Original Article

Association between Dietary Intake, Profibrotic Markers, and Blood Pressure in Patients with Chronic Kidney Disease

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Abstract

Background: Among profibrotic and oxidant factors, matrix metalloproteinases (MMPs) and advanced glycation end products (AGEs) have a major impact on the progression of chronic kidney disease (CKD). However, very limited studies evaluated the relationships between nutrient intake and the mentioned factors in patients with CKD. Therefore, the present study aimed to investigate the correlation between dietary intake and the levels of MMPs, AGEs, and blood pressure (BP) in these patients.

Materials and Methods: This cross-sectional study was performed on 90 patients with CKD (stages 2–5). To evaluate the dietary intake of patients, three days of 24-hour food recall were completed through face-to-face and telephone interviews. Measurement of MMP-2 and MMP-9 concentration was done by enzyme-linked immunosorbent assay. The fluorimetric technique was used to measure the total serum AGEs.

Results: The patients' average dietary intake of sodium, potassium, phosphorus, energy, and protein was 725 mg/day, 1600 mg/day, 703 mg/day, 1825 kcal/day, and 64.83 g/day, respectively. After adjustment of confounding variables, a significant inverse relationship was observed between dietary intake of insoluble fiber and serum levels of MMP-2 ($\beta = -0.218$, $P = 0.05$). In addition, a significant positive relationship was found between molybdenum (Mo) intake and diastolic BP ($\beta = 0.229$, $P = 0.036$).

Conclusion: A higher intake of insoluble fiber might be associated with lower serum levels of MMP-2. Also, a higher Mo intake can be correlated to a higher DBP in patients with CKD. It is suggested to conduct future studies with longitudinal designs and among various populations to better elucidate the observed relationships.

Keywords: Advanced glycation end products, blood pressure, chronic kidney disease, dietary intake, matrix metalloproteinases

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Introduction

Chronic kidney disease (CKD) is associated with decreased kidney function, and the factor used to determine kidney function is glomerular filtration rate (GFR). A person with a GFR of less than 60 ml/min/1.73 m² for at least three months is diagnosed with CKD.[1] CKD is one of the most progressive chronic diseases that affects more than 10% of the general population worldwide.[2,3] Based on the results of a meta-analysis study in 2018, the overall prevalence of CKD in Iranian general population was 15.14%.[4]

Nutritional planning plays an important role in slowing down the decline in kidney function.[5] Recently, the relationship

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between nutritional factors, and the inflammatory and profibrotic indicators of CKD progression has been attractive to researchers.

Among the profibrotic factors that play a crucial role in the pathogenesis of CKD, matrix metalloproteinase-2 (MMP-2) and MMP-9 can be mentioned.[6] MMP-2 and MMP-9 are zinc-dependent endopeptidases and can cause the progression of CKD through interaction with monocyte chemo-attractant proteins, tumor necrosis factors (TNFs), growth factors, and oxidative stress.[7,8] Some previous animal studies evaluated the effects of dietary interventions on MMP-2 and MMP-9.[9-11] However, human studies investigating the relationship between nutrient intake and the serum levels of MMP-2 and MMP-9 are very scarce. The study by Foroumandi *et al*.[12] has reported a significant positive correlation between dietary protein intake and serum MMP-9 in patients with diabetes mellitus.

Another important factor in the progression of CKD is advanced glycation end products (AGEs).[13] AGEs are a heterogeneous group of substances that are increased in hyperglycemia or oxidative stress conditions, such as diabetes. The kidney plays a vital role in clearing and metabolizing AGEs. As a result, serum concentrations of AGEs increase in CKD due to increased oxidative and carbonyl stress.[14] Increased levels of AGEs in patients with CKD are associated with decreased GFR, anemia, malnutrition, and an increased risk of cardiovascular diseases (CVDs).[15] There have been very limited studies regarding the relationship between dietary intake and serum levels of AGEs in patients with renal diseases. The study conducted by Demirci *et al*.[16] found a significant inverse correlation between dietary fiber intake and AGEs in patients undergoing hemodialysis; however, such a relationship has not been investigated in predialysis CKD patients until now.

Hypertension affects the progression of the disease and increases the risk of CVD in patients with CKD.[17] Recently, a clinical trial study was conducted by Turban *et al*.[18] to compare the effect of a diet containing high versus low amounts of potassium on blood pressure (BP) in patients with CKD. They reported no significant effects of treatment diets on BP.[18] It seems that more studies are needed to shed light on the relationship between dietary factors and BP in patients with CKD.

Considering the importance of examining the relationship between dietary intake and CKD risk factors, the present study evaluated the association between dietary intake and profibrotic factors (MMP-2 and MMP-9), AGEs, and BP in patients with CKD.

Materials and Methods

Study population

The present cross-sectional study was conducted on patients with CKD referred to the renal disease clinic affiliated with Kashan University of Medical Sciences during 2021–2022. Inclusion criteria were: 1: ages above 18; 2: estimated GFR (eGFR) less than 90 ml/min/1.73 m^2; 3: the absence of pregnancy and breastfeeding; 4: not suffering from various cancers, lung diseases, mental retardation, or dementia; 5: lack of hemodialysis, peritoneal dialysis, and kidney transplant; and 6: not receiving immunosuppressive medications, and supplements containing antioxidants. The exclusion criteria were unwillingness to participate and incomplete answers to the questionnaires. In the present study, first, the objectives and method of the study were explained to the participants and then the written informed consent was signed by them. All stages of the research have been approved by the Ethics Committee of Kashan University of Medical Sciences (code of ethics: IR.KAUMS.MEDNT.REC.1400.065). The present study was a secondary analysis of the previous research.[19] The method of sample size calculation and the details of the study have been described elsewhere.[19] Briefly, the minimum sample size of 80 subjects was required to detect a correlation coefficient that differs from zero between serum zinc and diastolic blood pressure (DBP), where the value of alpha (α) and beta (β) parameters were considered equal to 1% and 2%, respectively.[19] Also, the simple random sampling method was used to select the participants. After obtaining written consent from the patients, the researcher used the general questionnaire to collect demographic data (age, gender, education, marriage, and employment), history of diseases, medications, and nutritional supplements. To evaluate the diet of the patients, three days of 24-hour food recall (one weekend and two weekdays) were completed through face-to-face and telephone interviews by a trained dietitian. Participants were trained to recall the quantity of all food and beverages consumed by portion size and household measures and to report brand names, methods of food preparation, and ingredients or recipes. Then the recalled consumed food items were converted to grams based on the national references for household measures and weights. The Nutritionist IV (N4) software was used to calculate the total nutrient intake from the entered weights (in grams) of food items. Of note, the food items in this software were adapted to the native ones of the region under study.

In addition, the researcher evaluated anthropometric variables at the beginning of the study, including height and weight. Height was measured in a standing position without shoes using a stadiometer with an accuracy of 0.1 cm. Weight was measured using a scale without shoes and minimal clothing with an accuracy of 0.1 kg.

Other variables evaluated in the study were the patients' systolic and diastolic blood pressure (SBP and DBP), which were measured by a digital sphygmomanometer (Glamor, Model: TMB-1112). For this purpose, people were asked to sit still for 5 to 10 min. Then, the patient's right arm was placed in front of the heart and BP was measured three times, each time at an interval of 3–5 min. Then the average of three measurements was recorded as the individual's BP. If the difference in the measurements was more than 10 mmHg, this measurement was repeated three more times.[20]

Biochemical variables

In this study, to measure the concentrations of MMP-2, MMP-9, AGEs, fasting blood glucose (FBG), and creatinine, 10 ml of venous blood samples were collected from the study participants after fasting for 8–12 hours. The collected blood samples were kept at the laboratory temperature for at least 30–45 min to form a clot. Then they were centrifuged for 10 min at a speed of 1,500–2,000 rpm to separate the serum from the blood sample. Then, the isolated serum of each patient's sample was transferred to the microtubes using a sampler. The patient's profile, code, and sampling time were written on each microtube, and it was kept in a freezer at −80°C until biochemical analyses were performed.

The measurement of MMP-2 and MMP-9 concentrations in the present study was done by enzyme-linked immunosorbent assay method (Zellbio laboratory kit, Germany). To evaluate the total serum concentration of AGEs, the fluorimetric technique was used based on the fluorescence properties of AGEs compounds. eGFR values in the present study were estimated using the CKD-EPI formula.[21]

Statistical analysis

Descriptive statistics such as mean and standard deviation were used to show the dietary intake of participants. Pearson or Spearman correlation coefficients were used to evaluate the correlation of dietary intakes with the serum levels of MMP-2, MMP-9, and AGEs as well as SBP and DB*P* values. Multivariate linear regression was used to control confounding variables to investigate the independent relationship of dietary data with MMP-2, MMP-9, AGEs, SBP, and DBP. Data analysis was done using SPSS software, version 16, and a P value < 0.05 was considered as significance level.

Results

At the beginning of the study, the researchers evaluated 2,500 files of CKD patients according to the inclusion and exclusion criteria to collect the desired samples. After reviewing the existing files and making telephone calls to the target patients, 2,410 were not included in the present study due to the exclusion criteria or unwillingness to participate. Finally, 90 patients with CKD were eligible to participate. Then, the researchers examined the selected patients regarding demographic and disease characteristics. Out of 90 patients included in the study, 64 were men and 26 were women. The age range of the studied subjects was 34–76 years, and their mean age was 60.68, with a standard deviation of 8.81. The average body mass index of the participants in the present study was 30.47 ± 5.65 kg/m^2 and the average eGFR of the participants in the study was 43.23 ± 7.19 ml/min/1.73 m^2. Blood lipid-lowering drugs were the most commonly used drugs and hyperlipidemia was the most common underlying disease among the participants in this study. Regarding the use of supplements, 51.1% of the patients in the study were taking Nephrovite supplements (supplements containing zinc plus vitamin B complex) and 10% of them were taking iron supplements. Based on the eGFR, most of the participants in this study (62.2%) are in stage 3 of CKD. The patients' average dietary intake of sodium, potassium, phosphorus, energy, and protein was 725 mg/day, 1,600 mg/day, 703 mg/day, 1,825 kcal/day, and 64.83 g/day, respectively [Table 1]. The mean and standard deviation of the other nutrients' daily intake have been presented in Table 1. In addition, Table 2 shows the mean values of blood pressure and biochemical variables in the study participants.

Figure 1 shows the correlation between dietary intake and the outcome variables. Significant inverse correlations were found between dietary intake of insoluble fiber and serum MMP-2, dietary intake of vitamin K and serum MMP-9, dietary intake of iron and SBP, and dietary intake of vitamin B1 and SBP. However, a significant positive correlation was observed between the dietary intake of molybdenum (Mo) and DBP. The results of the linear regression analysis are shown in Table 3. After adjusting for confounding variables such as age, gender, energy, BMI, diabetes, and taking supplements, the association between dietary intake of insoluble fiber and MMP-2 levels (β = -0.218, P = 0.050) as well as the dietary intake of Mo and DBP (β =0.229, P = 0.036) remained significant.

Table 1: The average daily dietary intake of the participants

Variables	Values (mean±SD) (n=90)
Energy (Kcal/d)	1825±661
Carbohydrate (g/d)	259±118
Protein (g/d)	64.83±30.45
Fat (g/d)	60.26±26.35
SFA (g/d)	15.16±8.75
MUFA (g/d)	18.01±10.96
PUFA (g/d)	17.74±9.79
Total fiber (g/d)	13.48±7.90
Soluble fiber (g/d)	0.43±0.49
Insoluble fiber (g/d)	2.48±2.73
Sodium (mg/d)	725±542
Potassium (mg/d)	1600±808
Calcium (mg/d)	548±309
Phosphorus (mg/d)	703±365
Magnesium (mg/d)	147±77
Iron (mg/d)	14.2±6.33
Zinc (mg/d)	6.26±4.18
Molybdenum (µg/d)	15.78±22.19
Vitamin A (µg RAE/d)	1049±3686
Vitamin E (mg/d)	2.46±1.73
Vitamin B1 (mg/d)	1.68±0.76
Vitamin B2 (mg/d)	0.96±0.90
Vitamin B3 (mg/d)	18.2±9.58
Vitamin B6 (mg/d)	1.04±0.94
Folic acid (µg/d)	190±131
Vitamin B12 (µg/d)	4.15±19.26
Vitamin C (mg/d)	97.9±82.8
Vitamin K (µg/d)	91.7±94.6

MUFA=Monounsaturated fatty acids, PUFA=Polyunsaturated fatty acid, SFA=Saturated fatty acid, SD=Standard deviation

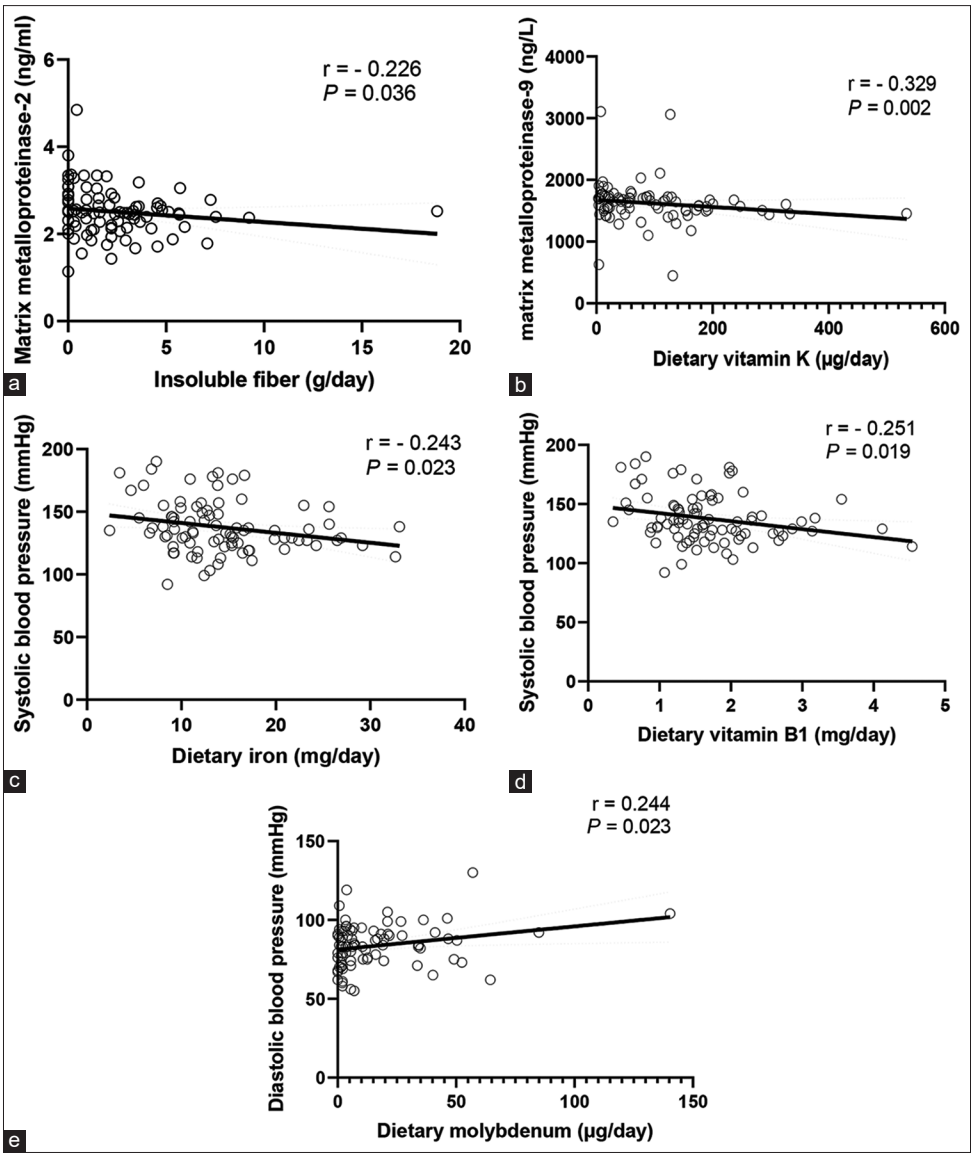

Figure 1: Association between serum levels of matrix metalloproteinase-2 and dietary insoluble fiber intake (a), association between serum level of matrix metalloproteinase-9 and dietary vitamin K (b), association between systolic blood pressure and dietary iron (c), association between systolic blood pressure and dietary vitamin B1 (d), association between diastolic blood pressure and dietary molybdenum (e)

Discussion

In the present study, we found a significant inverse correlation between the intake of insoluble fiber and serum MMP-2 in patients with CKD. In addition, a significant positive relationship was obtained between the Mo intake and DBP in these participants.

Previously, Kerem *et al*.[22] reported that a diet supplemented with soluble fiber decreased the MMP-2 levels significantly and consequently improved colon anastomosis in rats undergoing radiation therapy. They proposed that the short-chain fatty acids (SCFAs), which are produced by the fermentation of the soluble fibers in the colon, might be a mediated factor in reducing the MMP levels.[22] SCFAs (propionate and butyrate) reduce the expression of some pro-inflammatory factors such as TNF-α, which play an important role in the expression of the MMPs gene.[23] Also, in a study conducted by Kawamura *et al*.,[24] the inhibitory effects of SCFAs on the secretion of MMP from human colonic subepithelial myofibroblasts were observed. Contrary, in the present study, it was insoluble fibers that were inversely correlated with MMP-2 levels. Some studies have shown that insoluble fibers can also increase the production of SCFAs in the colon, although the evidence in this field is very limited.[25,26] A hypothetical mechanism for finding such a relationship in the present study may be the role of other factors along with insoluble fibers. For example, food sources containing insoluble fibers (such as fruits and vegetables) are also good sources of antioxidants in the diet. There is a lot of evidence about the anti-inflammatory role of antioxidants by which they reduce inflammatory factors such

Table 2: The mean and standard deviation of the blood pressure and biochemical variables in the study patients (*n*=90)

Variables	Mean	SD
SBP (mmHg)	137.97	20.7
DBP (mmHg)	83.8	13.5
FBG (mg/dl)	119.62	44.82
AGEs (arbitrary unit)	207.97	43.22
MMP-2 (ng/ml)	2.5	0.54
MMP-9 (ng/ml)	1.62	0.325

AGEs=Advanced glycation end products, DBP=Diastolic blood pressure, FBG=Fasting blood glucose, MMP-2=Matrix metalloproteinase-2, MMP-9=Matrix metalloproteinase-9, SBP=Systolic blood pressure, SD=Standard deviation

Table 3: The results of linear regression analysis for the prediction of MMP-2, MMP-9, SBP, and DBP in patients with CKD

Outcome variables	Crude model		Adjusted model*	
Dietary predictors	β	*P*	β	*P*
MMP-2				
Insoluble fiber	−0.222	0.062	−0.218	0.05
MMP-9				
Vitamin K	−0.155	0.156	−0.130	0.264
DBP				
Molybdenum	0.243	0.023	0.229	0.036
SBP				
Vitamin B1	−0.251	0.019	−0.106	0.592
Iron	−0.243	0.023	−0.109	0.604

CKD=Chronic kidney disease, DBP=Diastolic blood pressure, MMP-2=Matrix metalloproteinase-2, MMP-9=Matrix metalloproteinase-9, SBP=Systolic blood pressure * Adjusted for age, gender, BMI, energy intake, having diabetes mellitus and taking supplements

as TNF-α and CRP.[27-29] The reduction of these inflammatory factors also reduces the expression of the MMPs genes.[30,31] Future studies with a different design may better reveal the possible mechanisms of the relationship between insoluble fibers and MMPs.

Another result from the current study was a significant positive correlation between dietary intake of Mo and DBP in patients with CKD, even after adjusting for some confounders such as energy intake. Contrary to the findings of our research, in the study by Li *et al*.,[32] which aimed to investigate the relationship between Mo plasma levels and metabolic syndrome in a case-control design on 5,356 patients, a significant inverse relationship was observed between Mo plasma levels and hypertension. Mo is a trace element found naturally in many foods, and it is also available as a dietary supplement. As a cofactor, Mo is synthesized by the body and required by four enzymes: sulfite oxidase, xanthine oxidase, aldehyde oxidase, and mitochondrial amidoxime-reducing component.[33] These enzymes metabolize sulfur-containing amino acids, purines, and pyrimidines.[33] Mo is found in abundance in legumes. Also, whole grains, nuts, and beef liver are high in Mo.[34] Of note, Mo is mainly excreted through the kidneys, which regulate its levels.[35] As a result, it seems that in conditions of reduced kidney function, the levels of this element in the blood and body fluids increase. Previous research findings have shown that serum Mo levels were higher in CKD patients than in healthy people.[36-38] Also, there is some evidence that Mo accumulation in the body might be associated with higher BP in occupationally exposed workers.[39] This could be an explanation for finding a connection between Mo intake and BP in the present study. Since the subjects of the present study were suffering from CKD, the urinary Mo excretion might decrease and consequently, the serum and body levels of this element would increase due to its intake from diet. This rise in Mo levels may have caused an increase in BP. The causes of the relationship between Mo and BP in the human body are still unknown and the findings of the present study may provide a basis for further studies in this regard.

One of the results of the present study was the existence of a significant inverse correlation between dietary intake of thiamine (vitamin B1) and SBP in patients with CKD; however, after adjusting for confounding variables, this relationship did not remain significant. There are many contradictions regarding the relationship between thiamine and BP in previous study findings. For example, the results of a trial by Rabbani *et al*.,[40] which aimed to investigate the effect of high-dose thiamine supplementation on BP in patients with type 2 diabetes mellitus, showed no significant effect of thiamine on SBP and DBP. However, in the study by Alaei-Shahmiri *et al*.,[41] which aimed to assess the effect of thiamine supplementation on BP in patients with hyperglycemia, a dose of 300 mg/day of thiamine decreased DBP significantly. Of note, thiamine has several effects on the cardiovascular system. It has important hemodynamic effects on the circulatory system and a direct positive pharmacological impact on the heart. Thiamine deficiency has been shown to cause cardiac hypertrophy, decreased cardiac contractility, and rhythm disturbances.[42]

In the current study, we found a significant negative correlation between dietary iron intake and SBP in patients with CKD; however, this relationship was not significant after adjusting for confounding variables. Similarly, Kim *et al*.[43] did not find any correlation between dietary iron intake and SBP or DBP among healthy subjects. However, a significant inverse relationship was observed between total dietary iron intake and SBP and DBP in the study by Tzoulaki *et al*.[44] Further studies are needed to shed light on the association between dietary iron intake and BP, especially in patients with CKD.

Finally, we obtained a significant negative correlation between dietary intake of vitamin K and MMP-9 levels in patients with CKD; however, after adjusting for confounding variables, this result remained insignificant. Some previous studies that have been conducted on cells, animals, and human samples have shown the protective function of vitamin K against inflammation.[45-47] Some investigators proposed that

vitamin K might have an inhibitory effect on inflammation via deactivating nuclear factor kappa B (NF-kB) and reducing the production of TNF-α which is important in the production of MMPs.[48] A previous study reported lower levels of MMP-3 in patients with rheumatoid arthritis (RA) treated with vitamin K2 than in the control group.[45] However, in a clinical trial by Shishavan *et al*.,[49] vitamin K supplementation could not decrease the MMP-3 levels significantly in women with RA. Even though in the present study, no association was found between dietary intake of vitamin K and the levels of MMPs after controlling for confounding factors, the presence of evidence of the anti-inflammatory effects of this vitamin requires further research in this field among patients with CKD.

This study had some limitations. One of them is the study's cross-sectional nature, which does not determine the cause-and-effect relationship. Another limitation was using the 24-hour food recall questionnaire, which does not give us accurate information about dietary intake because it depends on the subject's memory. However, we tried to increase the accuracy of estimating food intake by completing the three-day food recalls (two weekdays and one weekend).

To the best of our knowledge, the present study was the first one that evaluates the relationship between dietary intake and the levels of MMP-2, MMP-9, AGEs, and BP among patients with CKD. In addition, the significant association between dietary intake and outcome variables in the present study was independent of some potentially confounding factors.

Conclusion

According to the results of the present study, a higher intake of insoluble fiber was associated with lower serum levels of MMP-2. Also, a higher Mo intake was correlated to a higher DBP in patients with CKD. It is suggested to conduct future studies with longitudinal designs and among various populations to better elucidate the observed relationships in the current research.

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Conflicts of interest

The authors have no competing interests to declare that are relevant to the content of this article. The authors have no relevant financial or non-financial interests to disclose.

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