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PREDIABETES: AN ALARM FOR DIABETES?

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ABSTRACT

Prevalence of prediabetes in India is alarmingly increasing and the percentage of prediabetics exceeds than that of the diabetics. Prediabetes, being asymptomatic and non-diabetic hyperglycemia, could be diagnosed early in order to prevent from advancing to diabetes. Various risk factors such as increased BMI, increased waist-to-hip ratio, gender, sedentary lifestyle and family history for diabetes have been found to be associated with prediabetes. The identification of the predictor for prediabetes among these variables is difficult because the association varies in different ethnic groups based on their lifestyle habits. Thus this review aims at relating the various risk factors and comorbidities associated with prediabetes. It also emphasizes the various possible interventions for the prediabetic individuals in order to prevent them from diabetes.

KEYWORDS: **Prediabetes, predictors, lifestyle habits and interventions.**

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INTRODUCTION

Prediabetes state also referred as non – diabetic hyperglycemic state which does not satisfy the diagnostic criteria.[1] According to American Diabetic Association (ADA) 2015 the prediabetic state is defined as, an impaired fasting glucose (IFG) of 100-125mg/dl (5.6 mmol/L to 6.9 mmol/L) or an impaired glucose tolerance (IGT) of 140-199 mg/dl (7.8 mmol/L to 11 mmol/L) or glycated hemoglobin (HbA1C) of 5.7%-6.4%.[2] Studies states that prediabetes is a term used to indicate individuals with either IFG or IGT or sometimes both. Both IFG and IGT are not separate clinical entities but they are the risk factors for diabetes and CVD.[2]All forms of diabetes pass through the prediabetic state before evolving into a complete diabetic state.[1]IFG represents the presence of plasma glucose of the range 5.6 mmol/L to 6.9 mmol/ L after an overnight fast. Experts believe that the measurement of HbA1C would be more appropriate than fasting plasma glucose because HbA1C represents the glycemic status for the past three months regardless of the food intake. It also represents the long-term glucose concentration which would help in avoiding false positive or false negative results.[3,4,5] Still there are case studies being reported which reveals the interference of hemoglobinopathies in diabetes subjects with the glycated hemoglobin levels.[6] In patients with diabetes and hemoglobinopathy half of the red blood cells remain normal and half of them are sickled.[7] Thus the technique used for the measurement of glycated hemoglobin levels must be robust in order to use as a gold standard for the diagnosis of diabetes or prediabetes. Recently Hong et al., (2016) reported that HbA1C is more robust in the diagnosis of prediabetes stage and much research is required to design age specific diagnostic criteria for prediabetes as an accurate concordance between FPG and HbA1C.[8] HbA1C levels measures the glycemic status in prediabetes and undiagnosed diabetes and results in a direct assessment of risk of diabetes complications in subjects with prediabetes and undiagnosed diabetes which could be used for providing interventions for early management of diabetes complications.[9]

Prevalence

A review on prediabetes and the risk of developing diabetes published in 2010[10] reported a worldwide prevalence of prediabetes (Fig 1). The phase I reports of prevalence of prediabetes estimated by Indian Council of Medical Research-India DIABetes (ICMR-INDIAB) study in 2011 reported a total of 77.2 million individuals with prediabetes in India and among which 3.9 million from Tamil Nadu.[11] The prevalence of diabetes in India study (PODIS) has reported the prevalence of IFG in urban and rural regions of India. Of the 18,363 subjects studied for the prevalence of IFG, 1012 subjects were found to be having IFG and among which 733 subjects were from urban areas and 279 subjects were from rural areas. The study also reported a higher prevalence of IFG (5.2% among the studied population) compared to diabetes (4.3%).[12] Table 1 represents the prevalence of prediabetes in different regions of India in the duration 2001-2012. A higher prevalence has been observed in Nepal and in Chennai population. It has been estimated that about 70% of individuals with prediabetes will develop diabetes in the future.[12] Studies on prediabetes have reported the association of cardiovascular disease with the prediabetic state.[13,2] This review aims at correlating the various risk factors associated with prediabetes and emphasizes the importance of provided proper intervention for the prediabetic individuals for an early management in order to prevent them from becoming diabetics.

Risk factors associated with the prediabetic state

Several risk factors have been associated with prediabetes. The extent of association of various risk factors differs in each ethnic group and thus it becomes mandatory to take into account all the possible factors that might be associated with the prediabetic state during the screening process. Study on the modifiable risk factors of prediabetes conducted by Diaz-Rodendo (2015) reported various lifestyle habits and anthropometric variables associated with prediabetes such as, obesity, hypertension and dyslipidemia, gender, family history for diabetes (FHD) and lifestyle habits.[13]

Obesity

In the current scenario, increased intake of high calorie food and reduced energy expenditure causes obesity which is interrelated to the risk of developing T2DM.[14] Obesity eventually causes insulin resistance and leads to the predisposition of type 2 diabetes.[14] Studies state that Asians (particularly Indians) have an increased intra-abdominal fat and thicker truncal skin folds which is strongly associated with glucose intolerance.[15] A study conducted in Madhya Pradesh by Sahai et al., (2011) has reported a strong association of anthropometric parameters such as increased BMI and waist to hip ratio with impaired fasting glucose.[16] The study was also reported that the higher waist to hip ratio is the best predictor for prediabetes.[16] A study conducted by Balagopal et al., (2008) in Tamilnadu has shown a significant association of higher BMI with IFG.[17] The CUPS has reported a significant association of abdominal obesity with diabetes risk in prediabetes subjects.[18]

Figure 1
Worldwide prevalence of prediabetes[10]

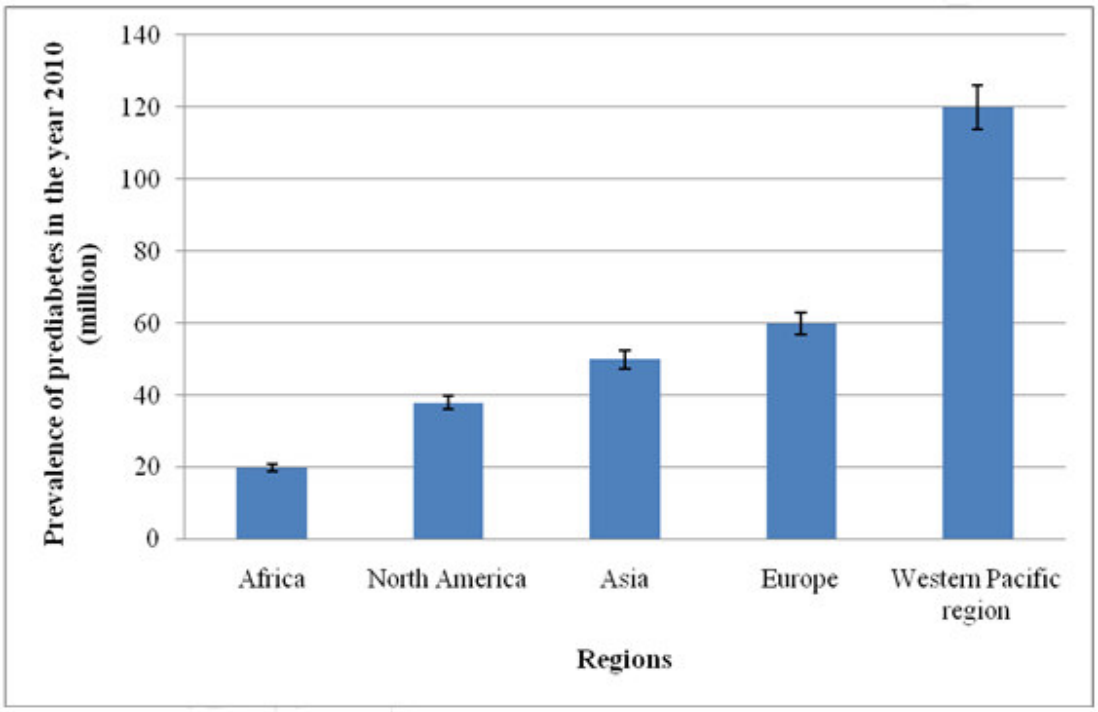


Table 1
Prevalence of prediabetes (both IFG & IGT) in various regions of India in the duration 2001-2015

S.No	Year	Region	Prevalence in percentage	Sample size	Reference
1	2001	Urban cities of India	14%	11,216	Ramachandran et al., (2001)[44]
2	2003	Chennai	5.90%	1,216	Mohan et al.,(2003)[18]
3	2003	Western India	10.80%	1,123	Gupta et al., (2003)[45]
4	2004	Urban and rural areas of India	5.2%	18,363	Anjana et al., (2011)[11]
5	2006	Kerala	11.20%	3,069	Menon et al., (2006)[46]
6	2007	Nepal	19.20%	740	Ono et al., (2007)[47]
7	2008	Chennai	5.30%	11,000	Ajay et al., (2008)[48]
8	2008	Chennai	10.10%	564	Mohan et al.,(2008)[49]
9	2011	Karnataka	12.04%	1,370	Zaman et al., (2011)[15]
10	2012	Rural areas of India	4.60%	Meta analysis	Jayawardena et al., (2012)[50]
11	2014	Karnataka	11.57%	2,013	Dasappa et al., (2014)[51]
12	2015	Chennai	51.7%	2,207	Anjana et al., (2015)[52]

Hypertension and Dyslipidemia

T2DM and prediabetes are found to cosegregate with hypertension and dyslipidemia.[19] Recent studies have reported the association of hypertension with the prediabetic state.[20] In another study Ishikawa et al., (2009) reported 51.2% of subjects with prehypertension and prediabetes.[21] A cross sectional study conducted in Spanish population has reported association of abdominal obesity, hypertension and reduced HDL levels in women with prediabetes.[21]Similar to hypertension, dyslipidemia also poses an equal risk of CVD in prediabetes subjects.[22,23] According to ATP III guidelines dyslipidemia is the condition of increased total serum cholesterol, increased LDL levels and decreased HDL levels. Dyslipidemia in prediabetic subjects is reported due to abnormality in insulin action.[23] Increased levels of postprandial triglycerides are found to be observed in early stages of T2DM.[24] A case-control study conducted by Lalitha et al., (2013) in Andhra Pradesh population has reported a significantly higher prevalence of dyslipidemia in prediabetic subjects. This study has also stated dyslipidemia as a most common risk factor for the predisposition of CVD and atherosclerosis in prediabetic subjects.[24] Since prediabetic subjects with dyslipidemia and hypertension are more prone to CVD and atherosclerosis[23] there was an inevitable need to consider hypertension and dyslipidemia as major risk factors in prediabetic subjects during the initial screening process in clinical practice which would help in providing necessary interventions for the same.

Gender

Studies have reported gender differences[25,26] among the prediabetic state with female having a higher prevalence of IGT and men having a higher prevalence of IFG.[25,26] A retrospective study conducted by Sawant et al., (2008) in Mumbai population showed a significantly higher prevalence of prediabetes and dyslipidemia in males than in females.[26]

Family history of diabetes (FHD)

Family history of diabetes (FHD) doubles the risk for diabetes or the prediabetes condition in the offspring.[27] FHD is the major risk factor for prediabetes. Zaman et al., (2011) reported 42.42% of prediabetic subjects with FHD in Karnataka. The study has shown a significantly higher percentage of FHD in patients with IGT than the normoglycemic subjects.[15]A meta-analysis of four German studies conducted by Robert et al., (2013) in prediabetic subjects reported a positive association of FHD with IFG.[27]In Swedish population, prediabetic subjects have also shown a 50% increase in IFG in subjects with FHD.[28]

Lifestyle habits

Other than anthropometric parameters, FHD and gender, lifestyle habits such as sedentary lifestyle, smoking and alcoholism have also been reported to be associated with prediabetic state.[29] Physical activity of an individual has a direct effect on the glycemic status and insulin sensitivity.[30] A study conducted by Diaz – Redondo et al., (2015) reported a possible association of alcoholism with prediabetes in men. Though smoking proves to be a high risk factor for diabetes, the association of smoking with prediabetes is still inconsistent.[13] The Indian diabetic risk score represents the risk and the possibility of an individual to become diabetic (Fig 2).World health organization (WHO) provides a specific instrument with various steps for the screening of diabetic and prediabetic subjects which involves three steps namely, demographic information, behavioral measurements and physical measurements. ADA 2015 guidelines provide certain criteria for screening of diabetes or prediabetes in asymptomatic adults. It states that testing should be considered in all adults who are overweight and have any of the following conditions namely: physical inactivity, first degree relatives with diabetes, high risk ethnicity (Eg: African American, Latino, Native American, Asian American, Pacific Islander), women diagnosed with gestational diabetes mellitus, hypertension (≥ 149/90 mmHg), HDL levels < 35 mg/dl (0.9 mmol/L), triglycerides > 250 mg/dl (2.82 mmol/L), HbA1C ≥ 5.7% and history of CVD.[2] Thus the screening of prediabetic subjects must include all the above mentioned risk factors. Even though the predictor for prediabetes differs in each ethnic group, the knowledge about all the risk factors of study participants would help in designing proper interventions for the prediabetic subjects.

Figure 2
Indian diabetic risk score

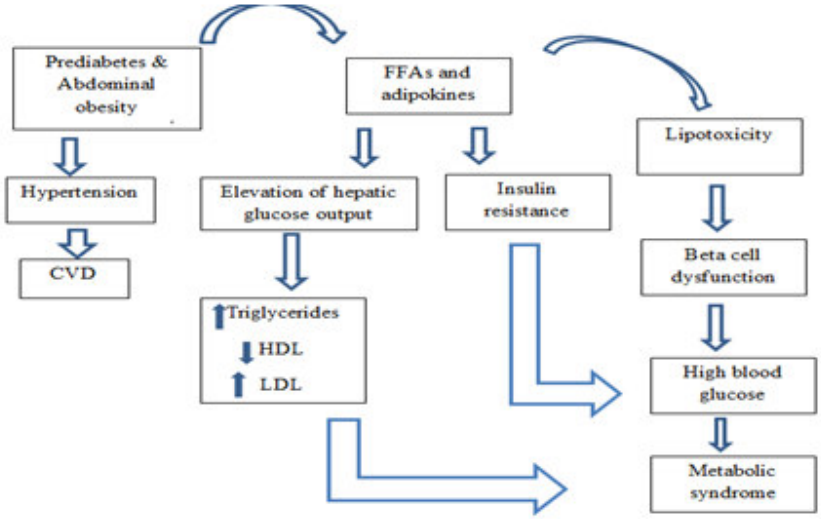
Particulars	Score
Age [years]	
< 35 years]	0
35 - 49	20
≥ 50	30
Waist Circumference [Pant size]	
Waist <80 cm [32" female] , <90 [36" male]	0
Waist ≥80 – 89 cm [32"-35"] [female], ≥90 – 99 [36"-39"] [male]	10
Waist ≥90 cm [36" female], ≥100 cm [40" male]	20
Physical activity	
Vigorous exercise [regular] or strenuous [manual] labour at	0
home/ work	10
Moderate exercise [regular] or moderate physical activity at	20
home/ work	30
Mild exercise [regular] or mild physical activity at home/ work	
No exercise and sedentary activities at home/work	
Family history	
No family history	0
Either parent	10
Both parents	20
Score: ≥60- Very high risk; 30-50- Moderate risk; < 30 – Low risk	

Associated comorbidities

The most studied comorbidity of prediabetes is metabolic syndrome.[31] According to ATP III guidelines any individual with abdominal obesity, elevated blood pressure, elevated triglycerides, elevated LDL and reduced HDL is diagnosed to have metabolic syndrome. The most common risk factor between prediabetes and metabolic syndrome is abdominal obesity.[31] Abdominal obesity releases free fatty acids (FFAs) and adipokines. This causes insulin resistance and the elevated FFAs in a long run lead to lipotoxicity which causes impairment of beta cell function which again promotes the higher blood

glucose levels. The elevated FFAs also cause elevation of hepatic glucose output (HGO) and also an increase in triglycerides, decrease in HDL and an increase in LDL leading to metabolic syndrome. Thus abdominal obesity is a best predictor for prediabetes and its associated comorbidity, mainly metabolic syndrome. Obesity, which is associated with blood pressure increases the risk for cardiovascular diseases but the association between blood pressure and hyperglycemic state in prediabetic subjects were to be analysed.[31,32] Prehypertension represents another high risk state for cardiovascular diseases.[33] Prediabetes coupled with prehypertension reveals a higher degree of risk for cardiovascular diseases.[34,35] Currently research on diabetes education must not only involve screening individuals for prediabetes but also for preobesity and prehypertension since these conditions are interlinked and the intervention provided for any of these above mentioned conditions would prevent them from becoming diabetes subjects.[12] New risk assessment strategies have to be recommended for early diagnosis of the disease condition. Schrom et al., (2013) reported a data mining technique called 'association rule mining' to screen individuals at high risk for T2DM. The study has also reported dyslipidemia as a major risk factor in prediabetes subjects to become diabetics. The application of these risk assessment strategies would help in bringing out better management strategies for the disease condition.[36]

Figure 3
Comorbidities associated with prediabetes.



Transition state

Prediabetic state can also be termed as a transition state from non-diabetic hyperglycemia to diabetes. The mechanisms underlying this transition state is quite complex. It might be because of insulin resistance or because of beta cell dysfunction or even both. Initially in the prediabetic state when there is an increase in the blood glucose level, the beta cell starts to secrete more insulin to compensate the increasing blood glucose levels. When this condition is prevailing at a long term in an individual, normal beta cells would be able to compensate the need at a long term and the individual would still remain in a normoglycemic state. Whereas, when there is impairment in the beta cells, there occurs an over load or stress on the beta cells which eventually leads to impaired insulin secretion. This state of beta cell failure is called as beta cell dysfunction.[37] The beta cell dysfunction over time leads to reduced beta cell mass which is due to the oxidative stress induced over the cells. The another mechanism called insulin resistance, where there is a reduced sensitivity of cells to the secreted insulin. Both beta cell dysfunction and insulin resistance contributes to the prediabetic state.[12] The mechanism of beta cell dysfunction and insulin resistance does not occur as single as there are different mechanisms related to it such as lipid metabolism. Thus it is important to screen subjects for prediabetes and the diagnostic criteria for prediabetes should include estimating the lipid profile, BMI, waist circumference, GPAQ and lifestyle habits of an individual in addition to the measurement of blood glucose levels. This will help in identifying if the individual at prediabetes state has the risk for other disorders like metabolic syndrome and cardiovascular disorders (CVD).[12]

DISCUSSION

Necessary interventions for early management

The concern for prediabetes does not halt with the screening process. It involves providing necessary interventions for the risk population. As discussed above there are many anthropometric parameters and lifestyle habits which are to be taken into consideration while providing the intervention for the high risk group. Many

government programs have been conducted for creating awareness among the public about the severity of diabetes but the need of the hour is the prediabetic group. The National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular diseases and Stroke (NPCDCS) states three stages of interventions to prevent diabetes, cardiovascular diseases and blood pressure. It can be applied to the high risk group as follows.[38]

Primary intervention

Primary intervention involves behavioral changes in the high risk group. Studies have shown a positive association of lifestyle habits such as smoking, alcoholism and physical inactivity with prediabetes.[29] Thus prediabetic individuals have to be counseled by professionals such as yoga practitioners and physical activity trainers to involve in physical activity in order to maintain the glucose homeostasis in the body. They may also be counseled by physicians to avoid smoking and alcohol consumption. This intervention has to be performed on a regular basis and regular follow up of the risk group is essential. Table 2 represents few lifestyle modification programs conducted in Tamil Nadu population in subjects with IFG and IGT and the respective outcomes.

Secondary intervention

As discussed earlier various risk factors such as BP, high cholesterol, HDL and LDL contributes to the prediabetic and diabetic state. Thus bringing dietary changes among the high risk group is highly essential. Awareness has to be created among them about the effect of high calorie food with a help of a nutritionist and dietary changes has to be made for the individuals who are found to consume a high calorie diet. But in a developing country like India, bringing such a transition in diet requires financial assistance. Thus government organizations have to extend financial aid to achieve this goal. Balagopal et al., (2008) in Tamil Nadu population has reported a significant reduction in the fasting blood glucose (FBG) levels in individuals with type 2 diabetes and IFG by providing knowledge about the effect of diet in incidence of diabetes. Simple educational intervention has been provided for the high risk group with dietary modification (high fibre containing diet and reducing fat intake), improvement of physical activity and simple yoga with breathing exercises. The study has also reported that intervention has reduced FBG levels by 3% in adults, 11% in adults with IFG and 25% in adults with type 2 diabetes.[17] Recently the Sydney diabetes prevention program (SDPP) reported a significant control of glycemic levels in prediabetes subjects who were under continuous monitoring and reduction of body weight through a balanced diet.[39]

Tertiary intervention

Tertiary intervention is mainly concerned with the group of individuals with uncontrolled hyperglycemia. They must be provided with proper medication in order to bring their blood glucose levels in a controlled range. The commonest drug prescribed for type 2 diabetes subjects is metformin.[40] A study conducted in diabetes subjects of United States has shown a significant reduction in the blood glucose levels in both lifestyle changes and with administration of anti-hyperglycemic drugs (metformin).[41] Thus medication for the high risk group is highly essential. Different types and combination of drugs have been studied in treating T2DM subjects. Other than metformin drugs such as thiazolidinediones, insulin and lipase inhibitors have been studied recently for the treatment of both prediabetes and undiagnosed diabetes.[42] Drugs such as lipase inhibitors and bromocriptine maintains the blood glucose levels and also helps in the maintenance of body weight in obese subjects by resetting the circadian clock in the patients with both prediabetes and undiagnosed diabetes.[41] The anti-diabetic activity of each drug varies based on the glycemic levels of the subjects, dosage of drug administered and other anthropometric parameters. Recent study on the comparison of activity of metformin and sulfonylurea drug in newly diagnosed diabetes subjects have reported that Glibenclamide (a class of sulfonylurea drug) was found to be more efficient in maintaining the glycemic status of newly diagnosed diabetes subjects compared to the metformine.[56] Although Glibenclamide is cost effective compared to Metformine the disadvantage of weight gain due to the administration of sulfonylurea drug has not been addressed in the study.[56] Thus various factors such as glycemic levels, cost of the prescribed drug, dosage of the drug are to be considered while planning the tertiary interventions for prediabetes and undiagnosed diabetes subjects. The National program for prevention and control of diabetes, cardiovascular disease and stroke (NPPCDCS 2008-2009) states the various ways of risk assessment for diabetes and the various intervention strategies to be provided for the high risk group. The report strongly recommends the involvement of various primary and secondary health care centres, Non – governmental organisations (NGOs) and private practitioners to implement the intervention programs especially in the rural areas.[38] Although administration of anti-diabetic and anti-obesity medications would maintain the glycemic levels of subjects at risk, it is necessary to bring lifestyle habit modifications in prediabetes and undiagnosed diabetes subjects in order to maintain their metabolic profile and to prevent glucose dysregulation.[43,55]

Table 2
***Interventions for high risk group.*[38]**

S.No	Stage of intervention	Steps to be taken
1	Primary intervention	Behavioral changes
2	Secondary intervention	Dietary changes
3	Tertiary intervention	Medication and routine follow up

Table 3
Primary interventions in Tamil Nadu population with IFG and IGT.

S.No	Year	Region	Interventions	Outcome of the study	Reference
1	2006	Chennai – Indian Diabetes Prevention Program 1 (IDPP 1)	Lifestyle modification and administration of metformine in subjects with IGT	Both lifestyle modification and metformine showed a significant decrease in incidence of diabetes in subjects with IGT	Ramachandran et al., (2006) (53)
2	2008	Tamil Nadu	Lifestyle modification - education on improvement of physical activity, simple yoga and diet in subjects with IFG	Intervention significantly reduced fasting blood glucose in subjects with IFG	Balagopal et al., (2008) (17)
3	2009	Chennai – Indian Diabetes Prevention Program 2 (IDPP 2)	Lifestyle modification and administration of metformine in subjects with IGT	Both lifestyle modification and metformine showed a significant decrease in incidence of diabetes in subjects with IGT	Ramachandran et al., (2009) (54)

CONCLUSION

The increasing trend in the prevalence of prediabetes worldwide and in India requires an immediate need for the execution of proper screening programs for prediabetes subjects. The screening programs should also include necessary interventions in order to prevent the progression to diabetes. Since diabetes is a multi-factor disorder, various factors discussed in this review has to be taken into consideration while counseling the prediabetic individuals for management of the condition.

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