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COMMENT

Body Mass Index and C-174G Interleukin-6 Promoter Polymorphism Interact in Predicting Type 2 Diabetes

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Increased levels of IL-6 add further risk to the impact of obesity in respect to the development of type 2 diabetes mellitus (T2DM). A C-174G polymorphism within the IL-6 promoter region was shown to influence transcription rate of IL-6. We made use of a nested case-control study within the European Prospective Investigation into Cancer and Nutrition-Potsdam cohort of 27,548 individuals, selecting 188 T2DM cases and 376 controls to investigate this polymorphism in respect to development of T2DM. This polymorphism was found to modify the correlation between body mass index (BMI) and IL-6 by showing a much stronger increase of IL-6 at increased BMI for CC genotypes compared with GG genotypes. Interestingly, C-174G polymorphism was found to be an effect modifier for the impact of BMI regarding T2DM. Whereas BMI greater than or equal to 28 kg/m^2 increased the risk of T2DM 3.44-fold [95% confidence interval (CI), 1.34- to 8.24-fold] for GG genotypes and 2.94-fold (95% CI, 1.56- to 5.56-fold) for GC genotypes, we found a 17.68-fold (95% CI, 3.57- to 87.66-fold) increase in risk for CC genotypes. In conclusion, obese individuals with BMI greater than or equal to 28 kg/m^2 carrying the CC genotype showed a more than 5-fold increased risk of developing T2DM compared with the remaining genotypes and, hence, might profit most from weight reduction. (*J Clin Endocrinol Metab* 89: 1885–1890, 2004)

SEVERAL PROSPECTIVE STUDIES have recently found increased levels of inflammatory markers, such as C-reactive protein and IL-6, a central stimulus for acute-phase responses, being associated with increased risk of type 2 diabetes mellitus (T2DM) (1–6). These data support the hypothesis that T2DM is a manifestation of a persistent subclinical inflammatory process. Serum levels of IL-6 were further positively correlated with body fat (7) and negatively correlated with insulin resistance (8) and were shown to decrease during weight loss in women (9, 10). IL-6 might deteriorate glucose homeostasis by increasing insulin resistance as shown in hepatocytes (11), even if short-term administration in healthy humans did not impair whole-body glucose disposal (12). IL-6 gene transcription was found to be influenced *in vitro* by the C-174G polymorphism within the IL-6 promoter (13). However, data about the effects of this polymorphism on IL-6 levels in humans are contradictory. Subjects with CC genotype were described as having lower IL-6 levels in a cohort suffering from Sjögren's syndrome (14), whereas in a cohort of humans with abdominal aneurysms, CC genotype was associated with higher IL-6 values (15). In contrast to Fishman *et al.* (13) who described IL-6 levels in 102 healthy subjects as being lower in case of CC genotype, Hulkkonen *et al.* (14) found IL-6 not significantly different among the genotypes of their 400 controls. Furthermore, the IL-6 C-174G polymorphism was found to be associated with insulin resistance (16, 17) and energy expenditure (17); again, the results of these two groups were partially contradictory.

Subjects and Methods

Subjects

A nested case-control study was designed within the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort, which is part of the European multicenter, population-based EPIC study (18) including 27,548 subjects from the area around Potsdam, Germany (women aged 35–65 yr and men aged 40–65 yr). Informed consent was obtained from all study participants. Baseline examination and blood sampling were conducted between 1994 and 1998. Data presented here are based on the first follow-up questionnaires sent to the study participants on average 2.3 yr after baseline examination (19). Cases were free of T2DM at baseline and developed T2DM during the follow-up. Potential cases of incident diabetes were identified from self-reports of incident disease, or current medications, or current dietary treatment for diabetes (n = 399). Diagnosis for each potentially incident subject was confirmed by sending a special questionnaire to the individual's primary care physician. Two hundred one cases of incident diabetes were identified. Nine were excluded because of positive diabetes-related antibodies indicating type 1 diabetes. The 192 remaining cases were matched with two control subjects each by age and sex (n =

Abbreviations: ACE, Angiotensin-converting enzyme; BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HbA1c, hemoglobin A_{1c}; T2DM, type 2 diabetes mellitus.

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384). Individuals with missing values in one of the variables used were not considered (cases, n = 4; controls, n = 8), thus leaving 188 cases and 376 controls for the final analysis. Further details of recruitment are published elsewhere (5, 20).

Body mass index (BMI) was calculated as body weight (kilograms) divided by body height (meters) squared. Physical activity level was calculated from the self-administrated physical activity using the EPIC core questions on physical activity (21) taking into account the metabolic equivalents of Ainsworth *et al.* (22) as described in detail for the EPIC cohort elsewhere (23). Dietary intake was assessed by a self-administered, validated food-frequency questionnaire (24, 25). The questionnaire consisted of 148 food items. Macronutrient intake was calculated using the data of the German food code (26). Information on drug use was obtained during the interview at baseline and comprised all medications being taken during the previous 4 wk in detail on the level of medication name.

Laboratory procedures

Peripheral venous citrate blood samples were taken, and plasma was stored immediately after centrifugation at −80 C until assaying. IL-6 was measured by ELISA (R&D Systems, Minneapolis, MN), and diabetes-associated antibodies GAD65 and IA-2 were analyzed by RIA (Medipan Diagnostica, Selchow, Germany). Hemoglobin A_{1c} (HbA1c) was determined using enzyme immunoassay (Dako Diagnostika, Hamburg, Germany). DNA was extracted from blood cells using Magnasep magnetic beads, following the manufacturer's instruction (Agowa, Berlin, Germany). PCR was performed with the upper primer 5′-TAGCCTGTTAATCTGGTCACTG and the lower primer 5′-TAAATCTTTGTTGGAGGGTG at 64 C annealing temperature and with 2.5 mM $MgCl_2$ concentration. The single-nucleotide polymorphism diagnostic was performed by elongating the primer 5′-AATGTGACGTCCTTTAGCAT using SNuPE and following the instructions and recommendations for purification of the manufacturer (Amersham, Piscataway, NJ). Detection was performed on a MegaBACE 1000 (Molecular Dynamics, Sunnyvale, CA) using single-nucleotide polymorphism profiler 1.0 software.

Statistical analyses

SPSS software 8.0 (SPSS, Inc., Chicago, IL) and SAS software 8.0 (SAS Institute, Cary, NC) were used. All significances are two sided. Values of IL-6 below the limit of quantification were set at 0.7 times the detection limit (27). BMI was dichotomized at 28 kg/m^2. Nonparametric tests were used for testing significant differences (Mann-Whitney *U* test if two groups were compared, otherwise Kruskal-Wallis test). Differences in frequencies were tested by the Pearson χ^2 test. Unconditional logistic regression analysis was used to estimate odds ratios and 95% confidence intervals (CI; likelihood). Odds ratios and 95% CIs for the BMI effects of the different genotypes on development of T2DM were calculated by taking into account the effects of BMI, the genotype present, and the interaction term between BMI and the genotype (28). Odds ratios were used to approximate the relative risk (29). Risk estimates in the fully adjusted model were obtained after adjustment for sex, age, alcohol consumption (grams per day, continuous), carbohydrate consumption (grams per day, continuous), fat consumption (grams per day, continuous), protein consumption (grams per day, continuous), physical activity level (continuous), use of angiotensin-converting enzyme (ACE) inhibitors (dichotomized), use of antihypertensive drugs other than ACE inhibitors (dichotomized), use of statins (dichotomized), use of lipid-lowering drugs other than statins (dichotomized), use of corticoid drugs (dichotomized), use of antiphlogistic drugs (dichotomized), sporting activities (continuous), smoking status (current smoker, nonsmoker), educational attainment (basic training, technical school, or university), and HbA1c (continuous).

TABLE 1. Baseline characteristics of cases and controls

Characteristic	Cases (n = 188)	Controls (n = 376)	P^a
Men [no. (%)]	111 (59)	221 (58.8)	0.51
Age (yr)	55.6 (6.8)	55.6 (6.7)	0.94
Current smokers [no. (%)]	36 (19.1)	79 (21.0)	0.35
Less than high school education [no. (%)]	83 (44.1)	142 (37.8)	0.09
BMI (kg/m^2)	30.7 (4.8)	26.7 (3.5)	<0.001
Physical activity			
Physical activity level	1.8 (0.4)	1.8 (0.4)	0.34
Sport (h/wk)	0.5 (1.2)	0.9 (1.6)	0.009
Dietary habits			
Protein intake (g/d)	81.6 (26.2)	77.8 (22.8)	0.16
Carbohydrate intake (g/d)	238.9 (80.0)	241.3 (76.2)	0.64
Fat intake (g/d)	87.0 (33.4)	85.3 (32.9)	0.61
Saturated fatty acids (g/d)	35.6 (15.0)	32.3 (15.3)	0.96
Monounsaturated fatty acids (g/d)	30.4 (12.6)	29.6 (11.7)	0.63
Polyunsaturated fatty acids (g/d)	15.2 (5.9)	14.7 (5.7)	0.29
Alcohol consumption (g/d)	18.5 (28.2)	16.1 (16.4)	0.48
Drug use [no. (%)]			
β-blockers	39 (20.7)	42 (11.2)	0.002
ACE inhibitors	24 (12.8)	18 (4.8)	0.001
Ca-channel blockers	30 (16)	35 (9.3)	0.016
Other antihypertensive drugs	23 (12.2)	23 (6.1)	0.011
Statins	7 (3.2)	11 (2.9)	0.39
Fibrates	11 (5.9)	8 (2.2)	0.022
Other lipid-lowering drugs	1 (0.5)	0	0.33
Steroids	1 (0.5)	2 (0.5)	0.74
Antiphlogistic drugs	37 (19.7)	54 (14.4)	0.068
IL-6 (pg/ml)	2.45 (1.8)	1.67 (1.6)	<0.001
HbA1c (%)	6.4 (2.2)	4.7 (0.7)	<0.001
Genotypes [no. (%)]			0.77
CC	32 (17)	71 (18.9)	
GC	103 (54.8)	208 (55.3)	
GG	53 (28.2)	97 (25.8)	

Data are presented as mean (SD) or frequency [no. (%)] of baseline characteristics of cases and controls.
[a] *P* values test for significant differences between cases and controls in corresponding characteristics.

Results

To evaluate the predictive value of the IL-6 C-174G polymorphism with respect to T2DM, we made use of a nested case-control study within the EPIC-Potsdam study cohort (27,548 individuals) consisting of 188 case subjects identified in a 2.3-yr follow-up period. Cases were defined as being disease-free at baseline and having developed T2DM during follow-up. Three hundred seventy-six disease-free controls were matched for age and sex to case subjects. Characteristics of cases and controls were previously described (5, 20) and are summarized in Table 1. Cases showed a higher BMI and less sporting activity, and a higher percentage of cases were on antihypertensive drug and fibrate therapy. These variables were not different between the C-174G genotypes (Table 2). Furthermore, IL-6 concentrations were not significantly different between the genotypes. Age was the only deviating parameter across the genotypes due to age differences in the control group. Age was controlled for in all subsequent statistical models. The frequencies of the different genotypes at C-174G in the study population were as follows: 18% CC, 55% GC, and 27% GG. The genotype distributions were not different between the case and the control groups. However, interesting results were revealed regarding the relationship between BMI and IL-6 levels dependent on the C-174G polymorphism. The correlation between BMI and IL-6 levels among subjects with the CC genotype was higher (0.52; 95 CI, 0.366–0.650; n = 103) than among subjects with the GG genotype (0.2; 95% CI, 0.036–0.344; n = 150). In case of the GC genotype, the correlation was in between (0.31; 95% CI, 0.209–0.410; n = 311). Such correlation-modifying properties of the C-174G genotype might also influence the risk estimates for BMI in respect to the development of T2DM. Therefore, we first applied a risk model for T2DM that included interaction terms of continuous BMI and C-174G genotypes. In this model, the interaction term of BMI and CC genotype was of borderline significance after adjustment for age and sex ($P = 0.08$). There was no interaction between BMI and IL-6 with respect to T2DM risk.

Subsequently, we applied models with dichotomized BMI at 28 kg/m^2 because we assumed a threshold value of BMI for the modifying effect of the genotype. The interaction term of dichotomized BMI and C-174G was significantly associated with the risk of T2DM for the CC genotype after adjustment for sex and age ($P = 0.016$, Table 3), and this interaction regarding the risk of T2DM remained significant both in a model further adjusting for HbA1c, alcohol consumption, sporting activity, education, and smoking status ($P = 0.033$, Table 3) and in the fully adjusted model, as described in *Subjects and Methods* ($P = 0.042$, Table 3). Within the group with a BMI greater than or equal to 28 kg/m^2, there were 122 controls and 135 cases. For all models calculated, the interaction terms between BMI and the GC and GG genotypes were not significantly associated with the risk of T2DM, and for these genotypes, the BMI effect was largely determined by the main effect of BMI (Table 3). From the statistical model, we calculated the T2DM risk of BMI greater than or equal to 28 kg/m^2 compared with BMI less than 28 kg/m^2 for the genotypes, considering the respective main and interaction terms. For the CC genotype, an increase in risk of T2DM for a BMI greater than or equal to 28 kg/m^2 was

TABLE 2. Characteristics of the genotypes at the C-174G polymorphism within the IL-6 promoter

Characteristic	CC (n = 103)	GC (n = 311)	GG (n = 150)	*P*
Cases [no. (%)]	32 (31.1)	103 (33.1)	53 (35.3)	0.77
Men [no. (%)]	58 (56.3)	182 (58.5)	92 (61.3)	0.72
Age (yr)	54.4 (7.0)	56.2 (6.6)	55.2 (6.8)	0.034
Current smokers [no. (%)]	18 (17.5)	63 (20.3)	34 (22.7)	0.60
Less than high school education [no. (%)]	40 (38.8)	124 (39.9)	61 (40.7)	0.96
BMI (kg/m^2)	28.5 (4.7)	27.9 (4.4)	28.0 (4.4)	0.62
Physical activity				
Physical activity level	1.80 (0.36)	1.78 (0.4)	1.84 (0.42)	0.28
Sport (h/wk)	0.96 (1.9)	0.74 (1.4)	0.69 (1.4)	0.67
Dietary habits				
Protein intake (g/d)	75.7 (22.5)	80.8 (25.3)	77.8 (22.1)	0.21
Carbohydrate intake (g/d)	229.4 (70.3)	245.9 (81.6)	236.9 (72.5)	0.16
Fat intake (g/d)	83.7 (29.8)	86.4 (35.2)	86.1 (30.6)	0.77
Saturated fatty acids (g/d)	34.1 (13.7)	35.5 (16.1)	35.9 (14.4)	0.58
Monounsaturated fatty acids (g/d)	29.1 (10.8)	30.1 (12.9)	29.9 (10.7)	0.76
Polyunsaturated fatty acids (g/d)	14.9 (5.2)	15.0 (6.1)	14.5 (5.7)	0.73
Alcohol consumption (g/d)	16.5 (20.9)	17.5 (22.5)	16.0 (18.1)	0.76
Drug use [no. (%)]				
β-blockers	19 (18.4)	37 (11.9)	25 (16.7)	0.17
ACE inhibitors	8 (7.8)	25 (8.0)	9 (6.0)	0.73
Ca-channel blockers	8 (7.8)	38 (12.2)	19 (12.7)	0.41
Other antihypertensive drugs	10 (9.7)	24 (7.7)	12 (8.0)	0.81
Statins	2 (1.9)	12 (3.9)	4 (2.7)	0.58
Fibrates	1 (1.0)	11 (3.5)	7 (4.7)	0.27
Other lipid lowering drugs	1 (1.0)	0	0	0.11
Steroids	0	2 (0.6)	1 (0.7)	0.71
Antiphlogistic drugs	15 (14.6)	54 (17.4)	22 (14.7)	0.68
IL-6 (pg/ml)	1.77 (1.23)	1.96 (1.75)	1.97 (1.90)	0.82
HbA1c (%)	5.3 (1.4)	5.3 (1.7)	5.4 (1.6)	0.62

Data are presented as mean (SD) or frequency [no. (%)].
P values test for significant differences between the genotypes.

estimated to be 17.68 (95% CI, 3.57–87.66) in the fully adjusted model. In contrast, for the GG genotype, a BMI greater than or equal to 28 kg/m^2 increased the risk only by 3.44 (95% CI, 1.34–8.24), and for the GC genotype, the risk increased only by 2.94 (95% CI, 1.56–5.56; Fig. 1). Thus, a BMI greater than or equal to 28 kg/m^2 was associated with a more than 5-fold higher increase in risk of T2DM in subjects carrying the CC genotype than in subjects with the GC or GG genotypes. Further inclusion of multiplicative interaction terms between genotype and statin use, use of ACE inhibitors, and protein, carbohydrate, and fat intake revealed no significant interactions, and these interaction terms were, therefore, not included in the full model. Even in the larger model including the just mentioned further interaction terms, the interaction between CC genotype and BMI greater than or equal to 28 kg/m^2 remained significantly associated with the development of T2DM ($P = 0.022$). Among the confounders, HbA1c was found to be most strongly associated with T2DM risk in all models applied.

TABLE 3. Results of unconditional regression analysis

Variable	Odds Ratio	95% CI	*P*
Adjusted[a]			
BMI ≥ 28 kg/m^2	5.10	2.50–10.81	<0.001
GC or CC at C-174G	1.04	0.54–2.06	0.910
CC at C-174G	0.24	0.06–0.71	0.022
BMI ≥ 28 kg/m^2 by GC or CC	0.80	0.33–1.92	0.619
BMI ≥ 28 kg/m^2 by CC	5.53	1.54–26.79	0.016
Further adjusted[b]			
BMI ≥ 28 kg/m^2	3.95	1.68–9.61	0.002
GC or CC at C-174G	1.10	0.52–2.41	0.802
CC at C-174G	0.18	0.03–0.68	0.028
BMI ≥ 28 kg/m^2 by GC or CC	0.81	0.28–2.31	0.700
BMI ≥ 28 kg/m^2 by CC	6.39	1.37–47.06	0.033
Fully adjusted[c]			
BMI ≥ 28 kg/m^2	3.32	1.35–8.39	0.01
GC or CC at C-174G	1.15	0.53–2.59	0.73
CC at C-174G	0.18	0.03–0.69	0.029
BMI ≥ 28 kg/m^2 by GC or CC	0.89	0.29–2.63	0.83
BMI ≥ 28 kg/m^2 by CC	6.01	1.25–45.00	0.042

BMI was dichotomized at 28 kg/m^2.

Variables for genotypes were GC or CC at C-174G (GC or CC = 1, other = 0) and CC at C-174G (CC = 1, other = 0). Interaction terms describe multiplicative interaction between dichotomized BMI variable and the variables for the genotypes.

[a] Adjusted for sex and age.

[b] Further adjusted for HbA1c, alcohol consumption, sporting activities, educational attainment, and smoking status.

[c] Fully adjusted model additionally including physical activity level, protein intake, carbohydrate intake, fat intake, ACE inhibitor use, use of other antihypertensive drugs, statin use, use of other lipid-lowering drugs, use of corticosteroids, and use of antiphlogistic drugs as covariates.

Discussion

In this prospective study, we demonstrate that the C-174G polymorphism within the IL-6 promoter affects the correlation between BMI and IL-6 levels. Increasing BMI was correlated with higher IL-6 concentrations for the CC genotype than for GG the genotype. Therefore, in respect to the risk factor IL-6, obesity is more deleterious for persons carrying the CC genotype than for those with the GG genotype. Furthermore, C-174G polymorphism modifies the association between BMI and the risk of T2DM. Being obese was associated with a higher risk of developing T2DM (>5 times higher in our study cohort) among subjects with the CC genotype than among subjects with the remaining genotypes. This conclusion was also valid in the fully adjusted model including additional environmental factors such as nutrient intake (protein intake, fat intake, carbohydrate intake, and alcohol consumption) or drug use (ACE inhibitors and other antihypertensive drugs and statins and other lipid-lowering drugs, as well as corticosteroids and antiphlogistic drugs). Statins and ACE inhibitors were independently fit into the model because there is evidence that both reduce diabetes risk (30–32). For the risk of coronary heart disease, a protective effect of statin use was shown in case of CC genotype (33). Therefore, we included further interaction terms between C-174G and statin use, ACE inhibitor use, and macronutrient intakes into the model. None of these interaction terms yielded significant impact on T2DM risk. Neither further subdividing the medications into the specific substances mentioned in Table 2 nor the additional inclusion of a variable for acute infection (flu) at baseline substantially altered the interaction between BMI and CC genotype described here (data not shown).

Effect modification between a genotype and an environmental factor is a scientifically important concept. Here we

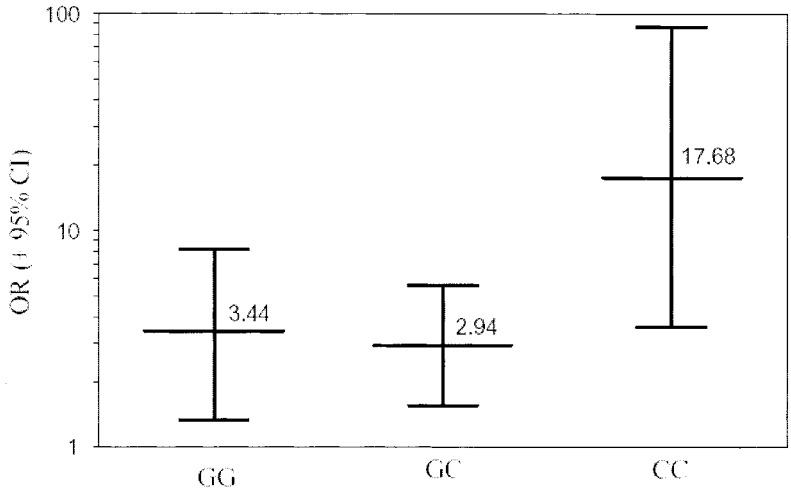

FIG. 1. Odds ratios (OR) and 95% CIs for the effect of BMI greater than or equal to 28 kg/m^2 with regard to risk of T2DM dependent on IL-6 C-174G polymorphism. BMI less than 28 kg/m^2 is set as reference. Data obtained from the fully adjusted model.

demonstrated such a phenomenon in case of the C-174G polymorphism within the IL-6 promoter and BMI. The statistical analyses clearly indicate that, for the CC genotype, a high BMI is associated with a higher risk of T2DM compared with the remaining genotypes. However, the relatively small study population certainly limited the precise risk estimation and resulted in large CIs. Therefore, our point estimates of relative risk need confirmation in studies with larger sample sizes. Accepting the concept of an interaction between C-174G polymorphism and BMI, other reports regarding the effect of this genotype may be interpreted properly together with BMI. Otherwise, genotype-specific effects might be misinterpreted. The interaction of the C-174G polymorphism with BMI leading to an increased risk of T2DM in obese CC genotypes in our cohort might also explain the differences in the results of a recent cross-sectional study (34). This study described the GG genotype as being more common in diabetics *vs.* nondiabetics, and one might speculate whether this result is driven by differences in BMI between the genotypes. Berthier *et al.* (35) described recently the G allele at C-174G as being more common in lean subjects. This result fits well with the finding of a lower basal metabolic rate in case of CC genotype (17), possibly leading to body weight gain. However, in our study focusing on the development of T2DM, BMI was not significantly different between genotypes.

The impact of the IL-6 C-174G polymorphism on IL-6 levels in humans has been controversial (13–15). Again, one might speculate that the interaction with BMI as described here is responsible for the different results described in the literature. The different slope of correlation between BMI and IL-6 concentrations dependent on the C-174G polymorphism implies, in the case of CC genotype, a lower IL-6 concentration for lean individuals and a higher IL-6 concentration for obese persons compared with GG genotypes. BMI was not significantly different between the genotypes of the current study population, and the mean BMI was in the range of the intersection between the two fitting lines for the correlations between IL-6 and BMI for both CC and GG genotypes. Therefore, it is reasonable that we found IL-6 levels not significantly different between the genotypes. Again, it seems to be necessary to take the BMI values into account in discussing IL-6 levels in the different genotypes at the C-174G polymorphism.

Epidemiological studies, like the one performed here, in principal cannot elucidate the mechanisms responsible for the interactions described. Therefore, which factors linked to BMI differentially regulate IL-6 gene expression dependent on the C-174G polymorphism within the IL-6 promoter remain to be evaluated.

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