ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.31609/jpmrs.2021-87387

The Effect of Hemoglobin, Folate, Vitamin B_{12}, and 25 (OH) Vitamin D_3 Levels on Function, Disability, Pain, and Balance in Patients with Post-Stroke Hemiplegia

İnme Sonrası Hemipleji Gelişen Hastalarda Hemoglobin, Folat, Vitamin B_{12} ve 25 (OH) Vitamin D_3 Düzeylerinin Fonksiyon, Disabilite, Ağrı ve Denge Üzerine Etkisi

Mehmet OKÇU[a], Figen TUNCAY[b], Fatmanur Aybala KOÇAK[b], Yıldız Gonca DOĞRU[b], Zeynep KARAKUZU GÜNGÖR[c], Samet Sancar KAYA[b]

[a]Department of Physical Medicine and Rehabilitation, Marmara University Faculty of Medicine, İstanbul, Türkiye
[b]Department of Physical Medicine and Rehabilitation, Kırşehir Ahi Evran University Faculty of Medicine, Kırşehir, Türkiye
[c]Clinic of Physical Medicine and Rehabilitation, Batman Training and Research Hospital, Batman, Türkiye

ABSTRACT Objective: Although hemoglobin, folate, 25 (OH) vitamin D_3, and vitamin B_{12} levels have been reported to be associated with the risk of stroke, there are limited data on the relationship between these levels and functional status, disability, pain or balance in those who develop post-stroke hemiplegia. The present study aimed to investigate the relationship between parameters such as functional status, pain, balance, and hemoglobin, folate, 25 (OH) vitamin D_3, and vitamin B_{12} levels in patients with post-stroke hemiplegia. **Material and Methods:** Thirty-nine patients were included in the study. Brunnstrom recovery stages, Berg Balance Scale, Functional Ambulation Category (FAC), Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale, Barthel Index scores were determined. In addition, the patients' central pain and hemiplegic shoulder pain were evaluated using numerical rating scales. The hemoglobin, folate, vitamin B_{12}, and 25 (OH) vitamin D3 levels of the participants were noted. **Results:** Hemoglobin levels were significantly higher in functional ambulatory patients (FAC Stage 3-5) than in non-functional ambulatory (FAC Stage 0-2) patients (mean±standard deviation 13.77±2.38, 12.13±1.58, respectively) (p=0.019). In addition, hemoglobin levels were positively correlated with Barthel Index (r=0.496, p=0.002) and Berg Balance Scale (r=0.458, p=0.005). Folate, vitamin B_{12}, and 25 (OH) vitamin D_3 levels were not associated with any of the scales. According to the results of the multivariate logistic regression analysis, the increase in the hemoglobin values of the patients increases the probability of being in the functional ambulatory group 1,655 times (p=0.024). **Conclusion:** In this study, hemoglobin level was found to be associated with disability, ambulation and balance status in patients with post-stroke hemiplegia. For better rehabilitation success, it should be kept in mind to evaluate the hemoglobin levels of the patients.

Keywords: Hemiplegia; hemoglobin; balance; ambulation; disability

ÖZET Amaç: Hemoglobin, folat, 25 (OH) vitamin D3 ve vitamin B12 düzeylerinin inme riski ile ilişkili olduğu bildirilmiş olsa da, bu düzeyler ile inme sonrası hemipleji gelişenlerin fonksiyonel durum, disabilite, ağrı veya denge durumları arasındaki ilişkiler hakkındaki veriler kısıtlıdır. Bu çalışmada, değişkenlerin düzeyleri ile inme sonrası hemipleji gelişen hastalardaki fonksiyonel durum, ağrı ve denge gibi parametreler arasındaki ilişkinin araştırılması amaçlandı. **Gereç ve Yöntemler:** Çalışmaya 39 hasta dâhil edildi. Brunnstrom iyileşme evreleri, Berg Denge Skalası, Fonksiyonel Ambülasyon Sınıflaması (FAS), Leeds Nöropatik Semptom ve Belirtilerin Değerlendirmesi Ağrı Skalası, Barthel İndeks skorları belirlendi. Ayrıca hastaların santral ağrıları ve hemiplejik omuz ağrıları nümerik derecelendirme ölçeği kullanılarak değerlendirildi. Katılımcıların hemoglobin, folat, vitamin B_{12} ve 25 (OH) vitamin D_3 seviyeleri kaydedildi. **Bulgular:** Fonksiyonel ambülasyonu olan (FAS Evre 3-5) hastalarda, fonksiyonel ambülasyonu olmayan (FAS Evre 0-2) hastalara göre hemoglobin seviyeleri anlamlı olarak daha yüksekti (sırasıyla ortalama±standart sapma 13,77±2,38, 12,13±1,58) (p=0,019). Ayrıca hemoglobin seviyeleri Barthel İndeksi (r=0,496, p=0,002) ve Berg Denge Skalası (r=0,458, p=0,005) ile pozitif ilişkiliydi. Folat, vitamin B_{12} ve 25 (OH) vitamin D_3 seviyeleri hiçbir skala ile ilişkili bulunmadı. Çok değişkenli lojistik regresyon analizi sonuçlarına göre hastaların hemoglobin değerlerindeki bir birimlik artış fonksiyonel ambulatuar grupta olma olasılığını 1.655 kat artırmaktadır (p=0,024). **Sonuç:** İnme sonrası hemiplejili hastalarda hemoglobin düzeyi ile disabilite, ambülasyon ve denge durumu ilişkili bulunmuştur. Daha iyi rehabilitasyon başarısı için hastaların hemoglobin düzeylerini değerlendirmek akılda tutulmalıdır.

Anahtar Kelimeler: Hemipleji; hemoglobin; denge; ambülasyon; disabilite

Correspondence: Mehmet OKÇU
Department of Physical Medicine and Rehabilitation, Marmara University Faculty of Medicine, İstanbul, Türkiye
E-mail: dr.okcu@gmail.com

Peer review under responsibility of Journal of Physical Medicine and Rehabilitation Science.

Received: 05 Dec 2021 ***Received in revised form:*** 21 Apr 2022 ***Accepted:*** 27 Apr 2022 ***Available online:*** 09 May 2022

Stroke is a common cause of disability and patients may develop hemiplegia after stroke.[1,2] Various risk factors for stroke have been reported. Diabetes mellitus, smoking, and obesity are some of them.[3-6] In addition, vitamin B_{12}, folate, vitamin D deficiencies, and anemia have been reported to be a potential risk for stroke.[3,7-11] In addition, it has been reported that appropriate management of vascular risk factors can have a positive effect on functional status after stroke.[3,7,12]

Folate plays a vital role in some mechanisms in the body, especially in the production of DNA and RNA.[13] Low plasma folate concentration is known to be a risk factor for stroke.[9,14] Studies have generally examined associations between folate and stroke risk. Data regarding the potential relationship between folate levels and the functional status of post-stroke hemiplegics are still insufficient.[8]

Vitamin D deficiency is common in patients with post-stroke hemiplegia.[15,16] Vitamin D has been associated with stroke risk.[15] There is evidence that maintaining normal levels of vitamin D reduces the risk of stroke and improves muscle function and balance.[15,17]

Vitamin B_{12} deficiency occurs in 10-40% of the general population and has been associated with an increased risk of stroke and cognitive decline.[18,19] It is an easily treatable and often overlooked condition.[19]

Decreased hemoglobin (Hb) levels have been found to increase the risk of stroke through various mechanisms.[10,11] Studies examining the relationship between Hb level and functional outcomes in patients with post-stroke hemiplegia are limited.[20]

Studies have generally focused on the association of vitamin D, vitamin B_{12}, folate deficiencies, and anemia with the likelihood of developing a stroke; however, studies dealing with the relationship between the patient's functional status after stroke are very limited. This study aimed to examine the relationship between Hb, folate, vitamin B_{12}, and vitamin D levels and functional status, ambulation level, pain level, neuropathic pain, and balance in patients who developed hemiplegia after stroke.

MATERIAL AND METHODS

Patients who were admitted to the Kırşehir Ahi Evran University Training and Research Hospital Physical Medicine and Rehabilitation Clinic between December 2019 and May 2020 for post-stroke hemiplegia rehabilitation were included in the study. Patients with hemiplegia aged over 18 years who had a stroke at least 3 months ago were included. Patients with heart, kidney or liver failure, malabsorption conditions, active infection or active malignancy, and history of folate, vitamin B_{12} or vitamin D replacement were excluded from the study.

The study protocol was approved by the local Ethics Committee of Kırşehir Ahi Evran University Faculty of Medicine Clinical Research (date: November 5, 2019, no: 2019-19/185). All patients provided written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Age, gender, disease duration and stroke etiology of the patients were recorded. Patients were assessed by the same physiatrist (ZKG) using the Barthel Index (BI) for daily life activities, Brunnstrom Recovery Stages (BRS) for motor evaluation, the Berg Balance Scale (BBS) for balance, the Functional Ambulation Category (FAC) for ambulation, and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale for neuropathic symptoms and signs. In addition, the central pain levels of the patients and the shoulder pain level of the hemplegic side were evaluated using numerical rating scales (NRS) (0, none; 10, worst pain imaginable).[21]

BRS scores consist of 6 stages (from 1 to 6) and indicate the clinical severity of hemiplegia. Hands, lower extremities, and upper extremities are evaluated separately.[22] With the FAC, ambulation is assessed at 6 levels ranging from 0 to 5. Zero means that at least 2 assistants are required to walk, and 5 means walking independently at any speed and anywhere.[23] The BBS consists of 14 items and evaluates fall risk and balance. Items are scored between 0 and 4. Lower scores mean worse balance.[24,25] BI measures the level of independence in activities of daily living. It consists of 10 items; the highest score is

100, which indicates complete independence.[26] The LANSS pain scale consists of 7 items, 5 of which question pain symptoms. The other 2 are for sensory examinations, which include allodynia and pinprick testing. The scale is scored between 0 and 24 points and scores over 12 points suggest neuropathic pain.[27] All scales had Turkish validity and reliability.[28-31]

The patients were included in one of the non-functional ambulatory (FAC score 0-2) and functional ambulatory (FAC score 3-5) groups. In addition, 2 groups were determined according to BRS scores. Patients with a BRS score of 1-3 (no deviation from synergy) were defined as category I, and patients with a BRS score of 4-6 (deviation from synergy) were defined as category II.

After at least 12 h of fasting, venous blood samples were taken from the antecubital vein. A hemogram was performed using an automatic analyzer (Sysmex XN-1000, Sysmex Company, Japan). Vitamin B_{12}, 25 (OH) vitamin D_3, and folate levels were measured on an immunoassay automatic analyzer (Cobas e601, Roche Diagnostic Corp., Manheim, Germany).

STATISTICAL ANALYSIS

Statistical analyses of the study data were performed using the SPSS for Windows version 25.0 software (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp., USA). Normality assumption was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The assumption of homogeneity of variances was tested using the Levene test. Explanatory statistics of the variables are given as mean±standard deviation (minimum-maximum), and frequencies n (%). The independent t-test was used for univariate analyses of the variables in the study. In order to determine the risk factors determining ambulation status and impaired balance, firstly, univariate logistic regression analysis was performed by taking the variables one by one, and then multivariate logistic regression analysis was performed to determine the combined effects of the variables. Relationships between variables were examined using Pearson correlation coefficients. In all statistical analyses, cases with a p value below 0.05 were interpreted as statistically significant. Since there was no study in the same method, the sample size was not calculated before the study. Power analysis was performed after the participants were included in the study. The G*Power 3.1.9.7 program was used for post-hoc power analysis of the study. The power of the study was calculated as 80.17%, with α=0.05.

RESULTS

A total of 39 patients with a mean age of 62.51±13.11 (range, 25-84) years were included in the study. Twenty-six (66.7%) of the patients were female and 13 (33.3%) were male. Thirty-three (84.6%) of the patients had ischemic stroke and 6 (15.4%) had hemorrhagic stroke. The disease duration was widely distributed between 3 and 552 months, with a median value of 12 months, and those with ≤12 months constituted 51.3% of the entire group.

Thirteen of the patients had anemia. Six patients had vitamin D insufficiency and 31 patients had vitamin D deficiency. The Hb levels of the patients in the functional ambulatory (FAC score 3-5) group were significantly higher than the non-functional ambulatory (FAC score 0-2) group ($p<0.05$). There were no significant differences between the functional ambulatory and non-functional ambulatory groups in terms of B_{12}, folate, and vitamin D values ($p>0.05$) (Table 1).

There is a statistically significant difference between functional ambulatory patients and non-functional ambulatory patients in terms of disease duration (p=0.001). The duration of illness of functional ambulatory patients [3.0 (0.10-46.0)] is longer than the duration of illness of non-functional ambulatory patients [0.45 (0.10-5.0)].

Patients were divided into 2 categories according to their BRS scores (i.e. synergy status) for the hands and upper and lower extremities. There were no significant differences between category 1 (no deviation from synergy) and 2 (deviations from synergy) groups in terms of Hb, folate, vitamin D, and B_{12} levels ($p>0.05$) (Table 2).

In addition, the relationship between shoulder pain and central pain NRS levels and Hb, vitamin

TABLE 1: Hb, vitamin B_{12}, 25 (OH) vitamin D_3 levels by ambulation status.

	Non-functional ambulatory (n=17) Mean±SD (minimum-maximum)	Functional ambulatory (n=22) Mean±SD (minimum-maximum)	p*
Hb (g/dL)	12.13±1.58 (8.10-15.60)	13.77±2.38 (8.30-17.70)	**0.019***
Vitamin B_{12} (pg/mL)	381.94±183.77 (148.0-766.0)	346.72±167.89 (127.0-773)	0.537
Folate (ng/mL)	8.41±4.35 (3.0-18.0)	6.60±2.36 (3.0-12.10)	0.106
25 (OH) vitamin D_3 (ng/mL)	14.76±9.39 (3.0-37.0)	14.59±4.86 (8.0-24.0)	0.941

*Independent t-test; Hb: Hemoglobin; SD: Standard deviation.

TABLE 2: Hb, vitamin B_{12}, 25 (OH) vitamin D_3 levels according to the hand and upper and lower extremity BRS scores.

		Hb (g/dL) Mean±SD	Vitamin B_{12} (pg/mL) Mean±SD	Folate (ng/mL) Mean±SD	25 (OH) vitamin D_3 (ng/mL) Mean±SD
Upper BRS	Category 1 (n=27)	12.97±2.40 (8.10-17.70)	341.92±154.78 (127.0-766.0)	6.76±3.29 (3.0-18.0)	15.29±6.06 (3.0-32.0)
	Category 2 (n=12)	13.25±1.75 (11.0-16.10)	407.41±210.13 (148.0-766.0)	8.80±3.50 (4.60-15.50)	13.25±9.13 (3.0-37.0)
	p*	0.712	0.283	0.088	0.413
Lower BRS	Category 1 (n=21)	12.66±1.86 (8.10-16.0)	365.42±177.82 (127.0-766.0)	7.24±3.50 (3.0-18.0)	14.14±6.35 (3.0-32.0)
	Category 2 (n=18)	13.51±2.52 (8.30-17.70)	358.16±173.42 (148.0-758.0)	7.56±3.47 (3.20-15.50)	15.27±8.0 (3.0-37.0)
	p*	0.236	0.898	0.782	0.625
Hand BRS	Category 1 (n=28)	12.98±2.36 (8.10-17.70)	342.17±151.89 (127.0-766.0))	7.07±3.36 (3.0-18.0)	15.03±6.10 (3.0-32.0)
	Category 2 (n=11)	13.24±1.84 (11.0-16.10)	412.72±219.54 (148.0-766.0)	8.20±2.93 (4.60-14.80)	13.72±9.42 (3.0-37.0)
	p*	0.746	0.259	0.367	0.610

*Independent t-test; Hb: Hemoglobin; BRS: Brunnstrom recovery stages; SD: Standard deviation. Category 1: Patients with a BRS score of 1-3 (no deviation from synergy), Category 2: Patients with a BRS score of 4-6 (deviation from synergy).

B_{12}, and 25 (OH) vitamin D_3 levels was not statistically significant (p>0.05).

It was determined that there was a significant positive correlation between Hb and BI (r=0.496, p=0.002). The relationship between Hb and BBS was also significantly positive (r=0.458, p=0.005). No significant correlation was found between Hb levels and LANSS scores. In addition, no significant correlation was found between vitamin B_{12}, folate, 25 (OH) vitamin D_3, and LANSS, BI, and BBS scores (Table 3).

Odds ratio values obtained as a result of logistic regression analysis are given in Table 4. According to the results of univariate logistic regression analysis, an increase in Hb value by one unit increases the probability of the patient to be in the functional ambulatory group 1,480 times (Table 4). This amount of risk is statistically significant (p=0.034). The effects of vitamin B_{12}, folate and 25 (OH) vitamin D_3 values on being in the non-functional ambulation group and determining the impaired balance were not statisti-

TABLE 3: Relationship between patients' Hb, vitamin B_{12}, folate, 25 (OH) vitamin D_3, and LANSS, BI, and BBS scores.

	Hb (g/dL)	Vitamin B_{12} (pg/mL)	Folate (ng/mL)	25 (OH) vitamin D_3 (ng/mL)	LANSS	BI	BBS
Hb (g/dL)		-0.163	0.062	-0.018	-0.106	0.496**	0.458**
Vitamin B_{12} (pg/mL)			0.395*	0.082	-0.368	-0.245	-0.190
Folate (ng/mL)				0.266	-0.250	-0.150	-0.172
25 (OH) vitamin D_3 (ng/mL)					0.110	0.086	0.085
LANSS						-0.153	-0.106
BI							0.869**
BBS							

Pearson correlation analyses; **Correlation is significant at the 0.01 level; *Correlation is significant at the 0.05 level; HB: Hemoglobin; LANSS: Leeds Assessment of Neuropathic Symptoms and Signs; BI: Barthel Index; BBS: Berg Balance Scale.

TABLE 4: Logistic regression analysis results.

	OR (95% CI)	p value	OR (95% CI)	p value
Hb (g/dL)	1.480 (1.031-2.124)	0.034	1.655 (1.067-2.567)	0.024
Vitamin B_{12} (pg/mL)	0.999 (0.995-1.003)	0.610	1.001 (0.997-1.006)	0.530
Folate (ng/mL)	0.861 (0.700-1.059)	0.156	0.767 (0.576-1.022)	0.070
25 (OH) vitamin D_3 (ng/mL)	0.996 (0.909-1.090)	0.924	1.055 (0.937-1.189)	0.375

OR: Odds Ratio; CI: Confidence interval; HB: Hemoglobin.

cally significant (p>0.05). The power of the model obtained according to the Hosmer and Lemeshow test score to accurately determine risk factors is quite good (c^2=11.160, p=0.193). According to the results of the multivariate logistic regression analysis, the increase in the Hb values of the patients increases the probability of being in the functional ambulatory group 1,655 times. This effect of Hb values is statistically significant (p=0.024). As in univariate logistic regression, the effects of vitamin B_{12}, folate and 25 (OH) vitamin D_3 values in multivariate logistic regression analysis are not statistically significant (p>0.05).

DISCUSSION

Stroke is an important cause of mortality, and survivors may develop varying degrees of loss of function and increased pain.[1] Many studies are showing that vitamin B_{12}, folate, vitamin D deficiencies and anemia increase the risk of stroke; however, limited studies are investigating its association with functional outcomes in stroke survivors.[3,7-11] In this study, it was determined that Hb levels were associated with ambulation status, balance, and disability in patients who developed post-stroke hemiplegia. It should be kept in mind that this situation may adversely affect the effectiveness of rehabilitation and could be a negative prognostic factor in rehabilitation. We found no relationship between B_{12} folate, and 25 (OH) vitamin D_3 levels and functional outcomes and pain.

Chan and Ganasekaran found that patients who developed hemiplegia after ischemic stroke had a higher Functional Independence Measure (FIM) score improvement in the non-anemic group compared with the anemic group.[20] Chang et al. found that the modified-Rankin score (mRS) and BI scores at the 48th hour of patients with ischemic stroke were associated with low Hb, but they did not evaluate functional measures in the later stages.[32] Yoshimura et al. also found that low Hb values were associated with low FIM scores and improvement in Hb levels positively affected FIM scores.[33] In the present study, low Hb was found to be associated with disability, worse ambulation and balance.

Some mechanisms may explain this effect of anemia. First, anemia is thought to be a crucial factor for oxygenation and ischemia in penumbra tissue.[20] It has been claimed that anemia may decrease the oxygen-carrying capacity and cause ischemic damage to the distal area tissue, which plays an important role in the pathophysiology of ischemic stroke.[34] Insufficient oxygenation of the penumbra and surrounding oligemic areas at the time of stroke causes wider tissue damage. Therefore, the level of Hb, which plays a key role in the oxygen-carrying capacity, is an important determinant of the level of tissue damage after stroke.[35] However, it has been reported that iron has great importance in processes such as synaptogenesis, myelination, synaptic plasticity (SP), and behavior. Iron deficiency has been shown to negatively affect various functions of the brain, such as neural plasticity.[36] It is also known that anemia itself is associated with reduced physical performance, muscle strength and disability.[37] All these negative effects of anemia may be the reason for the relationship between low Hb and ambulation, balance, and disability in our study.

In their study, Coşkun Belindayı and Başaran found lower folate levels in patients with non-functional ambulatory (FAC score 0-2) and BRS score Stage 1-3 compared with patients with functional ambulatory (FAC score 3-5) and BRS score Stage 4-6.[8] In the present study, no significant relationship was found between folate levels and ambulation status or BRS scores. These different results may be due to differences between the 2 studies, such as the age of the participants, duration of disease, the number of patients, and the study design.

Sari et al. examined 2 groups with low vitamin D values, one group injected with vitamin D and the other group injected with saline. They found significant improvement in BBS and modified BI scores in 3 months in the vitamin D replacement group, but no significant improvement in BRS and FAC scores.[16] In another study by Coskun Benlidayi et al., no significant difference was found in vitamin D levels according to Brunnstrom scores. They found that functionally ambulatory (FAC 3-5) patients had a lower rate of vitamin D deficiency than non-functional ambulatory (FAC 0-2) patients.[38] Markišić et al. investigated the relationship between mRS, BI, and National Institutes of Health Stroke Scale (NIHSS) scores and homocysteine, vitamin B_{12}, vitamin D levels at baseline, and the 3rd and 6th months in 50 patients with acute ischemic stroke. In conclusion, they found that admission NIHSS scores were correlated with homocysteine, B_{12}, and vitamin D levels. They found no significant correlations with functional outcome measures at 3 and 6 months and homocysteine and vitamin D levels. They found a positive correlation between BI and vitamin B_{12} levels at 3 and 6 months, and between mRS and vitamin B_{12} levels only at 6 months.[3] In the present study, no correlation was found between B_{12}, 25 (OH) vitamin D_3 levels, and functional outcomes and pain. These differing results between studies may be due to different factors such as study designs, duration of disease, and the number of patients. A significant correlation (r=0.869) between BI and BSS was an expected result and may be an indication that the study data in functional evaluations were reliable.

The lack of evaluation of the patients' post-replacement outcome measures was one of the limitations of this study. In addition, the small number of patients, the lack of long-term results, and the absence of a control group can be counted as other limitations. In addition, the blood results at the time of stroke were not evaluated and patients had different disease duration. However, in this study, Hb, folate, and vitamins B_{12} and D were evaluated together. In addition, important problems such as ambulation, balance, disability, level of motor recovery, shoulder pain, central pain, and neuropathic pain in patients with hemiplegia are discussed in a wide range. To the best of our knowledge, this is the first study to show that Hb is associated with balance and ambulation in patients with post-stroke hemiplegia.

CONCLUSION

In conclusion, in this study, it was determined that low Hb was associated with disability, and worse ambulation and balance in patients who developed hemiplegia as a result of stroke. For a more effective rehabilitation, it should be kept in mind to evaluate the Hb levels of patients. More prospective and large-sample studies are needed to confirm these results.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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