ORIGINAL RESEARCH ARTICLE

Study of the Frequency of Nonalcoholic Fatty Liver Disease (NAFLD) in Type 2 Diabetes Mellitus (DM) in a Tertiary Care Centre

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ABSTRACT

Introduction: The diabetics are at a higher risk of developing Nonalcoholic fatty liver disease (NAFLD) and its related complications compared to general population at large. Study aimed to evaluate the prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) and associated demographic, metabolic and biochemical parameters in subjects with type -2 Diabetes Mellitus.

Material and methods: This was a hospital based, prospective, observational, descriptive (cross-sectional) and non-interventional study done on cohort of type 2 diabetes mellitus patients. This study was conducted over period of 18 months (October 2016 to March 2018). Diagnostic criteria for NAFLD: Alcohol consumption <20g/d and USG Abdomen suggestive of fatty liver.

Results: A total 170 patients were enrolled, of them 106 (62.35%) were males and 64 (37.64%) were females. There was statistically significant positive correlation between presence of non-alcoholic fatty liver disease and HbA1c (+0.25124), BMI (+0.34743) and duration of diabetes (+0.4237). Overall prevalence of NAFLD was 55.29% (94/170). Male gender, age > 45 years, HbA1c > 6.5, BMI > 25 Kg/M^2 and duration of diabetes mellitus > 10 years together were the risk factors associated with presence of NAFLD in present study (p=0.0002).

Conclusion: Present study highlighted the significant burden of Non-Alcoholic Fatty Liver Disease in cohort of type -2 Diabetes Mellitus. About half of the subjects had NAFLD (55.29%). In present study high BMI, high HbA1c and duration of diabetes > 10 years were positively correlated with NAFLD.

Key words: Non-Alcoholic Fatty Liver Disease, type 2 Diabetes Mellitus, HbA1c, BMI, Duration of Diabetes Mellitus

INTRODUCTION

In western and Asian countries, changes in the diet and lifestyle have caused a noteworthy increase in the prevalence of obesity and metabolic syndrome, which has appreciably increased the incidence of non-alcoholic fatty liver disease (NAFLD). The NAFLD comprises of non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). The NAFL tends to be benign and non-progressive while the NASH can lead to development of cirrhosis and in rare cases gives rise to hepatocellular carcinoma. NAFLD occurs worldwide, with a prevalence ranging 10–50%. NAFLD is emerging as an important cause of liver disease in India with prevalence of 9% to 32% associated with obesity and Diabetes Mellitus.[1,2,3] NAFLD is increasingly prevalent in the Indian population, acquaintance regarding its burden and risk factors is limited. NAFLD and type 2 Diabetes Mellitus seems to be a costly and notorious combination of risk factors for various diseases. The NAFLD is commonly linked with type 2 DM despite the fact that its prevalence is not studied well in Indian context. This hospital based cross-sectional study was conducted to estimate the frequency and prevalence of NAFLD in subjects with type 2 DM. Study aimed to evaluate the prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) and associated demographic, metabolic and biochemical parameters in subjects with type -2 Diabetes Mellitus in a tertiary care centre, teaching hospital.

MATERIAL AND METHODS

This was a hospital based, prospective, observational, descriptive (cross-sectional) and non-interventional study done on cohort of type 2 diabetes mellitus patients.

Settings: This was hospital based study conducted in Krishna Institute of Medical Sciences, Karad, conducted over period

of 18 months (October 2016 to March 2018). This study was approved by protocol and ethical committee of Krishna Institute of Medical Sciences Deemed to be University, Karad.

Inclusion criteria: All consecutive adult subjects including all genders with type 2 DM fulfilling the inclusion criteria with age more than 18 years were enrolled for this study.

Exclusion criteria: Subjects with a history of alcohol intake more than 30 grams/day in males and more than 20 grams/day in females or with evidence of acute or chronic viral hepatitis or liver disease (HBsAg / HCV positive, with alcoholic liver disease, autoimmune hepatitis) due to any other cause were excluded from the study. Subjects who were on hepatotoxic medications were also excluded.[4,5] The subjects diagnosed as Diabetes Mellitus seeking treatment in the Department of Medicine IPD and OPD were included and investigated for presence of NAFLD. After taking informed consent, all subjects underwent history, examination and laboratory investigations (haemoglobin, total leukocyte count and metabolic parameters like blood sugar, glycosylated haemoglobin, liver function test, renal function test and lipid profile) and ultrasonography (USG) of abdomen.

NAFLD-diagnostic criteria: Alcohol consumption <20g/d, USG abdomen suggestive of fatty liver. The USG abdomen for detection of Fatty liver was performed by using B mode Siemens X -300 machine (3.5 - 5 MHz convex probe).[6,7] **Hepatic steatosis** if present, was classified based on standard ultrasonographic criteria as:

Grade 1 (mild steatosis): Normal visualization of diaphragm/ intrahepatic vessels.

Grade 2 (moderate steatosis): Impaired visualization of diaphragm/ intrahepatic vessels and

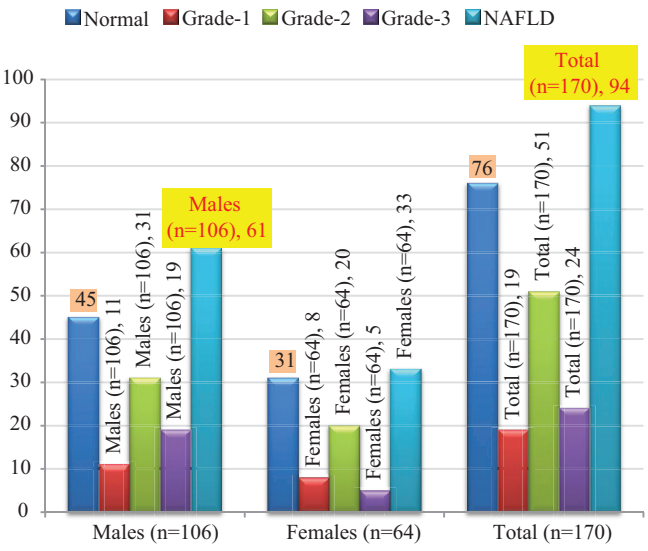
Grade 3 (severe steatosis): Poor visualization of diaphragm/ intrahepatic vessels.[6,7]

STATISTICAL ANALYSIS

Statistical analysis was done by using the Statistical Package for Social Science (SPSS version 16) trial version. Basic descriptive statistical analysis of the quantitative variables was performed in the form of frequencies, means, percentage, standard deviations, Odds ratio (OR), Relative risk (RR) and chi-square test. The continuous variables were shown as mean ± standard deviation (SD). The P values < 0.05 were considered as significant.

RESULTS

A total 170 subjects of both genders were enrolled for this



Graph-1: NAFLD in both gender in cohort of type-2 DM

Variable	Total			%		
Males	106			62.35		
Females	64			37.64		
Total	170			100		
χ^2: 20.75; DF:1; p<0.0001;Relative Risk(RR): 0.60; Odds Ratio(OR): 0.36						
	Normal	Grade-1	Grade-2	Grade-3	NAFLD	%
Males (n=106)	45	11	31	19	61	57.54
Females (n=64)	31	8	20	5	33	51.56
Total (n=170)	76	19	51	24	94	55.29

Table-1: Gender distribution and prevalence of NAFLD in cohort of type-2 DM

Variables	Normal USG (n=76)	Grade-1 fatty liver (n=19)	Grade-2 fatty liver (n=51)	Grade-3 fatty liver (n=24)
Age	59.15(±13.9)	55.21(±8.29)	59.9(±14.5)	57(±13.83)
Duration DM	7.09(±6.99)	11.78(±2.25)	12.6(±3.23)	12.41(±2.14)
BMI	26.17(±3.48)	29.66(±3.4)	29.06(±2.79)	28.69(±2.47)
BSL(F)	166.49(±71.94)	180.47(±75.25)	165.68(±55.29)	190.45(±71.82)
BSL(PP)	228.79(±84.64)	226.15(±91.39)	239.17(±58.62)	275.45(±97.95)
HbA1c	7.95(±1.47)	7.98(±1.24)	8.36(±1.7)	9.31(±1.8)
Total CHO	150.7(±42.95)	153.47(±38.74)	158.88(±35.3)	190.91(±57.49)
HDL	40.08(±17.68)	35.1(±12.35)	41.66(±15.8)	45.2(±14.29)
Triglyceride	105.74(±44.54)	159.21(±100.3)	118.58(48.91)	95(±32.85)

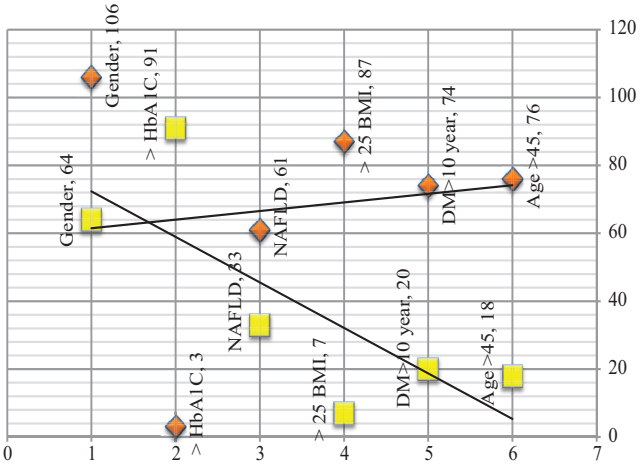
Table-2: Comparison of Mean and standard deviation

HbA1c	Normal USG (n=76)		NAFLD (n=94)	
≤6 (n=12)	9		3	
>6 (n=158)	67		91	
χ^2: 4.793; DF:1; P=0.028; Relative Risk (RR): 2.30; Odds Ratio (OR): 4.07				
HbA1c	Normal USG (n=76)	Grade-1 fatty liver(n=19)	Grade-2 fatty liver(n=51)	Grade-3 fatty liver(n=24)
≤6 (n=12)	9	1	2	0
>6 (n=158)	67	18	49	24
χ^2: 5.33177; DF:3; P=0.149054				
Gender	Normal USG (n=76)	Grade-1 fatty liver(n=19)	Grade-2 fatty liver (n=51)	Grade-3 fatty liver (n=24)
Male(n=106)	45 (42.5%)	11(10.37%)	31 (29.24%)	19 (17.92%)
Female(n=64)	31 (48.4%)	8 (12.5%)	20 (31.25%)	5 (7.81%)
χ^2: 3.424395; DF:3; p=0.330701				
Gender	Normal USG (n=76)		NAFLD (n=94)	
Male(n=106)	45 (42.45%)		61 (57.54%)	
Female(n=64)	31 (48.4%)		33 (51.56%)	
χ^2: 0.57; DF:1; p=0.44;Relative Risk (RR): 1.126; Odds Ratio (OR) 1.302				

Table-3: Relation of level of HbA1c to NAFLD

BMI	Normal USG (n=76)	Grade-1 fatty liver(n=19)	Grade-2 fatty liver(n=51)	Grade-3 fatty liver (n=24)
≤25(n=40)	33	2	3	2
>25(n=130)	43	17	48	22
χ^2: 30.40528; DF:3; P<0.001				
BMI	Normal USG (n=76)		NAFLD (n=94)	
≤25(n=40)	33		7	
>25(n=130)	43		87	
χ^2: 3.57; DF:1; p=0.058; Relative Risk (RR): 0.26; Odds Ratio (OR): 0.10				
Duration of DM	Normal USG (n=76)	Grade-1 fatty liver(n=19)	Grade-2 fatty liver(n=51)	Grade-3 fatty liver(n=24)
≤ 10 yrs (n=84)	64	5	11	4
>10(n=86)	12	14	40	20
p<0.001				
Duration of DM	Normal USG (n=76)		NAFLD (n=94)	
≤ 10 yrs (n=84)	64		20	
> 10 yrs (n=86)	12		74	
χ^2: 66.586; DF:1; p<0.001; Relative Risk (RR): 0.27; Odds Ratio (OR): 0.05				
Age	Normal USG (n=76)		NAFLD (n=94)	
≤45 yrs (n=33)	15		18	
>45 yrs (n=137)	71		76	
χ^2: 4.26; DF:1; p=0.038; Relative Risk (RR): 0.98; Odds Ratio (OR): 0.96				

Table-4: Relation of BMI, age > 45 years and duration of diabetes to NAFLD



Graph-2: Relation of NAFLD with risk factors

cross-sectional observational study as per inclusion criteria. Total 106 (62.35%) were males and 64 (37.64%) were females [p<0.0001]. Present study predominated by male subjects (62.35%) compared to female subjects (37.64%). Overall prevalence of NAFLD was 55.29% (94/170). The prevalence of NAFLD was 57.54% (61/106) and 51.56% (33/64) in males and females respectively. (Table 1 and Graph 1)

The mean of age, HbA1c and total cholesterol was relatively high in subjects with NAFLD compared to subjects without NAFLD. (Table 2)

The HbA1c >6 had statistically significant association with presence of NAFLD in present study [(p=0.028569) (Odds Ratio (OR) 4.074627)]. The severity and grades of NAFLD was not significantly associated with HbA1c >6 (p=0.149054). The severity and grades of NAFLD was not significant among genders (p=0.330701). The presence

of NAFLD was not significantly associated with gender (p=0.447021). (Table 3)

Variables		Correlation = *r*
HbA1c		+0.25124
BMI		+0.34743
BSL (F)		+0.0767
BSL(PP)		+0.16249
HDL level		+0.09981
SGOT/AST		+0.14338
SGPT/ALT		+0.06392
Duration of diabetes		+0.4237
Triglyceride		-0.0048
Age		-0.0205
SBP		-0.052
DBP		-0.0283
Bilirubin		-0.0431
Weight		-0.1596
Gender	Males (n=106)	Females (n=64)
> HbA1c	91	3
> 25 BMI	87	7
DM > 10 year	74	20
Age >45	76	18
χ^2:19.6789; DF:3; p=0.0002		

Table-5: Correlation of various demographic, clinical and laboratory parameters with NAFLD in cohort of type-2 DM subjects

The severity and grades of NAFLD was statistically significantly associated with BMI > 25 Kg/M^2 (p<0.001). The NAFLD was significantly associated with BMI >25 Kg/M^2 (p= 0.05866). The severity and grades of NAFLD was statistically significantly associated with duration of diabetes (p<0.001). The presence of NAFLD was statistically significantly associated with duration (>10 years) of diabetes (p<0.001). The severity and grades of NAFLD was not statistically significantly associated with age (p=0.9631406). The presence of NAFLD was statistically significantly associated with age > 45 years (p=0.03886854). (Table 4)

The severity and grades of NAFLD was not statistically significantly associated with high total cholesterol (p=0.07340511). The NAFLD was not statistically significantly associated with total cholesterol >150 mg (p=0.63183404). The severity and grades of NAFLD was not statistically significantly associated with serum triglyceride level >150 mg (p=0.06245557). The presence of NAFLD was statistically significantly associated with triglyceride > 150 mg (p=0.03498023). [Odds Ratio (OR): 0.511509; Relative Risk (RR): 0.748353] The severity and grades of NAFLD was not statistically significantly associated with serum HDL <50 mg (p=0.16467667). The presence of NAFLD was not statistically significantly associated with decreasing serum HDL < 50 mg [(p=0.21717278) Odds Ratio (OR): 1.883117; Relative Risk (RR): 1.380952].

Author	Total (n)	Prevalence/Incidence	Associated factors with NAFLD
Majumdar A et al	176	30.70%	Central obesity
Bhatt KN et al	100	45	BMI, higher HbA1c, higher triglyceride
Jaseem Ansari et al	100	26%	Hypertension, obesity, duration of Diabetes Mellitus
Lavekar A et al	302	28.10%	Metabolic syndrome and Diabetes Mellitus
Prabhakar A et al	114	41.20%	HbA1c, duration of diabetes and obesity
Gupta M et al	150	69.33%	DM, older age and increasing BMI
Bhardwaj et al	100	61%	HTN, MeTS and raised cholesterol, LDL triglycerides
Chandel K et al	185:105	55.68%/20%	High BMI, HbA1c, triglyceride, hypercholesterolemia, low HDL
Younossi ZM et al	-	9-40%	Asian countries
	-	15-40%	Western countries
	-	9-32%	In India
	-	12.5-87.5%	In cohort of type 2 Diabetes Mellitus
Sung K-C et al	5 1,418	12%	Incidence of NAFLD by USG
Tsuneto A et al	635	19.9 /1,000 person-yr	Incidence of NAFLD by ultrasound
Wong VW et al	565	13.5% (34/ 1,000 yrs)	Incidence by MRI and transient elastography (TE)
Chang Y et al	77425	29.7/1000	incidence rate 29.7 per 1,000 person yrs
Whalley S et al	-	29/1000	29 per 100,000 person-years
Zelber S et al	-	28/1000	28 per 1,000 person-years
Younossi ZM et al	Meta-analysis	52.34; 28	Asia: 52.34; West:28 per 1,000
Vernon G et al	-	7% - 46%	-
Williams CD et al	400	46%	Histologically confirmed NASH (12.2%)
Browning JD et al	-	31%	Dallas Heart Study by MR spectroscopy
Younossi ZM et al	The meta-analysis estimated prevalence of NAFLD by imaging was around 25.24%, Middle East (31.79%), South America (30.45%) and Africa (13.48%). The prevalence of NASH among NAFLD subjects by liver biopsy was 59.10% and by liver biopsy was 6.67% to 29.85%.		
Present study	Of total 170 subjects, 106 (62.35%) were males and 64 (37.64%) were females (p<0.0001). Prevalence of NAFLD was 55.29% (94/170). The presence of NAFLD was significantly associated with BMI > 25 Kg/M^2 (p<0.001), duration (>10 years) of diabetes (p<0.001) and age > 45 years (p=0.038).		

Table-6: Comparison of various studies prevalence with present study[10-28]

Correlation coefficient: There was statistically significant positive correlation between different grades of non-alcoholic fatty liver and HbA1c (+0.25124), BMI (+0.34743), BSL (F) (+0.0767), BSL (PP) (+0.16249), serum HDL level (+0.09981), SGOT/AST level (+0.14338), SGPT/ALT (+0.06392) and duration of diabetes (+0.4237). There was significant negative correlation between different grades of non-alcoholic fatty liver and serum triglyceride (-0.0048), age (-0.0205), systolic blood pressure (-0.052), diastolic blood pressure (-0.0283), total bilirubin level (-0.0431) and weight (-0.1596). (Table 5) In *multivariate analysis* after controlling age and gender there was statistically significant association between NAFLD (grade 2 fatty liver) and BMI, duration of Diabetes Mellitus and HbA1c ($p<0.01$). Male gender, age > 45, HbA1c> 6.5, BMI > 25 Kg/M^2, duration of Diabetes Mellitus > 10 years together were as a risk factors associated significantly with presence of NAFLD in present study ($p=0.0002$). (Table 5 and graph 2)

DISCUSSION

Non-alcoholic fatty liver disease (NAFLD) was a distinct hepatic condition that was strongly associated with insulin resistance and type 2 Diabetes Mellitus. NAFLD has become an important health issue globally. The NAFLD is increasingly seen to be associated with metabolic syndrome. There are limited number of studies on epidemiology and natural history of NAFLD in diabetes. In the present cross-sectional observational study a total 170 subjects of both genders were enrolled of them 106 (62.35%) were males and 64 (37.64%) were females ($p<0.0001$). The HbA1c >6 had statistically significant association with presence of NAFLD in present study ($p=0.028$). Overall prevalence of NAFLD was 55.29% (94/170). The prevalence of NAFLD was 57.54% (61/106) and 51.56% (33/64) in males and female respectively. The NAFLD was statistically significantly associated with BMI >25 Kg/M^2 ($p= 0.058$). The severity and grades of NAFLD was statistically significantly associated with BMI > 25 Kg/M^2 ($p<0.001$), duration of Diabetes Mellitus (>10 years) ($p<0.001$), age > 45 years ($p=0.038$) and triglyceride > 150 mg ($p=0.034$). Present study cannot be exactly compared with other studies from India and overseas because of different criterion for enrolment of subject for study, difference of criteria for diagnosing NAFLD, community based, different geographic area and genetic makeup of study population. Chen CH et al in their cross-sectional community based study of 3245 adults of Taiwan quoted prevalence of NAFLD of 11.5%. NAFLD was closely associated with obesity and Diabetes Mellitus. This prevalence is relatively low compared to present study [55.29% (94/170)] as it was hospital based study included only subjects with type 2 DM. The other parameters like obesity (BMI) ($p<0.001$) and hypertriglyceridemia ($p=0.034$) are comparable with present study.[8] Younossi ZM et al quoted prevalence of NAFLD in Asian countries varies from 9-40% and in western countries from 15-40%. In India, the prevalence of NAFLD was around 9-32% in the general population, but it was 12.5-87.5% in subjects with type 2 DM.[9] These findings are comparable with present study (55.29%). Majumdar A et al (2016) studied 176 participants with prevalence of NAFLD was 30.7% and was associated with central obesity. In current study the prevalence of NAFLD was quite high (55.29%) may be due to only cohort of type-2 DM were included. Association of BMI with NAFLD in present study was significant, similar to study by Majumdar A et al.[10] Bhatt KN et al (2017) in their study of total 100 subjects of type 2 DM the prevalence of NAFLD was 45% with obesity (measured by BMI), higher HbA1c, higher triglyceride levels had significant association with NAFLD.[11] These findings are comparable with present study with prevalence of NAFLD of 55.29% and association of BMI, TRG, HbA1c was enough significant with NAFLD. Compared to present study (55.29%), Jaseem Ansari et al (2017) found 26% prevalence of NAFLD which was significantly low, could be due to different inclusion and exclusion criteria.[12] Lavekar A et al (2015) studied 302 individuals with prevalence of NAFLD of 28.1%, which was relatively low compared to our study as we have enrolled only type -2 DM subjects which is one of the proved risk factor for NAFLD.[13] Prabhakar A et al (2017) quoted prevalence of NAFLD was 41.2% in the study group (n=114), which is similar to present study. Prevalence of NAFLD was significantly associated with HbA1c, duration of diabetes and obesity, these findings are comparable with our study.[14] Gupta M et al (2017) in their hospital based observational descriptive study (n=150) in subjects with T2DM, 104 (69.33%) had fatty liver on USG, 42.67% had grade 1, 24% had grade 2, and the remaining 2.67% had grade 3 fatty changes in liver.[15] These findings are comparable with present study with overall prevalence of NAFLD of 55.29% (94/170). The NAFLD was statistically significantly associated with BMI >25 Kg/M^2 ($p<0.001$), duration (>10 years) of Diabetes Mellitus ($p<0.001$), age > 45 years ($p=0.038$) and triglyceride > 150 mg ($p=0.034$). Bhardwaj et al (2016) in their cross-sectional study (n=100) with subjects of type 2 diabetes, the prevalence of NAFLD was 61%.[16] These findings are similar to present study with prevalence of NAFLD of 55.29% (94/170). The NAFLD was statistically significantly associated with BMI > 25 Kg/M^2, duration (>10 years) of diabetes, age >45 years and triglyceride >150 mg. Similarly Chandel K et al (2016) in their study of total of 185 diabetic and 105 non-diabetic subjects quoted prevalence of NAFLD in DM was 55.68% and in non-diabetic was 20%.[17] There is a paucity of data regarding the incidence of NAFLD in the general population. We compared the prevalence and risk factors of NAFLD in the general population with present study. (Table 6)

Limitations of the study: This was a hospital based study and conducted only on cohort of type-2 Diabetes Mellitus subjects. The present study lacks histological evidence for NAFLD and improved imaging modality like MRI spectroscopy.

CONCLUSION

Present study highlighted the significant Non-Alcoholic Fatty Liver Disease burden in cohort of type-2 Diabetes Mellitus; about half of the subjects had NAFLD (55.29%). NAFLD and type 2 DM seems to be a costly combination of risk factors for various diseases. In present study high BMI,

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high HbA1c and duration of diabetes > 10 years and age > 45 years were positively correlated with presence NAFLD. Physicians must have awareness about the complications associated with NAFLD. Lifestyle modification, remain the corner stone in management of NAFLD. Subjects with type 2 DM should always be assessed for NAFLD to ensure early diagnosis which might help in modifying the disease course and delaying its complications. Thus, subjects with Diabetes mellitus must be evaluated for the presence of NAFLD by inexpensive and non-invasive examination like abdominal Ultrasonography.

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