

Research Article

Analyzing the Correlation of Serum Iron Parameters with Paraoxanase, Arylesterase and Oxidative Stress Markers in Stem Cell Transplantation Patients

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Abstract

Background: Hematopoietic Stem Cell Transplantation (HSCT) itself is associated with morbidity and mortality, and impaired iron metabolism might have an impact on these complications. Iron, ferritin overload in tissues and systemic circulation, is importantly thought that (to) increase the oxidative stress.

Methods: In patients and controls serum iron, iron binding capacity and ferritin levels were measured. Antioxidant enzymes, Catalase (CAT), Glutathione peroxidase (GPx), Paraoxonase (PON), Arylesterase (ARE), and Glutathione-s Transferase (GST) activities were measured in the serum. These parameters and enzymes in relevance to malondialdehyde (MDA) were evaluated.

Results: Serum MDA levels were significantly increased in the autologous group compared with the control group (p < 0.05). Serum glutathione peroxidase and CAT activity levels were lower in allogeneic and autologous groups, a significant difference was not observed between groups (p > 0.05). Serum PON activity levels in autologous were found to be low when compared with the control group (p < 0.05). In terms of serum iron levels, statistically significant difference were found between allogeneic, autologous and the control group (p < 0.05). Serum ferritin levels were found high in allogeneic and autologous groups than the control group (p < 0.05). According to Spearman's correlation analysis, between serum MDA level and GPx activity in serum, a negative correlation was found. Between serum MDA and serum GST, and between serum PON activity and serum ARE activity were found a positive correlation.

Conlusions: Serum and tissues ferritin overload and the decrease in antioxidative enzymes activity levels may be harmful to body, causing some types of blood cancer diseases.

Keywords: Ferritin; Iron; Malondialdehyde; Oxidative stress; Paraoxonase; Stem cell transplantation

Introduction

Hematopoietic stem cell transplantation (HSCT) is increasingly used as curative therapy for a variety of disorders of the hematopoietic and immune systems. Depending on who the donor is, there are two types of transplantation: allogeneic and autologous HSCT [1,2]. Transplantation outcomes can vary greatly among diseases and are impacted by a range of complications such as infections, graft versus host diseases (GVHD), and toxicities related to the conditioning regimen, including hepatic sinusoidal obstruction syndrome (SOS). Iron is an essential element for life; however iron overload is a common problem in red cell transfusion-dependent patients, who undergo HSCT. Excess iron can cause tissue damage via protein oxidation, membrane lipid peroxidation, and nucleic acid modification, with conversion of hydrogen peroxide to reactive oxygen species [3]. The serum ferritin level is frequently show the body iron storage, and is also an inflammatory marker. For this reason serum ferritin is the most widely used test by clinicians to evaluate iron burden and to screen for iron overload [4]. Paraoxonase 1 (PON1) is a member of a three-gene family which also comprises PON 2 and PON 3, all clustered in tandem on the long arm of human chromosome 7 (q21.22).

PON 1 is synthesized primarily in the liver and a portion is secreted in the plasma, where it is associated with high density lipoproteins (HDL), PON1 also protects low density lipoproteins (LDL), as well as HDL from oxidation [5]. PON1 activity is lower in patients with lung, colorectal and breast cancer [6], esophageal cancer [7] diseases than in controls.

In this study, in allogeneic and autologous stem cell transplantation patients groups and control group's; serum iron, iron binding capacity (IBC), ferritin and MDA levels were measured. Alongside some toxic compound's metabolism, it has been found to have the ability of preventing oxidation of lipoprotein in plasma; antioxidative capacity of PON and aryesterase activities were also measured. Also, taking a role in antioxidative defense GPx, CAT and GST, enzyme levels were measured in stem cell transplantation patients (autologous and allogeneic) and the control group. Our aim is to evaluate and correlate each parameters in patients and the control group and showing the correlation between them.

Materials and Methods

This study was conducted between 2008 and 2012 years in the Stem Cell Transplantation unit of Hematology department in Gazi University

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Received April 30, 2015; Accepted July 08, 2015; Published July 15, 2015

Citation: Karageçili H, Paşaoğlu H, Sucak GT, Suyanı E (2015) Analyzing the Correlation of Serum Iron Parameters with Paraoxanase, Arylesterase and Oxidative Stress Markers in Stem Cell Transplantation Patients. Biochem Physiol 4: 169. doi: 10.4172/2168-9652.1000169

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Hospital. The study was approved by the local Ethics Committee of Gazi University. Written informed consent was obtained from all the patients. This study was supported by Scientific Research Projects unit (project no: 01/2010-60).

The cohort included 61 patients who underwent either autologous-HSCT (n = 35) or allogeneic-HSCT (allo-HSCT) (n = 26) or who underwent both autologous-HSCT and allo-HSCT with a further 36 control patients. Underlying diseases were acute myeloid leukemia (n = 5), acute lymphoblastic leukemia (n = 2), multiple myeloma (n = 16), severe aplastic anemia (n = 7), Non hodgkin lymphoma (n = 8), Hodgkin lymphoma (n = 19), chronic lymphoblastic leukemia (n = 1). The median age of the autologous-HSCT recipients was median 41 years (range, 20-66) with 10 female and 25 male. Median age of the allo-HSCT recipients was median 37 years (range, 17-58) with 11 female and 25 male. Blood samples were drawn from the recipients piror to the pretransplantation and serum samples were stored at -80°C until analysis.

Serum iron, serum iron binding capacity levels were measured using autoanalyzer (Olympus AU 2700 plus, Beckman Coulter) with spectrophotometric method. Serum ferritin levels were measured using autoanalyzer (Advia Centaur, Siemens) with chemiluminescence immunoassay method. Serum MDA levels were analyzed spectrophotometrically by the method of Yoshioka et al. [8]. The basic principle of the method is the colorimetric measurement of thiobarbituric acid reaction after serum protein and tricloroaseticacid precipitation (TCA), MDA couples to thiobarbituric acid to form a pink chromogen that has maximum absorbance at 532 nm. Results were expressed as nmol/ml.

GPx acitivity was measured according to the method described by Paglia DE, Valentina [9]. The enzyme reaction was initiated by addition of H_2O_2 and the rate of NADPH oxidation was monitored continuously in a spectrophotometer at 340 nm for 3 min and at 25°C. Glutathione peroxidase activity was given in nmol/min/ml.

GST activity was measured according to the method of Habig et al. [10]. using chlorodinitrobenzene (CDNB) as a substrate. The formation of GSH CDNB conjugate was monitored by the change in absorbance at 340 nm. One unit of glutathione S-transferase activity is the amount of enzyme catalysing the conjugation of 1 µmol substrate (CDNB) with GSH in min at 25°C and pH: 6.5. Results were given in µmol/min/ml.

The determination of CAT activity was carried out in accordance with the method of Aebi [11]. This assay involves the change in absorbance at 240 nm due to CAT dependent decomposition of hydrogen peroxide. CAT activity was calculated using the molar extinction coefficient(ϵ =0,040 mM⁻¹cm¹). Results were given in µmol/min/ml.

PON activities were measured in 0.1 M Tris-HCl (pH 8.5) buffer which included 2.5 mM CaCl₂, 1 M NaCl. Reaction was started with the addition of paraoxon concentration at 1.2 mM. The rate of generation of 4-nitrophenol was determined spectrophotometrically at 412 nm [12]. Enzymatic activity was calculated by using molar extinction coefficient 18000 M⁻¹ cm⁻¹. One unit of PON activity was defined as the enzyme quantity that disintegrates 1 nmol paraoxon substrate in one minute and enzyme activity was defined as nmol/min/ml (U/ml). ARE was measured in 10 mM Tris-HCl (pH 8) buffer which included 0.9 mM CaCl, with modified methods [12,13]. After addition of the appropriate amount of serum to reaction medium, reaction was started with addition of phenylasetate concentration to be 3.6 mM. Then phenol formation was followed at 270 nm at 37°C for 5 minutes. Arylesterase enzyme activity was calculated using 1310 M x cm as an extinction coefficient of phenol formed as a reaction product. ARE activity was expressed in U/mL and 1 unit was defined as 1µmol phenol formed per minute under the given conditions.

Statistical analysis

The statistical analysis was performed by using Statistical Package for Social Sciences (SPSS for Windows) software (version 15.0) (SPSS Inc., Chicago, IL, USA) and Microsoft Excel (for windows XP). The relation between the variables was determined by the Kruskal-Wallis varyans analysis. The Mann-Whitney test was used for nonparametric comparison of two groups. A Spearman correlation test was used to assess the association between parameters. The data was expressed as mean \pm standard deviation or median (range) according to the distribution properties, and value p < 0.05 was considered statistically significant.

Results

The results of serum levels of MDA, Iron, IBC, ferritin PON, ARE, GPx, GST and CAT enzyme activities of allo-HSCT, autologous-HSCT, autologous HSCT plus allo-HSCT applied patients and control are presented in Table 1. Statistical Results are shown (mean \pm standard error = $\bar{x} \pm$ SE).

Serum MDA levels in the control group were compared with the allogeneic group MDA levels were found to be higher. However, there was no statistically significant difference between them (p > 0.05). In the autologous group MDA levels were found higher than control group (p < 0.05). We found the autologous group GPx levels lower than the control group. There was a statistically significant difference

Biochemical Parameters	Group 1 (Control) n = 36	Group 2 (Allogeneic) n = 26	Group3 (Autologous) n = 35	Group 4 (Patient; allogeneic + autologous) n = 61		
MDA (nmol/ml)	6.72 ± 0.25	7.43 ± 0.33	7.93 ± 0.32^{a}	7.71 ± 0.23		
GPx (nmol/min/ml)	1197.72 ± 28.13	1133.80 ± 55.87	1110.87 ± 36.36ª	1120.64 ± 31.41		
GST (µmol/min/ml)	68.02 ± 2.72	63.52 ± 3.65	71.39 ± 2.9	68.03 ± 2.35		
CAT (µmol/min/ml)	1035.76 ± 69.77	944.71 ± 107.54	931.61 ± 106.31	937.19 ± 75.69		
ARE (µmol/min/ml)	133.78 ± 5.13	130.12 ± 5.31	130.65 ± 5.16	130.42 ± 3.70		
PON (nmol/min/ml)	118.55 ± 9.25	92.29 ± 7.94	89.18 ± 6.08ª	90.51 ± 4.82		
lron (μg/dL)	88.36 ± 5.59	118.81 ± 15.41	61.08 ± 6.58ª	85.69 ± 8.36		
IBC (µg/dL)	255.30 ± 13.63	274.15 ± 13.68	288.48 ± 12.16ª	282.38 ± 9.06		
Ferritin (ng/ml)	98.84 ± 17.05	841.94 ± 176.34ª	428.09 ± 109.51 ^{ab}	604.49 ± 100.60		

Table 1: The results of serum levels of MDA0. Iron0. IBC0. ferritin PON0. ARE0. GPx0. GST and CAT enzyme activities of allo-HSCT0. autologous-HSCT0. autologous HSCT plus allo-HSCT applied patients and control groups.

observed between them (p < 0.05). The GST levels were not statistically significant different between the groups (p > 0.05). CAT levels were found low in allogeneic and autologous groups when compared with the control group, however statistically significant difference were not found between them (p > 0.05). Serum ARE levels were not statistically different between the groups (p > 0.05). We found the autologous group PON levels low and statistically significant when compared with the control group (p > 0.05). The Control group iron levels were compared with autologous group, in the autologous group, iron levels were found to be low (p < 0.05). Statistically significant differences were also found between the allogeneic and the autologous groups in terms of iron levels (p < 0.05). In the autologous group iron binding capacity levels were found to be high when compared with the control group (p < 0.05). The allogeneic and autologous groups were compared with the control group according to serum ferritin levels, ferritin levels were found to be high in these groups (p < 0.05). The allogeneic group was compared with the autologous group, ferritin levels were found to be high in the allogeneic group (p < 0.05).

According to Table 2 above, there were found negative correlation between serum MDA levels and serum GPx activity ($r_{e} = -0.224^{*}$; p =

0.028). Positive correlation was found between serum MDA levels and serum GST activities ($r_s = 0.249^*$; p = 0.014). Positive correlation was found between serum PON activity and ARE activity ($r_s = 0.207^*$; p = 0.041).

Strong negative correlation was observed between the serum ferritin levels and the serum IBC levels ($r_s = -0.282^{**}$; p = 0.005). There was also observed a strong negative correlation between the serum iron levels and serum IBC levels ($r_s = -0.34^{**}$; p = 0.001).

Discussion

HSCT is an important intervention for malignant and nonmalignant blood diseases. However, HSCT is also associated with considerable morbidity and mortality, some of which may be related to iron overload [14]. Depending on who the donor is, there are two types of transplantation: allogeneic and autologous. Iron overload is a common problem in red cell transfusion-dependent patients, who undergo HSCT. The strongest evidence for the adverse impact of iron overload comes from the thalassemia literature [15]. Iron overload, as measured by pre-transplantation serum ferritin, is common in recipients of HSCT, particularly in those with hemoglobinopathies, acute

			MDA	Gpx	GST	CAT	ARE	PON	IRON	IBC	FERRITIN
Spearman's rho	MDA	Correlation Coefficient	10.000	-0.224 (*)	0.249 (*)	-0.141	-0.030	-0.132	-0.113	0.049	0.096
		Sig. (2-tailed)		0.028	0.014	0.168	0.771	0.199	0.268	0.631	0.348
		N	97	97	97	97	97	97	97	97	97
	Gpx	Correlation Coefficient	-0.224 (*)	10.000	-0.044	0.052	0.023	0.134	0.052	-0.011	-0.119
		Sig. (2-tailed)	0.028	•	0.668	0.614	0.822	0.189	0.611	0.911	0.246
		N	97	97	97	97	97	97	97	97	97
	GST	Correlation Coefficient	0.249 (*)	-0.044	10.000	-0.050	0.198	0.132	-0.250 (*)	0.212 (*)	-0.016
		Sig. (2-tailed)	0.014	0.668		0.627	0.052	0.197	0.014	0.037	0.873
		N	97	97	97	97	97	97	97	97	97
	CAT	Correlation Coefficient	-0.141	0.052	-0.050	10.000	0.184	0.123	0.015	-0.056	-0.053
		Sig. (2-tailed)	0.168	0.614	0.627	•	0.072	0.231	0.887	0.587	0.609
		N	97	97	97	97	97	97	97	97	97
	ARE	Correlation Coefficient	-0.030	0.023	0.198	0.184	10.000	0.207(*)	-0.092	-0.035	0.059
		Sig. (2-tailed)	0.771	0.822	0.052	0.072	•	0.041	0.373	0.732	0.564
		N	97	97	97	97	97	97	97	97	97
	PON	Correlation Coefficient	-0.132	0.134	0.132	0.123	0.207 (*)	10.000	0.092	-0.045	-0.090
		Sig. (2-tailed)	0.199	0.189	0.197	0.231	0.041	•	0.369	0.659	0.378
		N	97	97	97	97	97	97	97	97	97
	İRON	Correlation Coefficient	-0.113	0.052	-0.250 (*)	0.015	-0.092	0.092	10.000	-0.341(**)	0.098
		Sig. (2-tailed)	0.268	0.611	0.014	0.887	0.373	0.369	•	0.001	0.341
		N	97	97	97	97	97	97	97	97	97
	IBC	Correlation Coefficient	0.049	-0.011	0.212 (*)	-0.056	-0.035	-0.045	-0.341 (**)	10.000	-0.282 (**)
		Sig. (2-tailed)	0.631	0.911	0.037	0.587	0.732	0.659	0.001		0.005
		N	97	97	97	97	97	97	97	97	97
	FERRITIN	Correlation Coefficient	0.096	-0.119	-0.016	-0.053	0.059	-0.090	0.098	-0.282 (**)	10.000
		Sig. (2-tailed)	0.348	0.246	0.873	0.609	0.564	0.378	0.341	0.005	
		N	97	97	97	97	97	97	97	97	97

*Correlation is significant at the 0.05 level (2-tailed); **Correlation is significant at the 0.01 level (2-tailed)

 Table 2: Test parameters Spearman's correlation analysis.

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leukemia, and myelodysplastic syndromes. Red blood cell transfusion therapy as supportive care for chronic anemia is the principal cause of iron overload in such patients [16]. In this study serum iron levels were compared in control and patient groups, the difference between groups were found statistically significant (p < 0.05). IBC was compared between the control group and the patient group, the difference between the groups were found to be statistically significant (p < 0.05). Serum ferritin levels were compared between the control group and the patient groups, the increase of ferritin level in the patient groups were significant (p < 0.05). Armand et al. [17] reported that in an analysis of their study which was done with 543 elder myeloablative allogeneic HSCT patients, an elevated pretransplantation serum ferritin level was found. A prospective single-institution study of 190 adult patients undergoing myeloablative transplantation demonstrated that elevated pretransplant serum ferritin was associated with increased risk of 100day mortality, acute GVHD, and bloodstream infections or death as a composite end point [18]. Patients with sicle cell disease (SCD) and iron overload may thus be at an increased risk to develop organ failure compared to those with normal iron stores. 247 adult patients with SCD were regularly followed in the sickle cell center. Patients with low values of serum ferritin had a lower incidence of acute painful episodes and organ failure than those who had an iron overload, respectively [19]. The most common test used to estimate the burden of iron is the plasma or serum ferritin concentration [20]. Mortality was higher in heavily iron-overloaded patients, with liver and cardiac dysfunction being the primary cause. Mortality was observed in another study as the serum ferritin levels exceeded 1000 ng/mL [21]. Kataoka et al. [22] reviewed the records of 264 adult patients who underwent allogeneic HSCT for hematologic malignancies at the median value of pretransplantation, serum ferritin was 599 ng/mL (range: 5-8128 ng/mL). There was a strong relationship between pretransplantation serum ferritin and overall servival (OS). Among the various causes that might explain nonrelapse mortality (NRM), infection and organ failure were significantly more frequent in patients in the high ferritin group than those in the low ferritin group. These findings are consistent with the previous reports on the association between iron overload and transplant related complications, such as infection and chronic liver disease after HSCT [23]. Sucak et al. [3] recorded that the probability of survival was significantly lower when ferritin concentration was greater than 500 ng/mL in HSCT patients. A study shows that an elevated pretransplant serum ferritin level in reduced-intensity stem cell transplantation (RIST) is an independent prognostic factor for OS and disease free survival [24]. Mahindra et al. [25] studied 315 patients who underwent autologous stem cell transplantation for Hodgkin (HL) or non-Hodgkin lymphoma (NHL) at their institution in which a pretransplantation ferritin >685 ng/mL was associated with a significantly lower overall and relapse-free survival. Elevated iron stores may also be in relevance to tumor growth. Thus elevated ferritin levels might be in association with relapse and relapse mortality. Akı et al. [26] reported that pretransplantation increased body iron stores and iron regulatory proteins seemed to be important in the clinical risk assessment of patients undergoing HSCT. Yeğin et al. [27] in their study observed that serum ferritin was found to be positively correlated with non transferrin bound iron (NTBI) and negatively correlated with GPx and superoxide dismutase (SOD). An inverse correlation of NTBI with SOD, total antioxidant potential (TAP) and MDA was also demonstrated.

We found a negative correlation between serum MDA levels and serum GPx activity ($r = -0.224^*$; p = 0.028), and a positive correlation between serum MDA levels and serum GST activities ($r = 0.249^*$; p

= 0.014), also a positive correlation was found between serum PON activity and ARE activity ($r = 0.207^*$; p = 0.041) from Table 2, in our study.

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In recent years, increasing experimental and clinical data has provided compelling evidences for the involvement of oxidative stress in large number of pathological states including carcinogenesis. To analyze the importance of the oxidative stress. In this study serum MDA levels in the control group were compared with the patient groups. Serum MDA levels were observed higher in the autologous group than in the control group (p < 0.05). Serum GPx levels were decreased in the patient group when compared to the control group. Statistically significant difference was found between the two groups (p = 0.028; p > 0.05). Serum PON activity levels in the patient group were found lover than the control group were. Statistically significant difference was found (p = 0.015; p < 0.05). There were no significant difference found between the control and patient group's serum ARE activity level (p < 0.05). One of the most often used biomarker to investigate the oxidative damage on lipids is the measurement of MDA, the major lipid peroxidation product. Antioxidants are any substance that can prevent, reduce, or repair the ROS-induced damage of a target biomolecule. Antioxidant are classified in two groups; enzymatic and non-enzymatic.

Enzymatics are SOD, CAT and GPX, non-enzymatics are vitamin E, vitamin C, vitamin A (a-carotene), selenium, transferrin and lactoferrin. Antioxidants may often be intraselular, sometimes extrasellular [28]. Oxidative stress may increase as a result of an imbalance between free radicals and antioxidants. It is well established that oxidative DNA damage is responsible for cancer development [29]. In chronicle leukemia samples, Bakan et al. [30] found serum GPx levels in patients lower than in the control group and MDA levels in patients higher than the control group levels. In patients diagnosed with acute leukemia, Singh et al. [31] found an increase in the MDA level according to the control group. In newly diagnosed acute lymphoid leukemia (ALL) patients MDA levels were found to be higher than normal and decreased after treatment [32]. In gastric cancer patient group, an important increase was observed in GST activity when compared to the control group [33]. In this study, when compared to the activity of GST between the Patients and the control groups there was found no significant difference. Disruption in oxidative stress metabolism was observed as the general properties of altered tumor cells [34]. Battisti et al. [35] Showed that CAT activities were decreased in patients with ALL. Oltra et al. [36] confirmed that CAT activities were decreased in chronicle lymphoblastic leukemia (CLL) patients. Şentürker et al. [37] reported that similar results, CAT activities were decreased in lymphocytes of ALL patients. Çayır et al. [7] showed that basal serum PON1, salt stimulated PON1 and ARE activities in oesophageal cancer patients were significantly higher than healthy controls. Camuzcuoğlu et al. [38] observed that serum PON1 activities were significantly lower in patients with epithelial ovarian cancer compared to controls. Akcay et al. [39] found that PON and HDL levels were low in pancreatic and gastric cancer patients compared to healthy individuals. Similarly, Serum PON1 and ARE activity was found significantly lower in patients with lung cancer, but metastasis status was not observed to affect serum PON1 activity in patients with lung cancer [40]. Conversely, Korpacka et al. [41] found that PON1 activity was the marker of lymph node metastasis in gastrophagal cancer patients.

In our study, the control group and allogeneic groups were compared in terms of the level of serum MDA. MDA were higher in allogeneic group. However, there was no statistically significant difference

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between them (p > 0.05). Autologous group were compared with the control group, MDA levels were found to be higher in autologous group and there was found statistically significant differences between them (p < 0.05).

In this study, when the level of serum GPx activity in the autologous group was compared with the control group, GPx levels were found to be low in the autologous group. Statistically significant differences was found between them (p > 0.05). In our study, we compared the control group with the autologous group according to their serum PON level, in the autologous group the PON level was found to be low. There was detected statistically significant difference between them (p < 0.05). In this study, the allogeneic group was compared to the control group in terms of serum ferritin levels. Ferritin levels were found higher in the allogeneic group (p < 0.05). The autologous group compared with the control group. Autologous ferritin levels were found to be higher (p < 0.05). The allogeneic group were found to be high. Statistically significant difference were found between them (p < 0.05).

The results obtained in this study indicate the oxidative stress importance in the development of hematologic diseases. As a marker of oxidative stress, detecting the level of MDA is important. As well as the detection of serum CAT and GPx levels widely, PON is also an important antioxidant enzyme. It may be useful to detect ARE and GST enzyme levels in a great number of individuals and in different diseases. The important source of damage in hematological diseases is known to be free iron. But ferritin level is also important as the marker and storage form. As a marker of oxidative stress and iron overload; ferritin is studied sufficiently, and can be used reliably.

We found pretransplantation levels of antioxidative enzymes lower in the autologous patients than the allogeneic patients and ferritin level were also higher in the autologous patients than the allogeneic patients. We can say that, determination of stem cell transplantation types which may be autogologus or allojeneic should be evaluated according to the potential antioxidative enzymes activity levels and also to found significant difference between them and to choose suitable transplantation type for patients, larger clinical experiments should be done. Whenever the patient number increases and a defined disease group studied, more reliable results can be taken.

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