Original Article

Determinants of developing diabetes mellitus and vascular complications in patients with impaired fasting glucose

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ABSTRACT

Aims: To detect the risk factors of diabetes mellitus (DM) and cardiovascular complications in subjects with impaired fasting glucose (IFG). **Materials and Methods:** One hundred and twenty three subjects with proved IFG in Zanjan Healthy Heart Study (2002-2003) were recalled and participated in this study (2009-2010). Demographic and laboratoryinformation of the participants were collected.Ischemic heart disease (IHD) was assessed by the exercise tolerance test (ETT). All the subjects with abnormal ETT or documented past history of IHD confirmed by angiographic evaluation. Ophthalmic complications including cataract, glaucoma, and diabetic retinopathy were estimated by an ophthalmologist. **Results:** Incidence of DM was 19.5%. All the diabetic and pre-diabetic patients had at least one of the other components of metabolic syndrome. Obesity (*P*: 0.04, OR: 1.8, 95%CI: 1.2-9) and low physical activity *(P* < 0.001, OR: 9.6, 95%CI: 3.4-32) were the only independent prognostic risk factors for progression to DM in patients with IFG. Total incidence of IHD was 14.6% and had a strong correlation with sex (*P*: 0.01, OR: 1.8, 95%CI: 1.2-1.5), age (*P* < 0.001, OR: 23, 95%CI: 2.1-67) and cigarette smoking *(P* < 0.001, OR: 36.5, 95%CI: 3.9-337). Non-proliferative diabetic retinopathy was shown in 2 (1.6%) subjects who were all women. **Conclusion:** Obesity and low physical activity are the main factors of developing DM and its macrovascular complications in subjects with IFG.

Key words: Diabetes mellitus, impaired fasting glucose, ischemic heart disease, metabolic syndrome, retinopathy

INTRODUCTION

Diabetes mellitus (DM) as a major independent risk factor of micro- and macro-vascular complications is preceded by abnormal but reversible condition namedasimpaired fasting glucose (IFG).[1] Overt DM is considered as mainspring strong primary and secondary risk factor of ischemic heart disease (IHD) andis responsible for more mortality rate in this group.[2] In addition, different meta-analysis indicated that metabolic syndrome (MS) is responsible of elevated incidence of DM and IHD.[3]

There are limited publications indicating that accumulation of multiple metabolic components could increase the risk of IHD and its mortality in individuals with IFG or diabetes.[4-6] Despite many studies, the relation between IFG, MS, and cardiovascular disease is not well established. In addition, the prognostic factors for developing DM in patients with IFG are unclear.

Regarding to the importance of early diagnosis of DM and its complications, early detection of the main prognostic factors of developing DM is critical in order to effective interventions.

The aim of this study was to determine the incidenceof DM and its complications in subjects with IFG after seven years

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of the diagnosis and to detect the independent risk factors of developing overt DM in this population. In addition, we assessed some relations among glucose metabolism status, metabolic factors and vascular complications in this population.

MATERIALS AND METHODS

Three hundred and ninety five subjects with IFG who participated in Zanjan Healthy Heart Study (May 2002-June 2003) were listed to be reevaluated after 7 years of the initial diagnosis (July 2009-August 2011).

The original survey in brief, was a cross-sectional study (Healthy Heart Study), conducted by the Zanjan University of Medical Sciences between 2002 and 2003 in Zanjan, a province in northwest of Iran. The main ethnic groups living in this province are Azeries (Turks). The purpose of original survey was to investigate the prevalence and correlates of the anthropometric parameters, nutritional status and cardiovascular risk factors in the urban adult population of Zanjan. Healthy Heart Study recruited 2941 subjects (1396 men and 1545 women) aged 21-75 years old.

Demographics, medical history, dietary habits, anthropometric and laboratory data for the present study were taken from both the first examination of the Healthy Heart study and present evaluation.

Subjects completed a questionnaire which included, past medical history, smoking status, physical activity, and educational levels. An Oral Glucose Tolerance Test (OGTT) was done for all the participants and in the cases with abnormal glucose results, the test was repeated.

We recalled all the subjects with IFG result recorded in the original survey. Out of 395 subjects with IFG in original assessment, only 123 subjects were available.

The information including age, sex, weight, height, waist circumference, family history of DM, past history of hospital admission, and laboratory finding such as fasting plasma glucose and lipid profile were collected from all subjects.

IHD was assessed by exercise tolerance test (ETT) performed by a cardiologist. All subjects with proven IHD based on documented past medical history or those with abnormal ETT confirmed by abnormal angiography were considered to have IHD. In addition, cardiovascular complications defined as incident myocardial infarction, Approved cardiac ischemia, positive cardiac angiography, cardiac arrest, stroke, stroke death and other Crdiovascular desease (CVD) death.

Ophthalmic complications like retinopathy, cataract, Glaucoma, and diabetic retinopathy were estimated by an ophthalmologist. Diabetic retinopathy was evaluated by fundus examination via dilated pupil.

Waist circumference between the lowest rib and the iliac crest at the level of umbilicus was measured in duplicate to the nearest mm with flexible tape.

Blood pressure was measured in sitting position with a random zero sphygmomanometer. Systolic (Korotkoff phase I) and diastolic (Korotkoff phase V) blood pressure was measured twice on the left upper arm and the average used for the analysis. Hypertension was defined as average systolic blood pressure more than 130 mmHg or diastolic blood pressure more than 85 mmHg or current use of antihypertensive medications.

The global physical activity questionnaire was used to evaluate physical activity of the participants.[7] The questionnaire was developed by WHO for physical activity surveillance and collects information on physical activity participation in three settings (or domains) including: Activity at work, Travel to and from places and Recreational activities.

Laboratory measurements were done at the laboratory of Zanjan University of Medical Sciences, Valie-E-Asr Hospital. Fasting plasma glucose was measured by the glucose-peroxidase colorimetric enzymatic method with a sensitivity of 5 mg/dl and intra-assay coefficients of variation I.7% in lower limit and 1.4% in upper limit concentrations. Fasting plasma glucose more than 100 mg/dl was defined abnormal in this study. All the subjects had at least two tests for their Fasting Plasma Glucose (FPG) and all of the people with two glucose levels more than 126 mg/dl or those with previous history of DM based on their documents were diagnosed to have overt DM.

Serum cholesterol and triglyceride (TG) of all the participants were measured after 12-14 h of fasting with colorimetric method with a sensitivity of 5 mg/dl. Hypertriglyceridemia was defined as TG concentration more than 150 mg/dl. High density lipoprotein (HDL) Cholesterol <50 mg/dl in females and <40 mg/dl in males was considered to be abnormal. In this study, MS was defined when subjects have three or more of the following criteria according to the modified NCEP III: (1) TGs 150 mg/dl, (2) HDL cholesterol <40 mg/dl in men and <50 mg/dl in women, (3) systolic blood pressure 130 mmHg or diastolic blood pressure 85 mmHg, (4) fasting plasma glucose 100 mg/dl and (5) Truncal obesity (waist circumference more than 102 cm in men and >88 cm in women). Subjects with

a history of hyperlipidemia, hypertension, or diabetes were considered to have the risk factor, regardless of the biochemical or clinical values.

This study was approved by the ethical committee of Zanjan University of Medical Sciences and all the subjects were informed about the aims of the study.

Statistical analyses

The data are presented as frequencies, percentages, and 95% confidence intervals. The prevalence of different abnormalities was compared using χ^2 test. Logistic regression analysis was used to detect the value of variables such as body mass index (BMI) and physical activity to predict the existence of DM and its complications. The analysis was done with SPSS 16.5 software package. $P < 0.05$ was considered statistically significant.

RESULTS

Only 123 subjects out of 395 persons with IFG were found after seven years of the original study and accepted to be reevaluated. The remainders were not found because of immigration or change in their addresses. The baseline characteristics of the people who attended for secondary evaluation and those who were not available after 7 years of diagnosis have been compared in Table 1.

The founded subjects including 45 (36.6%) men and 78 (63.4%) women with the average age of 47 ± 15 years old were entered in the study. None of the subjects had special education for their lifestyle during the last 7 years. Table 1 shows the basal characteristics of study population and compares those between males and females [Table 2].

Table 1: Comparison of baseline characteristics between people with impaired fasting glucose who attended for reevaluation after 7 years of diagnosis and those who were not available

Variable	Active participants *N*:123	Absent participants *N*:272	*P* value
Age (Y)	40±14	38.9±15	0.1
BMI (Kg/m²)	27.5±4	26.9±5	0.3
Waist circumference (cm)	91±10.5	90.4±11	0.4
SBP (mmHg)	130±12	127±14	0.09
DBP (mmHg)	79±8	81±5	0.2
HTN (%)	24.8	26	0.08
Smoking (%)	4.8	5.7	0.1
Hypertriglyceridemia (%)	48	45	0.1
Low HDL-C (%)	83	87	0.09

IFG: Impaired fasting glucose, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HTN: Hypertension, HDL: High density lipoprotein, Hypertriglyceridemia: TG>150 mg/dl, Low HDL: HDL<40 for males and HDL<50 for females

MS was found in 59 persons (48%) and seven of them had all the five components of the syndrome and they were all female [Table 1]. Only 8 (6.5%) of the participants had no risk factor.

44 subjects (74.6%) with MS versus 36 subjects (56%) without the syndrome have low physical activity (*P*: 0.03, OR: 2.2, 95% CI: 1.06-4.9).

The prevalence of MS was higher in the subjects more than 40 years old (78% vs. 22%, *P*: 0.03). No significant relation was found between MS and other factors such as IHD (*P*: 0.4), Non-proliferative diabetic retinopathy (NPDR) (*P*: 1) and smoking (*P*: 0.9).

Progression to overt DM was detected in 24 (19.5%) subjects; eight of them were aware to have DM. Forty six (37.6%) subjects remained to have IFG (pre-diabetes state) and the plasma glucose concentration was returned to normal levels in 53 (43%) of the participants.

Converting to overt DM was more prevalent in women than men (23% vs. 13% respectively, *P*: 0.001). Twenty-three persons with overt DM (96%) versus 17 subjects with normal glucose metabolism (32%) had low physical activity. The risk of overt DM was significantly more in subjects with low physical activity [Table 3].

Furthermore, obesity was significantly more frequent in subjects with impaired glucose metabolism than those with normal glucose concentration (44% vs. 23% respectively, *P*: 0.001) and BMI was significantly lower in subjects with normal glucose metabolism than those with overt DM or pre-diabetes situation (*P*: 0.006) [Table 3].

Return to normal glucose metabolism was more prevalent in the younger subjects and progression to overt DM increased significantly after age 40 years (*P*: 0.001).

Logistic regression analysis revealed that only higher BMI or waist circumference and low physical activity are independent prognostic risk factors for developing overt DM in cases with history of IFG [Table 4]. Although subjects with low physical activity have significantly more BMI and waist circumference (*P*: 0.03) but, as mentioned before, in logistic regression analysis both factors showed significant predictive value for progression of DM independent of other factors.

Table 5 compares the prevalence of other cardiovascular risk factors between the subjects with impaired glucose metabolism (overt DM and IFG) and those who returned to normal glucose concentrations 7 years after the initial diagnosis of IFG.

Table 2: Demographics and laboratory characteristics of the study population (*N*:123)				
	Male	**Female**	***P* value, *t* or OR (95% CI)**	**Total mean±SD (min-max) or number (%)**
Age (mean)	46.8±18	47.3±13	0.8	47.14±15 (17-78)
Height (cm)	166.6±7.5	154.9±4.2	<0.001, 10.7 (9.5-13.8)	159.2±8 (143-184)
Weight (Kg)	73.02±15	70.19±12	0.2	71.2±13 (32-125)
BMI (Kg/m²)	26.26±5.3	29.10±4.9	0.004, 2.9 (1.9-4.7)	28±5.2 (15.6-46.4)
Waist (cm)	89.6±11.4	93.7±13.6	0.1	92±12.8 (63-118)
Systolic BP (mmHg)	134.8±21	125.7±17	0.01, 2.3 (1.9-16.2)	129±19 (98-193)
Diastolic BP (mmHg)	80.9±9.7	79.1±8.3	0.2	79.8±8.9 (60-100)
HTN (%)	16 (35.6)	18 (24.0)	0.2	34 (28.3)
Pre-diabetes (%)	10 (22.2)	36 (46.2)	0.001, 4.1 (1.9-9)	46 (37.4)
DM (%)	6 (13.3)	18 (23.1)	0.001, 4.1 (1.9-9)	24 (19.5)
Family history of DM (%)	13 (29.5)	22 (29.3)	1.0	35 (29.4)
TG≥150 (%)	18 (43)	31 (39)	0.04, 0.2 (0.07-0.6)	58 (47)
Low HDL*(%)	27 (72)	61 (94)	0.02, 0.3 (0.1-0.8)	88 (71)
IHD (%)	12 (29.3)	6 (8.2)	0.01, 1.8 (1.2-5)	18 (14.6)
NPDR (%)	0	2 (2.6)	0.5	2 (1.6)
Smoking (%)	7 (15.6)	0	0.001	7 (5.7)
MS (%)	15 (33.3)	44 (56.4)	0.01, 0.3 (0.1-0.8)	59 (48.0)
No. of MScomponents (%)				
0	7 (15.6)	1 (1.3)		8 (6.5)
1	12 (26.7)	12 (15.4)		24 (19.5)
2	11 (24.4)	21 (26.9)		32 (26.0)
3	9 (20.0)	24 (30.8)	0.006	33 (26.8)
4	6 (13.3)	13 (16.7)		19 (15.4)
5	0	7 (9.0)		7 (5.7)
Physical activity (%)				
Mild	18 (40)	62 (79.5)	0.001	80 (65)
Moderate	17 (37.8)	14 (17.9)		31 (25.2)
Severe	10 (22.2)	2 (2.6)		12 (9.8)
FBS (mg/dl)	94.8±33.8	106.1±28.6	0.05	102±31 (55-270)
TG (mg/dl)	150.2±88.1	167.7±92.1	0.3	161.4±90 (55-550)
Cholesterol (mg/dl)	188.8±39.9	208.7±44.4	0.01, 2.5 (3.8-36)	201±43.8 (101-305)
HDL (mg/dl)	39.8±5	42.3±8	0.06	41.4±7.1 (30-91)
LDL (mg/dl)	118.9±35.3	132.5±40.3	0.06	127.5±39 (80-218)

BMI: Body mass index, BP: Blood pressure, HTN: Hypertension, DM: Diabetes mellitus, TG: Triglyceride, HDL: High density lipoprotein, *Low HDL: HDL<40 for males and HDL<50 for females, IHD: Ischemic heart disease, NPDR: None proliferative diabetic retinopathy, MS: Metabolic syndrome, FBS: Fasting blood sugar, LDL: Low density lipoprotein, CI: Confidence interval, OR: Odds ratio, SD: Standard deviation

Table 3: Determinants of glucose metabolism status in subjects with impaired fasting glucose 7 years after diagnosis (univariable analysis)			
	Normal *n*:53	**Pre-diabetics *n*:46**	**Overt DM *n*:24**	**P value, OR (95% CI)**
Sex (male) (%)	29 (54.7)	10 (21.7)	6 (25)	0.001, 6.1 (1.9-9)
Age (%)				
>40	26 (49)	9 (20.4)	3 (13.6)	0.001, 5 (1.3-8)
40-60	14 (26.4)	25 (56.8)	16 (72.7)	
≤60	13 (24.5)	10 (22.7)	3 (13.6)	
BMI (%)				
>25	24 (47.1)	9 (20.5)	3 (13.16)	
25-30	15 (29.4)	16 (36.4)	6 (27.3)	0.006, 2.4 (1.2-6)
≤30	12 (23.5)	19 (43.2)	13 (59.1)	
Physical activity (%)				
No	17 (32.1)	40 (87)	23 (95.8)	>0.001, 16.2 (6-42)
Yes	36 (67.9)	6 (13)	1 (4.2)	

DM: Diabetes mellitus, BMI: Body mass index, CI: Confidence interval

The incidence of IHD was 14.6%(18 persons) in a 7-year period after diagnosis of IFG. IHD was significantly more frequent in males and in older subjects (>40 years) versus younger participants. The frequency of IHD increased to 60% after age 60 years. The most significant risk factor for IHD was cigarette smoking [Table 6].

The chance of IHD was estimated to be significantly more than non-smokers (OR: 36, CI95%:3.9-337, *P*: 00.1).

No association was found among IHD and metabolic syndrome, hypertension (HTN) and lipid profile [Table 6].

NPDR was found in two subjects (1.6%) who both were women with IFG. Cataract was detected in 7 (5.7%) of the participants. There was a significant higher frequency of cataract but not NPDR in older ages (*P*: 0.01). No association was found between ophthalmic complications and MS or IHD.

Table 4: Regression analysis results (independent predictors of diabetes mellitus in subjects with impaired fasting glucose)

Dependent variable	Independent variables	Odds ratio 95% CI	P value
Diabetes mellitus	Obesity	1.8 (1.2-8.7)	0.04
	Low physical activity	9.6 (3.4-32)	<0.001
	Sex	2 (0.7-6.4)	0.2
	Age	1.6 (0.3-3)	0.1

CI: Confidence interval

Table 5: Comparisons between subjects with normal and abnormal plasma glucose

	FBS<100 n:55	FBS≥100 n:67	P value OR (95% CI)
Age (%)			
>40	26 (47.2)	12 (19)	
40-60	15 (27.2)	39 (61.9)	>0.001, 5 (1.5-8)
≤60	14 (25.4)	12 (19)	
Sex (male) (%)	30 (54.4)	15 (22.4)	>0.001, 4.1 (1.9-9)
HTN (%)	18 (33.3)	25 (38.5)	0.5, 1.2 (0.5-2.6)
BMI (%)			
>25	25 (47.2)	11 (17.5)	
25-30	16 (30.2)	21 (33.3)	0.001, 2 (1.2-6)
≤30	12 (22.6)	31 (49.2)	
IHD (%)	12 (25)	6 (9.2)	0.02, 0.3 (0.1-0.8)
TG≥150 (%)	23 (41.8)	35 (53)	0.2, 1.5 (0.7-3.2)
LDL≥160 (%)	11 (20)	12 (19)	1, 0.9 (0.3-2.3)
Low HDL*(%)	39 (70.9)	49 (77.8)	0.4, 1.4 (0.6-3.2)
Physical activity (%)			
No	19 (34.5)	60 (89.6)	>0.001, 16.2 (6.2-42.4)
Yes	36 (65.5)	7 (10.4)	

FBS: Fasting blood sugar, HTN: Hypertension,
BMI: Body mass index, IHD: Ischemic heart disease, TG: Triglyceride,
HDL: High density lipoprotein, *Low HDL: HDL<40 for males and HDL<50 for females, LDL: Low density lipoprotein, OR: Odds ratio, CI: Confidence interval

Table 6: Correlation between ischemic heart disease and metabolic factors in study population

	IHD+	IHD-	P value OR (95% CI)
Age (%)			
>40	1 (5)	36 (39.1)	
40-60	6 (33.3)	45 (46.9)	0.001>23 (2.1-67)
≤60	11 (61)	11 (11.9)	
Sex (male) (%)	12 (29.3)	29 (70.7)	0.01, 1.8 (1.2-5)
Metabolic syndrome (%)	10 (18.5)	43 (79.6)	0.4
BMI (%)			
>25	4 (22.2)	30 (32.6)	
25-30	11 (61.1)	24 (26)	0.01, 0.4 (0.2-0.9)
≤30	3 (16.6)	38 (41.3)	
HTN (%)	10 (55.5)	31 (33.3)	0.06, 2.5 (0.8-6.9)
Smoking (%)	5 (27.7)	1 (1)	0.001>, 36.5 (3.9-337)
TG≥150 (%)	9 (50)	43 (45.2)	0.7, 1.2 (0.4-3.3)
LDL≥160 (%)	3 (16.7)	17 (18.5)	0.85, 0.8 (0.2-3.3)
Low HDL*(%)	12 (66.6)	72 (78.2)	0.3, 0.55 (0.18-1.66)
FBS (%)			
≥100	6 (33.3)	59 (62.1)	0.02, 0.3 (0.1-0.88)
<100	12 (66.6)	36 (37.8)	

BMI: Body mass index, HTN: Hypertension, TG: Triglyceride, HDL: High density lipoprotein, *Low HDL: HDL<40 for males and HDL<50 for females, FBS: Fasting blood sugar, LDL: Low density lipopro, IHD: Ischemic heart disease, CI: Confidence interval, OR: Odds ratio

DISCUSSION

This study showed that subjects with IFG are prone to develop overt DM and IHD. Among different risk factors family history of DM, obesity and low physical activity are independent prognostic factors to predict overt DM in this high-risk population. In addition, our investigation showed a strong association of male gender, older age and cigarette smoking with IHD in subjects with history of pre-diabetes state.

Although the risk of progression to diabetes in our study population was considerable (19.5%) during the 7-year follow-up, this rate of progression is much lower than what is reported by the Hoorn Study[8] (33%).The rate of progression to diabetes was also a little lower than in the finnish diabetes prevention study (DPS), which reported a progression rate of 23% after a 4-year follow-up period.[9] This may be due to the older age of the subjects in the DPS (mean age 55 ± 7 vs. 47 ± 15 years) and also their higher BMI (BMI 31 ± 5 vs. 28 ± 5 kg/m²). Our results are in keeping with the study on the Pima Indians that revealed a 5-year cumulative incidence of 20% for overt DM in subjects with IFG.[10] Lower rates of progression to overt DM have been reported by Lyssenko in which a progression rate of 12% after 5-year of follow-up period was seen.[11] These differences may be explained by different ethnicity of the study populations and their different lifestyles.

As expected, obesity and low physical activity were independent predictors of diabetes. Several previous studies have shown that BMI can predict subsequent diabetes.[12-15] As shown in our study central obesity was detected by waist circumference, is an independent risk factor for subsequent DM. This result has been confirmed by other researches which reported both waist to hip ratio and BMI independently can predict type 2 diabetes.[11,13] Although, there are some reports about the prognostic value of elevated TG and low HDL cholesterol concentrations as well as elevated diastolic blood pressure to predict diabetes, we did not find the same results after adjustment for BMI and age.

Recent studies discuss about the role of inflammation as an underlying mechanism that correlate obesity with insulin resistance and DM. They believe that adipose tissue inflammation induces insulin resistance in obese patients, and has a major role in the progression of DM. Chronic inflammatory processes share a common pathway in which increased production of reactive oxygen species activates p53 and NF-κBsignaling, resulted in up-regulation of

pro-inflammatory cytokine expression and impairment of glucose metabolism.[16] IL-1 family of cytokines, especially IL-1β, have shown to play an important role in obesity-associated inflammation and insulin resistance.[17] Faulhaber-Walter *et al*. in a study showed the absence of adenosine A1 receptor signaling resulted in impaired glucose tolerance, insulin resistance, and increased fat mass that show the role of adenosinein the regulation of glucose homeostasis and metabolic regulation of adipose tissue.[18]

In the genetically-altered rats that develop obesity and insulin resistance the hyperglycemia is associated with impaired pancreatic β-cell function, loss of pancreatic β-cell mass, and decreased responsiveness of liver and extrahepatic tissues to the actions of insulin and glucose.[19]

It is known that, during physical exercise, glucose uptake by the involved muscles rises 7-20 times, depending on the intensity of physical activity. Chronic physical training habits improves the reduced peripheral tissue sensitivity to insulin in impaired glucose tolerance and Type II diabetes.[20] Some studies have shown exercise could increases insulin content and basal secretion in pancreatic islets in type 1 diabetic mice.[21]

In our study age, male gender and cigarette smoking were independent risk factors for IHD. Surprisingly, we couldnot find any independent association of hyperglycemia or HTN with IHD.

Liu *et al*.[5] reported 10-year risk of cardiovascular incidence related to diabetes, pre-diabetes, and the metabolic syndrome. They found that Hyperglycemia without any concomitant disorders was not associated with significantly higher risk of CVD. The increased CVD risk in individuals with IFG or diabetes was largely driven by the coexistence of multiple metabolic disorders rather than hyperglycemia.[5] Furthermore, Wannamethee *et al*.[22] reported some risk factors to predict sudden cardiac death (SCD). Based on their study diabetes and BMI were not associated with risk of SCD after adjustment. Finally, recent studies showed that IFG and impaired glucose tolerance test (IGT) are associated with modest increase of cardiovascular disease risk.[23,24]

Based on our results there was no significant independent association between lipid abnormalities and IHD in subjects with past history of IFG. Although this result might be due to small sample size of the subjects with IHD in our study, there are some other studies with similar results. Suadicani *et al*.[25] revealed that high TG is an independent risk factor for IHD mortality only among men with BMI ≤ 27.5 kg/m² and also low HDL-C is an independent risk factor for IHD mortality only among men with BMI > 27.5 kg/m².

The results of this study determine a rate of 1.6% for diabetic retinopathy among subjects with a past history of IFG. Based on our data all the subjects with retinopathy have had consistent pre-diabetes state since 7 years. We could not find any significant association between occurrence of retinopathy and glucose level, BMI, blood pressure and smoking. The frequency of diabetic retinopathy reported here isnear to that reported by Rajala *et al*.[26] in the US (2.6%). In their study retinopathic changes were associated with higher fasting blood glucose levels, but not with any of the other background factors.[26] Despite, some reports about the importance of blood pressure in the progress of retinopathy in patients with pre-diabetes state, this relation is not clear. In a study by Tyrberg[27] subjects with retinopathy had significantly higher systolic and diastolic blood pressure levels and BMI independent of age, sex and known hypertension. They could not find any associations between FBS or haemoglobin A1C and retinopathy.

According to this study, subjects with IFG especially whose with family history of DM, higher BMI and lower physical activity should be under early screening and evaluation for DM and vascular complications. Early intervention focused on physical activity and the nutritional regimen for lowering BMI is recommended in these patients. We also recommend screening for silent IHD with ETT in people with IFG (especially males) older than 60 years and especially in those with cigarette smoking.

LIMITATION OF STUDY

Our study population was collected from Zanjan Healthy Heart Study. We had no access to all these subjects, and only 123 subjects were found to participate in our investigation, so it may affect our results.

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REFERENCES

1. Weiss R. Impaired glucose tolerance and risk factors for progression to type 2 diabetes in youth. Pediatr Diabetes 2007;8:70-5.
2. Muhlestein JB, Anderson JL, Horne BD, Lavasani F, Allen Maycock CA, Bair TL, *et al*. Effect of fasting glucose levels on

mortality rate in patients with and without diabetes mellitus and coronary artery disease undergoing percutaneous coronary intervention. Am Heart J 2003;146:351-8.

3. Iribarren C, Go AS, Husson G, Sidney S, Fair JM, Quertermous T, *et al*. Metabolic syndrome and early-onset coronary artery disease: Is the whole greater than its parts? J Am Coll Cardiol 2006;48:1800-7.

4. Koro CE, Bowlin SJ, Rabatin V, Fedder DO. Cardiovascular disease risk among subjects with impaired fasting glucose in the United States, Results from NHANES 1999-2004 United States. Diabetes and Metabolic Syndrome: Clinical Research and Reviews 2008;2:239-44.

5. Liu J, Grundy SM, Wang W, Smith SC Jr, Vega GL, Wu Z, *et al*. Ten-year risk of cardiovascular incidence related to diabetes, prediabetes, and the metabolic syndrome. Am Heart J 2007; 153:552-8.

6. Uzunlulu M, Oguz A. Is metabolic syndrome a condition independent of prediabetes and type 2 diabetes mellitus? A report from Turkey. Endocr J 2007;54:745-50.

7. Waxman A; World Health Assembly. WHO global strategy on diet, physical activity and health. Food Nutr Bull 2004;25:292-302.

8. de Vegt F, Dekker JM, Jager A, Hienkens E, Kostense PJ, Stehouwer CD, *et al*. Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: The Hoorn Study. JAMA 2001;285:2109-13.

9. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, *et al*. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343-50.

10. Tulloch-Reid MK, Williams DE, Looker HC, Hanson RL, Knowler WC. Do measures of body fat distribution provide information on the risk of type 2 diabetes in addition to measures of general obesity? Comparison of anthropometric predictors of type 2 diabetes in Pima Indians. Diabetes Care 2003;26:2556-61.

11. LyssenkoV, Almgren P, Anevski D, Perfekt R, Lahti K, Nissén M, *et al*. Predictors of and longitudinal changes in insulin sensitivity and secretion preceding onset of type 2 diabetes. Diabetes 2005;54:166-74.

12. Bjørnholt JV, Erikssen G, Liestøl K, Jervell J, Thaulow E, Erikssen J. Type 2 diabetes and maternal family history: An impact beyond slow glucose removal rate and fasting hyperglycemia in low-risk individuals? Results from 22.5 years of follow-up of healthy nondiabetic men. Diabetes Care 2000;23:1255-9.

13. Ohlson LO, Larsson B, Svärdsudd K, Welin L, Eriksson H, Wilhelmsen L, *et al*. The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. Diabetes 1985;34:1055-8.

14. Skarfors ET, Selinus KI, Lithell HO. Risk factors for developing non-insulin dependent diabetes: A 10 year follow up of men in

15. Eriksson KF, Lindgärde F. Poor physical fitness, and impaired early insulin response but late hyperinsulinaemia, as predictors of NIDDM in middle-aged Swedish men. Diabetologia 1996;39:573-9.

16. Shimizu I, Yoshida Y, Katsuno T, Minamino T. Adipose tissue inflammation in diabetes and heart failure. Microbes Infect 2012;12:S1286-4579.

17. Tack CJ, Stienstra R, Joosten LA, Netea MG. Inflammation links excess fat to insulin resistance: The role of the interleukin-1 family. Immunol Rev 2012;249:239-52.

18. Faulhaber-Walter R, Jou W, Mizel D, Li L, Zhang J, Kim SM, *et al*. Impaired glucose tolerance in the absence of adenosine A1 receptor signaling. Diabetes 2011;60:2578-87.

19. Shiota M, Printz RL. Diabetes in Zucker diabetic fatty rat. Methods MolBiol 2012;933:103-23.

20. Sato Y, Nagasaki M, Nakai N, Fushimi T. Physical exercise improves glucose metabolism in lifestyle-related diseases. Exp Biol Med 2003;228:1208-12.

21. Huang HH, Farmer K, Windscheffel J, Yost K, Power M, Wright DE, *et al*. Exercise increases insulin content and basal secretion in pancreatic islets in type 1 diabetic mice. Exp Diabetes Res 2011. [In Press].

22. Wannamethee G, Shaper AG, Macfarlane PW, Walker M. Risk factors for sudden cardiac death in middle-aged British men. Circulation 1995;91:1749-56.

23. FordES, ZhaoG, LiC. Pre-diabetes and the risk for cardiovascular disease: A systematic review of the evidence. J Am Coll Cardiol 2010;55:1310-7.

24. Levitzky YS, Pencina MJ, D'Agostino RB, Meigs JB, Murabito JM, Vasan RS, *et al*. Impact of impaired fasting glucose on cardiovascular disease: The Framingham Heart Study. J Am Coll Cardiol 2008;51:264-70.

25. Suadicani P, Hein HO, von Eyben FE, Gyntelberg F. Metabolic and lifestyle predictors of ischemic heart disease and all-cause mortality among normal weight, overweight, and obese men: A 16-year follow-up in the Copenhagen Male Study. Metab Syndr Relat Disord 2009;7:97-104.

26. Rajala U, Laakso M, QiaoQ, Keinänen-Kiukaanniemi S. Prevalence of retinopathy in people with diabetes, impaired glucose tolerance, and normal glucose tolerance. Diabetes Care 1998;21:1664-9.

27. Tyrberg M, Melander A, Lövestam-Adrian M, Lindblad U. Retinopathy in subjects with impaired fasting glucose: The NANSY-Eye baseline report. Diabetes Obes Metab 2008;10:646-51.

Uppsala. BMJ 1991;303:755-60.