than 5 years, the patients' data were split into two. Since the data did not follow the normal distribution, Wilcoxon-Mann-Whitney was utilized, and median, minimum, maximum, and interquartile range (IQR) were used to summarize them. The strength and direction of correlations between the parameters were represented with the Spearman's correlation coefficient rho. A p value of less than 0.01 was considered statistically significant. All computational analyses were carried out with statistical software R.

Results

The age of the participants ranged from 46 to 83 years. The average age of the patients with PD was 65.78 ± 9.03 years and the control group was 68.90 ± 9.16 years. Both in the patient and control groups, the number of females versus males was 19 (47%) to 21 (53%). There was no difference in sex ($p = 0.66$, Chi-square test) or age ($p = 0.13$, Welch t test) between patients with PD and control group. In our assessment by H&Y staging, 2 (5%) of the patients were at stage 1, 33 (83%) were at stage 2, 1 (3%) was at stage 3, and 4 (10%) were at stage 4 of the disease. The median value of the third section of UPDRS of the patients was 14 (min = 5, max = 38, IQR = 7). The mean Levodopa equivalent dose (LED) was 589.21 ± 393.91. Thirteen of the patients (32.5%) received a high dose of LED (≥ 600 mg) [16].

Mean GLP-1 and nesfatin-1 values of patients with PD were lower than those of the control group ($p < 0.001$, Welch t test), whereas their mean TOS value was higher ($p < 0.001$, Welch t test). Mean TAS values, on the other hand, did not reveal any statistically significant difference between the patient group and the control group ($p = 0.51$, Welch t test) (Table 1).

Table 1 Mean nesfatin-1, GLP-1, TAS, and TOS values of the patients with PD in comparison to those of the control group

	PD	Control	p value
Nesfatin-1 (pg/mL)	27.29 ± 11.07	100.49 ± 24.07	< 0.001
GLP-1 (ng/mL)	0.72 ± 0.32	1.76 ± 0.70	< 0.001
TAS (mmol Trolox equiv./L)	1.15 ± 0.27	1.20 ± 0.30	0.51
TOS (mmol H_2O_2 equiv./L)	9.05 ± 1.43	5.86 ± 1.13	< 0.001

There was no correlation between the disease duration and levels of nesfatin-1 (Spearman's rho = −0.15), GLP-1 (rho = 0.08), TAS (rho = −0.24) or TOS (rho = −0.10) in patients with PD. There was no statistically significant difference between nesfatin-1, GLP-1, TAS, and TOS levels of patients having disease longer than 5 years and having disease equal to or less than 5 years (all $p > 0,05$, Wilcoxon-Mann-Whitney, Table 2).

There was no correlation between UPDRS III and LED with nesfatin-1, GLP-1, TAS, and TOS in patient with PD (Table 3).

Looking at the relationship between nesfatin-1 and GLP-1 with TAS and TOS, there was no correlation between nesfatin-1 and GLP-1 with TAS and TOS in patients with PD or in control group (Table 4). When all cases were evaluated, there was a positive correlation between nesfatin-1 and GLP-1 (Spearman's rho = 0.62, $p < 0.001$) and negative correlations of nesfatin-1 and GLP-1 with TOS (Spearman's rho = − 0.67 and rho = − 0.62, respectively, both $p < 0.001$) (Table 4 and Fig. 1).

Discussion

This study for the first time determined that the novel two peptides, nesfatin-1 and GLP-1, were significantly decreased in patients with PD. Moreover, our findings set out that nesfatin-1 and GLP-1 demonstrate effective results in the prevention of lipid peroxidation via measuring TAS and TOS levels in PD. On the other hand, as these molecules were found decreased in patients with PD, there was no correlation with disease duration, clinical severity measured by UPDRS, and received levodopa equivalent dose (LED). Significant difference was not found between disease duration of less and more than 5 years. This might implicate that the molecular difference in patient group begins probably in the early stages of the disease. There was no correlation in patients with PD or in control group between nesfatin-1 and GLP-1, nesfatin-1 and TOS, and GLP-1 and TOS, while correlation was present in all cases (patients and controls). A reason for this may be the small number of cases. It is observed that the relationship with nesfatin-1 and GLP-1, nesfatin-1 and TOS, and GLP-1 and TOS with the increase in the number of cases occurred.

Table 2 Comparison of levels nesfatin-1, GLP-1, TAS, and TOS between patients with PD with disease duration under or over 5 years. *p* values were obtained from the Wilcoxcon-Mann-Whitney test

	Disease duration ≤ 5				Disease duration > 5				*p* value
	Min	Median	Max	IQR	Min	Median	Max	IQR	
Nesfatin-1	13.6	25.6	60.1	17.41	15.6	20.6	50.8	11.75	0.734
GLP-1	0.15	0.67	1.47	0.40	0.46	0.70	1.56	0.34	0.585
TAS	0.90	1.12	1.92	0.25	0.64	1.02	1.70	0.21	0.098
TOS	5.32	9.24	11.8	1.26	5.83	9.63	11.2	1.64	0.859

But we think that a more extensive study is needed to investigate the cause for this.

Studies on the neuroprotective effect in dopaminergic neurons have a recent acceleration. Nesfatin-1 and GLP-1 have been reported as molecules with neuroprotective effect that relieves oxidative stress [14, 17]. Various mechanisms including oxidative stress, mitochondrial dysfunction, exitotoxicity, insufficiency of neurotrophic factors, and neuroinflammation are blamed for the loss of dopaminergic neurons in PD [18–22]. Postmortem studies have shown the essential role of oxidative stress in neuronal degeneration in PD. Oxidative stress arises as a result of the inefficiency of the antioxidant defense systems in response to the reactive oxygen species [23]. Within the cell, elevated levels of superoxide anion, hydrogen peroxide, hydroxyl radicals, peroxyl radicals, and nitric oxide—collectively the reactive oxygen species—as well as of the reactive nitrogen species [24] pave the way to the cell death by promoting lipid peroxidation and disrupting the protein metabolism [25]. Antioxidative mechanism against the oxidative process stands for the defense system of body and avoids the cell death. Enzymes with antioxidative properties are catalase, superoxide dismutase (SOD), and glutathione peroxidase [25, 26]. Dopaminergic neurons at the substantia nigra are prone to oxidative stress and resulting neurodegeneration as the dopamine itself causes the generation of reactive oxygen species (hydrogen peroxide and hydroxyl radicals) [27]. Increase in free radicals, decrease of the reduced glutathione which has antioxidative effect, and elevated protein oxidation, lipid peroxidation, and DNA damage, all emerging as a result of the dopamine metabolism, are suggested as an evidence of the oxidative process [28, 29].

Table 3 Spearman's rho correlation between UPDRS third section scores and LED with nesfatin-1, GLP-1, TAS, and TOS in patients with PD

	UPDRS III		LED	
	Rho	*p* value	Rho	*p* value
Nesfatin-1	0.07	0.683	0.03	0.849
GLP-1	− 0.20	0.225	0.04	0.797
TAS	− 0.10	0.538	− 0.15	0.371
TOS	0.22	0.171	− 0.05	0.755

Studies also have demonstrated that substantia nigra of patients with PD has an increased oxidative damage of lipids, proteins, and DNA [23]. Likewise, in our study, TOS values of patients with PD found to be higher than that of the control group which is in parallel to the hypothesis of increased oxidative process in PD. Similarly, in the study of Kirbas et al. oxidative stress index (OSI) and TOS levels of patients with PD were higher than those of the control group [24].

In an experimental study, investigating the levels of oxidative process and antioxidant markers in the structures other than substantia nigra, namely, the caudate nucleus, putamen, and frontal cortex, oxidative damage and mitochondrial dysfunction were revealed to occur to a lesser extent in the named structures compared to the substantia nigra. Moreover, increased levels of glutathione were demonstrated in these structures which is the underlying reason of the protection against the oxidative damage [30]. In another study, on the other hand, caudate nucleus, putamen, and frontal cortex were reported to have no increase in the levels of antioxidant enzymes, catalase, SOD, glutathione reductase, and glutathione-s-transferase [31]. Despite the controversial results of the studies, it is clear that presence of antioxidative substances is substantial in the prevention of oxidative mechanism or at least slowing down the process. TAS levels of patients with PD in comparison to the control group were lower in the study of Kirbas et al. [24]. In our study, however, no significant difference was detected between TAS levels of patients with PD and control group. The study by Sharma and coworkers is alike in the sense that it revealed no difference between patients with PD and control individuals in the levels of antioxidatives glutathione peroxidase, glutathione reductase, and gamma-glutamyl transpeptidase [32].

Experimental studies on nesfatin-1 identified its anti-inflammatory, anti-apoptotic, and antioxidative property [8, 17, 33]. Another study has argued that nesfatin-1 protects dopaminergic neurons against rotenone-induced neurotoxicity through regulating the mitochondrial respiratory chain complex 1 activity and decreasing the reactive oxygen species [17]. In their study on intestinal ischemia-reperfusion injury, Ayada et al. compared the rats with or without nesfatin-1 intervention and detected lower TOS and TAS values in nesfatin-1-administered rats, concluding a protective role of nesfatin-1 against ischemia and reperfusion. The protective

Table 4 Spearman's rho correlation between nesfatin-1 and GLP-1 with TAS and TOS in entire cases, only in patients with PD, and only in control group

	All cases		Patient		Control	
	Rho	*p* value	Rho	*p* value	Rho	*p* value
Nesfatin-1 and TAS	0.07	0.522	− 0.11	0.492	0.02	0.907
Nesfatin-1 and TOS	*− 0.67*	*<0.001*	0.01	0.951	− 0.11	0.486
GLP-1 and TAS	0.21	0.065	0.14	0.385	0.27	0.091
GLP-1 and TOS	*− 0.62*	*< 0.001*	0.02	0.893	− 0.14	0.404
Nesfatin-1 and GLP-1	*0.62*	*< 0.001*	− 0.08	0.618	0.09	0.598

The italic data in the tables were p<0,001, this can be italic or nonitalic

effect was claimed to arise from the balanced oxidant capacity, unrelated to the antioxidant capacity [34]. In our study, patients with PD were found to have lower nesfatin-1, but higher TOS levels than those of the control group. These findings suggest that oxidative process might be enhanced by the decrease in nesfatin-1, which is a well-known antioxidant.

It was showed that nesfatin-1 can penetrate the blood-brain barrier, which maintains the possible therapeutic permission for nesfatin-1 as a therapeutic agent of neural deterioration [35]. Nesfatin-1 determined the protection of MES23.5 dopaminergic cells against rotenone-induced neurotoxicity by reversing mitochondrial dysfunction and its anti-apoptotic effects [17]. It has been reported that nesfatin-1 does the cardioprotective effect of isoprostale-induced myocardial injury by reducing apoptosis, inflammation, and oxidative stress [36].

GLP-1 peptide expressed by enteroendocrine cells located in the small intestine acts in regulation of blood glucose and is also recognized as a growth factor. In the brain, GLP-1 is also secreted from area postrema and nucleus tractus solitarii, and the GLP-1 receptor is expressed in the majority of the brain which includes the hippocampus, thalamus, striatum, substantia nigra, amygdala, nucleus basalis of Meynert, and temporal cortex [37]. In neurotoxin-producing PD models, GLP-1 receptor stimulation has been reported to exert benefits in dopaminergic cell survival and functionality and in the resolution of abnormal behavior in addition to its relieving function in oxidative stress which plays a role in neurodegenerative disorders [12, 14]. For this reason, lately, GLP-1 analogs, which have been in use for patients with type-2 diabetes mellitus, attract growing attention for their neuroprotective effect in PD, a neurodegenerative disorder. GLP-1 receptor agonist, exendin-4, has been shown to prevent dopaminergic neuron loss at substantia nigra in PD models [14]. In our study, GLP-1 levels of patients with PD found to be lower than those of the control group. This finding suggests a possible protective role of GLP-1 in dopaminergic neurons of patients with PD. GLP-1 could promote neuronal growth and proliferation, reduce oxidative stress and apoptosis, and modulate inflammatory pathways in neuronal cells in brain [38, 39]. Therefore, GLP-1 may be an attractive potential peptide modality for PD. In addition, glucose is important for neuronal cell energy and GLP-1 plays a crucial role in the regulation of glucose homeostasis. It is well known that high level of glucose leads to several damage in neuronal cell, neuropathy via reactive oxygen species (ROS). The imbalance between ROS and the ability to detoxify the reactive intermediates leads to oxidative stress. Neuronal cell is known to be vulnerable to oxidative stress due to a relatively high concentration of ROS without antioxidant defense mechanism. PD is characterized by neurodegeneration of the nigrostriatal dopaminergic system principally due to the increased the production of ROS in the brain with a decreased efficiency in the cellular responses

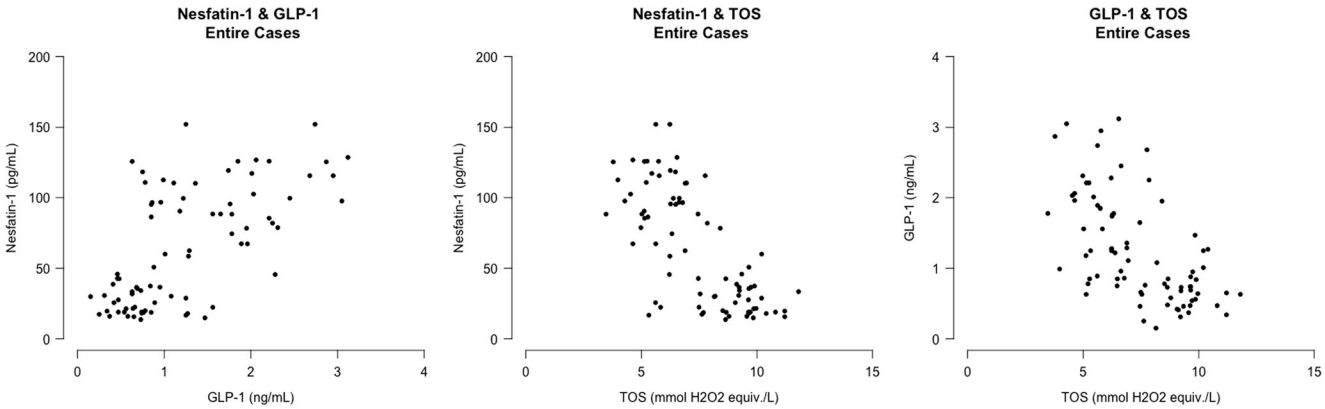

Fig. 1 Scatter plots of nesfatin-1, GLP-1, and TOS. There is a positive correlation between nesfatin-1 and GLP-1 (Spearman's rho =0.62) and a negative correlations of nesfatin-1 and GLP-1 with TOS (Spearman's rho = − 0.67 and rho = − 0.62, respectively)

to oxidative stress [40]. In our study, we found that the level of TOS was increased in patients with PD compared to control group. It was well known that oxidative stress is present in the degeneration of nigrostriatal dopaminergic neurons. The presence of oxidative stress and depletion of the peptides such as nesfatin-1 and GLP-1 may facilitate the process.

The most important limitation of this study is that patients receive dopaminergic treatment. In previous studies is proposed that dopaminergic treatment has an influence on proteome of PD patients [41]. Another point association of dopamine with oxidative stress is unclear. In some studies, it has been suggested that levodopa may cause neuronal damage by increasing oxidative stress. On the other hand, the many studies have shown that levodopa may have neuroprotective effects through decreased lipid peroxidation and toxicity evoked by oxidants and may evoke endogenous antioxidant mechanisms [42]. Although there was no correlation detected between LED with nesfatin-1, GLP-1, TAS, and TOS in patients with PD, we could not exclude the effect of dopaminergic treatment on both protein levels and oxidative stress.

Conclusion

Our study revealed lower nesfatin-1 and GLP-1 levels, in addition to higher TOS levels, in patients with PD. Our findings suggest that the decreased levels of nesfatin-1 and GLP-1 peptides might be the result of neuronal deterioration via the oxidative stress in PD. We believe that our study will contribute to further studies on these molecules to investigate their use as treatment options and the likelihood that they may prevent or slow down the disease progression.

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