Insulinemia in Children at Low and High Risk of NIDDM

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OBJECTIVE — Fasting hyperinsulinemia in the presence of normoglycemia usually indicates insulin resistance and is characteristic of populations at high risk for developing NIDDM. Hyperinsulinemia predicts the development of impaired glucose tolerance and NIDDM in Pima Indians, a population with a high incidence of NIDDM. Insulin concentrations in population-based samples of children who have different risks of developing NIDDM later in life have not been reported previously.

RESEARCH DESIGN AND METHODS — We compared fasting insulin concentrations in two populations of nondiabetic children, 6–19 yr of age: Pima Indians from southern Arizona and Caucasians from Minnesota.

RESULTS — Insulin concentration varied with age, sex, glucose concentration, and relative weight. Mean fasting insulin concentration was 140.3 pM in Pima Indian males, 94.4 pM in Caucasian males, 171.5 pM in Pima Indian females, and 107.1 pM in Caucasian females. For each sex, the mean fasting insulin concentration, controlled for age, glucose, and relative weight, was significantly higher in the Pima Indians than in the Caucasians ($P < 0.001$).

CONCLUSIONS — From a young age, Pima Indian children have higher fasting insulin concentrations than Caucasian children. As hyperinsulinemia predicts subsequent NIDDM, these data suggest that the susceptibility to NIDDM is manifest at a young age as fasting hyperinsulinemia.

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NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; NGT, NORMAL GLUCOSE TOLERANCE; IGT, IMPAIRED GLUCOSE TOLERANCE; OGTT, ORAL GLUCOSE TOLERANCE TEST; RIA, RADIOIMMUNOASSAY; CV, COEFFICIENT OF VARIATION; BMI, BODY MASS INDEX; DF, DEGREE OF FREEDOM.

Hyperinsulinemia indicates insulin resistance and is characteristic of adult Pima Indians (1–3) and of other populations at high risk for NIDDM (4–7). Hyperinsulinemia predicts the impairment of glucose tolerance in Nauruans (7), Pima Indians (8), Mexican Americans (9), and Caucasians (10). Few data are available comparing insulin concentrations in population-based samples of children. The Bogalusa Heart Study found black children had higher insulin concentrations than Caucasian children (11). In a small sample of 13 lean Pima Indian children and 10 lean Caucasian children, the fasting insulin concentrations were higher in the Pima Indians (12).

The purpose of this study was to determine, over a wide range of relative weights and ages, whether Pima Indian children with NGT were more hyperinsulinemic than Caucasian children.

RESEARCH DESIGN AND METHODS

— Study participants were 6–19 yr of age. The Caucasian children, living in Rochester, Minnesota, were members of families that had volunteered to participate in a study of the effects of environment and inherited traits on lipid transport and hypertension (13,14). The Pima Indian children were participants in a longitudinal population-based study of chronic diseases in the Gila River Indian Community in southern Arizona (15,16), and only those whose heritage was at least half Pima, Tohono O'odham (Papago), or a mixture of these two closely related tribes were included.

Children from both populations were recruited for the study regardless of health or family history of disease. Those with diabetes were excluded from both samples, and, among the Pima Indian children, all of whom had an OGTT, only those with NGT were included in analyses.

All children were seen in the morning, at which time venous blood

Table 1—*Clinical characteristics of the study populations*

	Males		Females	
	Pima Indian	Caucasian	Pima Indian	Caucasian
N	201	228	217	221
Age (yr)				
Mean*	13.9 (13.4–14.3)	13.4 (12.9–13.8)	14.1 (13.7–14.6)	13.6 (13.1–14.1)
Range	6.35–19.99	6.01–19.98	6.63–19.84	6.20–19.90
Height (cm)				
Mean*	160.5 (158.4–162.5)	158.4 (156.0–160.9)	155.5 (154.0–157.0)	154.9 (152.9–156.9)
Range	108.0–188.0	110.5–196.0	116.0–174.0	110.4–185.3
Weight (kg)				
Mean*	66.8 (63.4–70.2)	51.2 (49.0–53.5)	63.1 (60.2–66.0)	49.4 (47.2–51.6)
Range	19.0–143.0	19.5–93.5	21.0–139.0	18.5–111.7
Relative weight (%)				
Mean*	133.1 (128.8–137.4)	107.8 (105.7–109.8)	132.8 (128.5–137.2)	106.8 (104.6–109.0)
Range	86.0–251.0	75.4–161.6	78.9–263.8	80.7–203.1
Glucose (mM)				
Mean†	5.13 (5.07–5.18)	5.22 (5.18–5.27)	4.98 (4.93–5.03)	5.04 (4.99–5.08)
Range	4.1–6.6	4.2–6.4	3.7–5.9	4.0–6.8
Insulin (pM)				
Mean†	140.3 (129.9–151.5)	94.4 (90.2–98.9)	171.5 (158.9–185.2)	107.1 (101.1–113.5)
Range	24.0–630.0	36.0–258.0	48.0–3468.0	30.0–456.0

*Mean (95% CI).
†Geometric mean (95% CI).

was drawn for the determination of fasting glucose and insulin concentrations. Height and weight were measured with the participants wearing lightweight indoor clothing and no shoes. Of 916 children from these two populations, 49 children were excluded: glucose or insulin was not measured in 18; 2 Caucasians and 7 Pima Indians had previously diagnosed diabetes; 21 Pima Indian children had IGT; and 1 Caucasian had a fasting glucose of 7.0 mM. This study reports the findings from the remaining 449 Caucasian and 418 Pima Indian children.

At least one parent for each of the Caucasian children and for 404 of the Pima Indian children was examined, and medical records were reviewed for a diagnosis of diabetes. For 276 (66.0%) of the 418 Pima Indian children included in the study, a parent had been examined within the last 5 yr, so the family knew reasonably well whether or not a parent had diabetes. Of the 263 children known

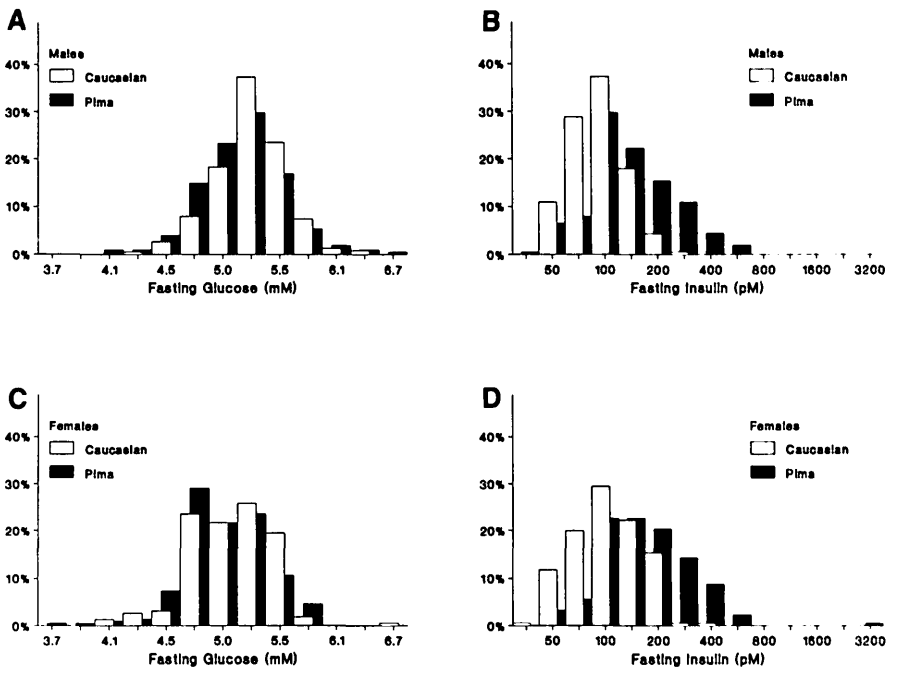

Figure 1—*Frequency distributions of fasting glucose and insulin concentrations for Caucasian and Pima Indian males (A and B) and females (C and D). Both glucose and insulin are on logarithmic scales.*

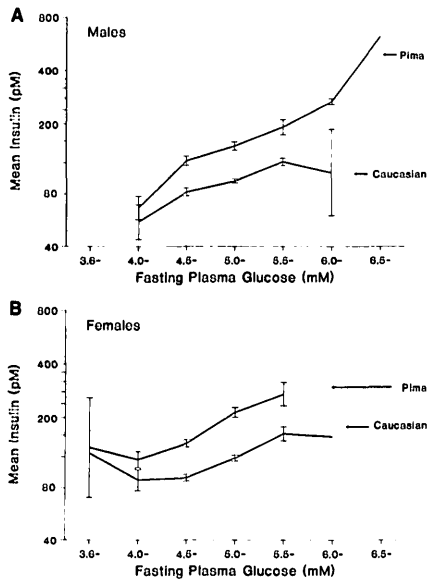

Figure 2—*Fasting insulin by fasting glucose concentration, both on logarithmic scales for males (A) and females (B). Bars represent ± SE. Points without bars represent only one participant.*

to be living in the community who were in the targeted age range but were not included in the study, a parent of 173 (65.8%) had been examined within the past 5 yr. Rates of diabetes were similar among the parents of those who were (44.9%) and those who were not (44.5%) included in the study. Our sample, therefore, was not overrepresented by children with a family history of diabetes.

Laboratory measurements

In Rochester, venous blood was collected in two tubes, one containing EDTA and one containing sodium fluoride to prevent glycolysis, and kept on ice until the plasma was separated. A sample of the plasma was frozen within 2 h of being drawn. Frozen samples periodically were shipped to Phoenix, AZ, where insulin was measured in the EDTA plasma, and glucose was measured in the fluoridated plasma. For the Pima samples, fluoridated plasma was frozen for transport from the field clinic to the laboratory in Phoenix where glucose measurements were made, usually within 3 days. Serum was separated shortly after collection and frozen until assayed for insulin.

We determined insulin concentrations with the Herbert modification (17) of the RIA of Yalow and Berson (18). Each assay contained approximately equal numbers of Pima and Caucasian samples. The interassay CV was 6–8% for concentrations of 42–558 pM. Insulin was reported in μU/ml and converted to pM (1 μU/ml = 6 pM). We measured glucose with a Technicon Autoanalyzer (Technicon Instruments, Tarrytown, NY) (19). We did not use other measures of insulin secretion, such as C-peptide and proinsulin.

Because serum samples were available from Arizona and plasma samples were available from Minnesota, paired samples were assayed for insulin in 26 nondiabetic Pima Indian children to assure comparability of results. The insulin concentrations in serum and plasma were virtually identical. The mean serum-to-plasma ratio was 0.97 with a range of 0.76–1.13 (r = 0.995).

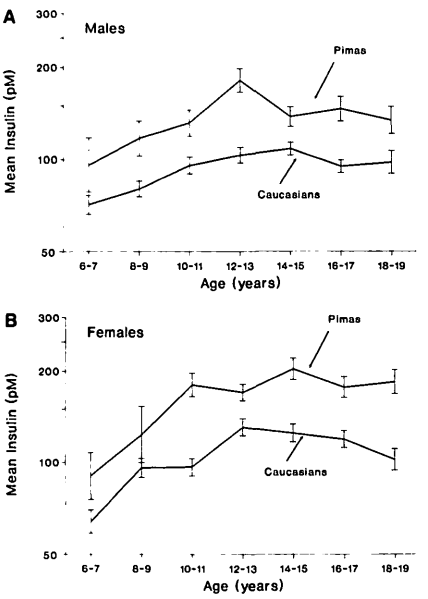

Figure 3—*Fasting insulin (on a logarithmic scale) by age for males (A) and females (B). Bars represent ± SE.*

Statistical analysis

We used age- and sex-specific standard weights for height (20) to determine the standard weight for each child. We did not use BMI because it is height-dependent in growing children. Six Caucasian and 4 Pima Indian children were taller than the maximum height for age in the table. For these 10 children and for 19-yr-old females, linear extrapolation determined standard weights. Relative weight, the ratio of the actual weight to the standard weight, served as a measure of obesity. In Pima Indian and Caucasian children in Arizona who were not part of this study, underwater weighing was used to estimate obesity as the percentage of body weight that is fat (21). In these children, a given relative weight indicated the same degree of obesity in each racial group (D.J.P., D.M.M.; unpublished observations).

We assessed the significance of the difference between insulin concentrations in Pima Indians and Caucasians with linear regression models that adjusted simultaneously for other variables related to the insulin concentration. A significant interaction was apparent between race and relative weight. Insulin and glucose concentrations are approximately log-normally distributed. Table 1 shows geometric means of the concentrations, and the logarithms of the concentrations of insulin and glucose were used in linear regression models.

All variables included in the model, except race, were standardized by subtracting the sex-specific sample mean from the value. Analyses were stratified by sex because of the differences in body composition between males and females (22) and because of interactions of sex with other terms when all participants were analyzed together. Because only one Caucasian had a relative weight of >180%, the regression analyses were limited to those whose relative weight was <180%.

RESULTS— In the Pima Indian children, the mean fasting insulin concentra-

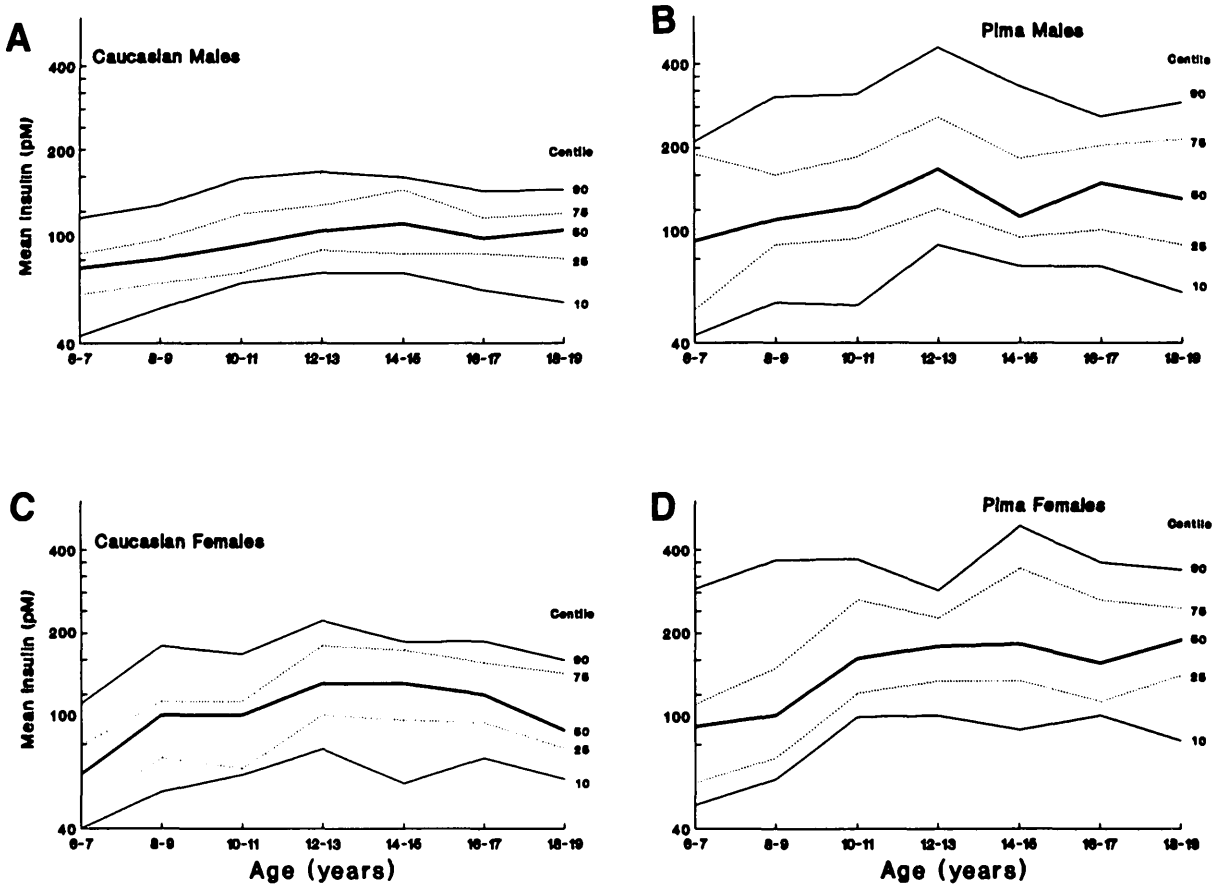

Figure 4—*Age- and sex-specific percentiles of fasting insulin (on a logarithmic scale) for Caucasian and Pima Indian males (A and B) and females (C and D).*

tions were 140 pM in males and 171 pM in females, compared with 94 and 107 pM in male and female Caucasian children, respectively (Table 1). The two populations were similar in mean age, height, and fasting glucose concentration, but the Pima Indians were heavier.

Frequency distributions of glucose and insulin concentrations for Caucasian and Pima Indian males and female are shown in Fig. 1. In both sexes, the glucose distributions (Figs. 1*A* and 1*C*) of the two populations were similar. The Pima Indian children, however, had higher insulin concentrations and broader insulin distributions (Figs. 1*B* and 1*D*) with higher values than those of the Caucasian children.

Figure 2 shows mean insulin concentrations by glucose concentration in the Pima Indian and Caucasian children. A positive relationship was evident between fasting insulin and glucose. For corresponding glucose concentrations, the Pima Indians had higher insulin concentrations.

Figure 3 shows the insulin concentration by age. The mean insulin varied directly with age in the younger groups in both populations, but the older groups showed little relationship between insulin and age. At both pre- and postpubertal ages, Pima Indian children had higher insulin concentrations than Caucasians. Figure 4 shows age- and sex-specific percentiles of insulin concentrations for Pima Indian and Caucasian children. At each age, the insulin concentrations at almost every percentile were higher in Pima Indians than in Caucasians.

Figure 5 shows the insulin concentration by relative weight. Among participants with low relative weight, the Pima Indian and Caucasian children had similar insulin concentrations. In those of either sex with higher relative weights, however, Pima Indians had higher mean insulin concentrations than Caucasians.

Differences in insulin concentration between the Pima Indian and Caucasian populations, controlled for age, glucose, and relative weight, were analyzed with linear regression models (Table 2). Age, glucose concentration, and relative weight were significantly associated with the insulin concentration in

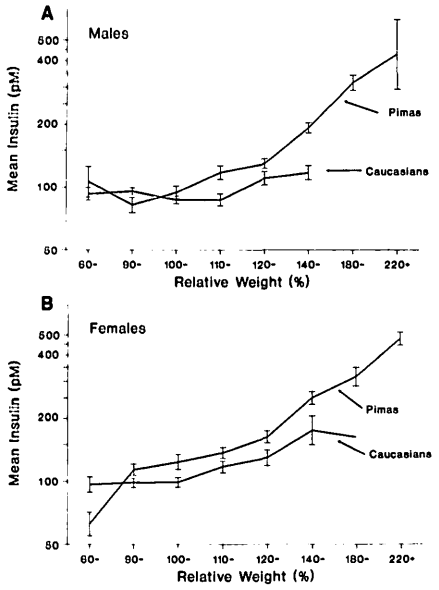

Figure 5—*Fasting insulin (on a logarithmic scale) by relative weight for males (A) and females (B). Bars represent ± SE. Point without bars represent only one participant.*

each sex. Age had a significant quadratic relationship, and a strong, statistically significant interaction occurred between race and relative weight. Thus, age, relative weight, and race were each in the model twice (indicated by brackets in Table 2), and the F-value for the combined effect of both terms was calculated from the incremental r^2 for the addition of those two terms. No other significant two-way interactions occurred.

In the limited data set of 509 offspring (437 Caucasian and 72 Pima Indian children) with two nondiabetic parents >25 yr of age (Table 3), race still had a significant effect when controlled for age, glucose, and relative weight. We included this restriction to exclude those participants most likely to have inherited a diabetes gene or genes.

CONCLUSIONS— Pima Indian children have higher insulin concentrations than Caucasians of the same sex and of similar age, relative weight, and glucose concentration. These data extend previous observations in adults (1–3) and children (12) and document the presence of relatively high insulin concentrations among the Pima Indian children, who are at high risk for developing NIDDM.

Our findings suggest that age, glucose, relative weight, and race explain much of the variation in insulin concentrations in the populations from which the samples were drawn. Although race was a strong predictor of insulin concentration after age, glucose, and relative weight were accounted for, other factors, which have not yet been identified, also contribute to variation. Because of the interaction between race and relative weight, the adjusted values of insulin concentration would vary with degree of obesity, and the two races would be similar at or below a relative weight of 100%.

Hyperinsulinemia in the presence of normoglycemia usually reflects insulin

Table 2—*Results of multiple linear regression models*

	Parameter estimate	F-value (df)*	P value
Male			
Age (yr)	0.162	12.8 (2,401)	<0.001
Age^2	−0.006		
$\log_e$ of glucose (mM)	1.903	59.4 (1,402)	<0.001
Relative weight (%)	1.240	72.8 (2,401)	<0.001
Relative weight and race (interaction)†	0.924	23.6 (2,401)	<0.001
Race†	0.173		
Intercept	4.735		
$r^2 = 0.494$			
Females			
Age (yr)	0.294	29.1 (2,411)	<0.001
Age^2	−0.010		
$\log_e$ of glucose (mM)	1.548	34.0 (1,412)	<0.001
Relative weight (%)	1.380	84.3 (2,411)	<0.001
Relative weight and race (interaction)†	0.530	11.7 (2,411)	<0.001
Race†	0.183		
Intercept	4.935		
$r^2 = 0.521$			

The dependent variable is the $\log_e$ of plasma insulin (pM).
*F-values are given for the combined contribution of bracketed variables.
†Effect of being a Pima Indian.

Table 3—*Results of multiple linear regression models in study participants without diabetic parents*

	Parameter estimate	F-value (df)*	P value
Male			
Age (yr)	0.169	7.8 (2,255)	<0.001
Age^2	−0.004		
Log$_e$ of glucose (mM)	1.774	28.3 (1,256)	<0.001
Relative weight (%)	1.175	17.4 (2,255)	<0.001
Relative weight and race (interaction)†	0.844	10.2 (2,255)	<0.001
Race†	0.129		
Intercept	4.696		
$r^2 = 0.370$			
Females			
Age (yr)	0.329	23.4 (2,240)	<0.001
Age^2	−0.012		
Log$_e$ of glucose (mM)	1.643	23.0 (1,241)	<0.001
Relative weight (%)	1.171	20.8 (2,240)	<0.001
Relative weight and race (interaction)†	0.310	5.7 (2,240)	<0.005
Race†	0.225		
Intercept	4.977		
$r^2 = 0.424$			

The dependent variable is the log$_e$ of plasma insulin (pM).
*F-values are given for the combined contribution of bracketed variables.
†Effect of being a Pima Indian.

resistance. We conclude that Pima Indians, even as children, are more insulin resistant than Caucasians.

Both hyperinsulinemia and insulin resistance predict NIDDM among Pima Indians (8,23,24). In the Pima Indians, insulin resistance is familial (25), and increased insulin resistance occurs in Caucasians who have first-degree relatives with NIDDM (26). Such familial aggregation of insulin resistance may be attributable to a major gene (27). Insulin resistance appears to be a metabolic defect that first leads to compensatory hyperinsulinemia to maintain normoglycemia, and subsequently leads to the development of IGT. NIDDM develops when β-cells become exhausted or fail to maintain the increased insulin secretion (8,24,28).

In both the Pima Indian and Caucasian children a direct, almost linear, association between age and insulin concentration was apparent in the younger age-groups, but little association was evident at older ages. Puberty may influence insulin concentration (29–31), and in this study the inflection points of the insulin-age curves correspond to ages when puberty occurs, although we did not estimate stage of puberty. The point of inflection occurred at an earlier age in females than males, consistent with the younger age of puberty in females (32–34). The differences in insulin concentrations between the Pima Indians and Caucasians, however, could not be attributed to differences in age of puberty because they were apparent even at very young ages, when all of the children were prepubertal, and persisted throughout the teenage years when virtually all children were well past puberty.

In conclusion, much of the variance in insulin concentrations in these two populations is explained by race, age, glucose concentration, and obesity as indicated by relative weight. The higher fasting insulin concentrations in the Pima Indians remain after accounting for any effect attributable to differences in age, glucose concentration, and obesity. We do not know how much of the difference attributed to race ultimately will be explained by genetic and environmental factors, but the most plausible explanation for our findings is that the higher insulin concentrations in the Pima Indian children reflect the presence of insulin resistance from an early age, and is related to the propensity to develop NIDDM in later life.

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