ORIGINAL RESEARCH PAPER
VOLUME-6 | ISSUE-6 | JUNE-2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

Clinical study of Macro vascular complications in newly detected Type 2 Diabetes Mellitus

Cardiology

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ABSTRACT

Introduction- India is claimed to be the diabetes capital of the world. In type 2 diabetes, vascular complications can occur. It is divided into microvascular and macrovascular complications. Aim of this study to analyze the clinical profile of macrovascular complications in newly diagnosed type 2 diabetes.

Methodology- 50 newly detected type 2 diabetes mellitus, age less than 40 years patients were selected. Detailed history like family history, past history, clinical examination , investigations like lipid profile, routine investigations, fundus examination, ECG, 2D-Echo, Carotid Duplex USG.

Result-. Factors associated with carotid atherosclerosis that were analyzed were Smoking, Hypertriglyceridemia and HBA1c levels .The factors which showed significant association with peripheral vascular disease where Smoking, Hypertension and HbA1C levels ,whereas Hypertriglyceridemia, Hypertension, HBA1c levels and Smoking showed significant association with coronary atherosclerosis. Cross tabulation of each of the three macrovascular complications showed a significant association with each other.

Conclusion- Presence of any one of the three macrovascular complications is good predictor of atherosclerotic changes in the other two vascular beds in newly detected diabetics. Aggressive approach to retard the progression of these atherosclerotic changes should begin early for patients with newly detected diabetes.

KEYWORDS:

Type 2 diabetes, Macrovascular, 2D-Echo, Coronary.

INTRODUCTION

India is claimed to be the diabetes capital of the world. Diabetes Mellitus is a silent disease. Majority patients are unaware of the disease and present late when complications have already occurred. Many studies have proven that persistent hyperglycaemia and associated metabolic syndrome features like hypertension; dyslipidemia and obesity contribute to development of vascular complications.[1]

The vascular complications of diabetes mellitus are divided into micro vascular (retinopathy, neuropathy, nephropathy) and macro vascular (coronary artery disease, peripheral artery disease and cerebrovascular disease) complications.[2]

The central pathological mechanism in macrovascular disease is the process of atherosclerosis, this leads to narrowing of the arterial walls throughout the body. Atherosclerosis, thereby, appears to be the most important pathology behind the development of the macroangiopathy which causes severe disability in diabetics.

In addition to atheroma formation, there is a strong evidence of increased platelet adhesion and hypercoagulability in type 2 diabetics. Impaired nitric oxide generation and increased free radical may promote platelet aggregation. This combination of increased coagulability and impaired fibrinolysis further increases the risk of vascular occlusion and cardiovascular events in type 2 diabetes patients.3

Type 2 diabetes typically occurs in the setting of a metabolic syndrome, which includes:-Hypertension, hyperlipidemia, abdominal obesity, smoking.

Other factors are –Age is also an important association with atherosclerosis. Glucose intolerance is increasingly prevalent with aging. The prevalence of PVD (Peripheral Vascular Disease) is higher in Type 2 Diabetics than in Non Diabetic. It is well known fact that PVD is more common in older individuals4. It is also seen that the Diabetic patients had increased subclinical atherosclerosis as measured by Intimal Media Thickness (IMT) and it is seen that carotid Intimal medial thickness increased with worsening grades of glucose intolerance as well as with increase in number of components of metabolic syndrome5. Aim of this research to analyze the clinical profile of macrovascular complications in newly diagnosed type 2 diabetics.

MATERIAL & METHODS

We conducted prospective study over period of 24 months. Study included 50 newly detected Type 2 Diabetes mellitus Patients greater than 40 years with the diagnosis of Type 2 diabetes mellitus by ADA criteria referred to Bharati Hospital, Pune, India was included. Institutional ethical committee approval was taken. Inclusion criteria included patients with greater than 40 years with newly detected Type 2 diabetes mellitus by the ADA criteria. Exclusion criteria included known case of Type 1 Diabetes Mellitus or any other severe illness or patients already diagnosed with Type 2 diabetes mellitus and are on treatment or refusal to be a part of study.

ADA Criteria for the diagnosis of diabetes:-

HBA1C ≥ 6.5%.OR Fasting plasma glucose ≥126 mg/dL. (Fasting is defined as no caloric intake for at least 8 hours) OR 2 hour plasma glucose ≥ 200 mg/dL (Test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.) OR In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL.

Data collected from the patients after obtaining a detailed written informed consent from the patient. After which a detailed history has been taken with due importance given to family history and presence of any co- morbidities. The detailed clinical examination was carried out under the following headings: Height- measured in centimetres, weight –measured in kilograms, BMI –WT (Kg)/ HT (m2) (Kg/m2), history of hypercholesterolemia. Any documented proof of the same and availability of any medical reports suggestive of the same. Beyond history all patients underwent a lipid profile for the purpose of analysis of data and correlation to macrovascular complications in the study.

Past history angina, stroke, peripheral vascular disease and hypothyroidism was also taken. Important personal history regarding smoking and alcohol consumption, as the association of these factors to be tested for the development of macrovascular complications. History eliciting associated symptoms of Type 2 diabetes related to autonomic and sensorimotor neuropathy was also taken such as history of orthostatic hypotension, tingling and numbness, burning pain in lower extremities etc.Important general examinations findings were noted in addition to routine findings such as -Xanthelesma (for assessment of hyperlipidemia),Thyroid swelling (as hypothyroidism could lead to decreased Basal Metabolic Rate, and altered sugar profile),Trophic ulcers (to assess severity of neuropathy) etc. A biochemical profile of these patients will be carried out. This data will be entered into a special proforma designed for this study.

Routine investigations like fasting blood sugar and Post Prandial blood sugar were measured. HbA1C levels used in study for analysis as they were more indicative of the diabetic status to the patient. HbA1C >6.5% considered abnormal in study group.Lipid profile was measured and LDL, HDL and Serum Triglyceride levels were used in study, they being the most important markers of the atherosclerosis leading to macrovascular complications. Urine routine was done to measure urine protein (albumin). Fundus examination was done for changes of retinopathy however correlation of these a changes and the development of macrovascular complications was beyond the scope of this study.

Table 1: Fundus characteristics for diagnosis of Diabetic Retinopathy

NSC	International Term	Symptoms	Features
R0	None	None	Normal Retina Grade 0 (US)
R1	Mild non-proliferative(mild pre-proliferative)	None	Haemorrhages and microaneurysms only Grade 1(US)
R2	Moderate non-proliferative,moderate pre proliferative	None	Previously termed mild pre-proliferative. Extensive Microaneurysm, Intraretinalhaemorrhage, and hard exudates. Grade 2(US)
R2	Severe non-proliferative, Severe pre proliferative	None	Previously termed severe pre -proliferative. Venous abnormalities, large blot haemorrhages, cotton wool spots (small infarcts), venous beading, venous loop Grade 3 (US)
R3		Floaters, sudden loss of vision	New vessal formation either at the disc (NVD) orelsewhere (NVE)Grade 4a (US)
R3	Proliferative retinopathy	Floaters, central loss of vision	Extensive fibrovascular proliferation, retinal detachment, pre-retinal or vitreous haemorrhage, glaucoma Grade 4b (US)
M0			No maculopathy
M1	Diabetic Maculopathy	Blurred central vision.	The macula is defined as a circle centred on the fovea, with a radius of the distance to disc margin. If the leakage involves or is near the fovea the condition is termed clinically significant macular oedema(CSME). Exudative maculopathy presents with leakage, retinal thickening, microaneurysms, hard exudates at the macula. Ischaemic form an have a featureless macular with NVE and poor vision.
	Photocoagulation	Reduced night vision,glare	Small retinal scars throughout the peripheral retina. Grade 4b (US)
OL/UG	Other lesion/ Ungradable		Un-gradable is usually due to cataract, other lesions usually referred for assessment.

DR=Diabetic retinopathy, NPDR=Non –Proliferative Retinopathy, NVE= New Vessels Everywhere, IRMA=Intra Retinal Microvascular Abnormalities, NSC=National Screening Committee(US)

Special investigations ECG, 2D-Echocardiography was done. CAROTID DUPLEX ULTRASONOGRAPHY was done for the measurement of Common Carotid Intima Media Thickness(C-IMT). Carotid artery disease was adjudged by presence of increase in C-IMT. Abnormal/increased Carotid IMT value was considered as ≥ 0.8 mm.

RESULTS

I. ANTHROPOMETRIC CHARACTERISTICS

TABLE 1: MEAN AGE, BMI AND WHR OF THE PATIENTS

Characteristics	Mean	SD	Minimum	Maximum	Median
Age (years)	50.0	5.4	41	60	49.5
BMI (kg/m2)	25.9	3.8	20.1	34.6	25.5
WHR	0.96	0.09	0.80	1.15	0.95

Out of 50 newly detected diabetics patients, 22 (44 %) were from the age group of 46-50 years, followed by 13 from 51-55 years and 10 from more than 55 years age group. The Body Mass Index (BMI) is measure of relative weight based on individual's mass and height. In the study group subjects 54 % of subjects had abnormal BMI i.e. they are slightly overweight as compared other study group subjects (46 %) who had normal BMI. The WHR has been used as an indicator of the health of a person and the risk of developing serious health conditions. In study group population out of 50, 43 (86%) patients had abnormal WHR. The study group sex distribution was in favour of males (56%) as compared to females (22%). The prevalence of smoking in study population was 58 % and all of whom were males. The prevalence of alcoholism in study population was 44 %, all of whom were males. In study group population 52% of individuals had abnormal triglycerides levels and 42% had normal triglycerides levels. In study group population 78% of individuals had abnormal LDL levels and 22% had normal LDL levels. In study group population 72% of individuals had abnormal HDL levels and 28% have normal HDL levels. 54% of study group population had Dyslipidemia i.e. both Hyperlipoproteinemia (LDL) and Hypertriglyceridemia. In the study group population 90% of individuals had abnormal HBA1c levels. HBA1c > 6.0 % considered abnormal in study group. 68% of study group were hypertensive while 32% of study group were non hypertensive. The prevalence of past history of stroke in study group is 6%. The prevalence of diabetic nephropathy adjudged by the presence of proteinuria was 28%. The prevalence of Diabetic Retinopathy was 20% in study population. Out of 50 individuals, GRADE1 Diabetic Retinopathy is present in 6 individuals, GRADE II Diabetic Retinopathy is present in 4 individuals, and none of the 40 individuals have Diabetic Retinopathy. The Prevalence in this study group of any or all of the symptoms suggestive of Diabetic Neuropathy (orthostatic hypotension, bladder symptoms, tingling, numbness, position sense abnormalities, diminished ankle jerk) was 36%.

TABLE 2: PREVALENCE OF MACROVASCULAR COMPLICATIONS BY GENDER

Complications	Gender		
	Male	Female	p-value
Carotid Artery Disease	13 (46.4)	11 (50.0)	0.513 ^{NS}
Peripheral Vascular Disease	11 (39.3)	8 (36.4)	0.533 ^{NS}
Coronary Artery Disease	10(35.7)	13(59.1)	0.047*
Macro-vascular complications	19(67.9)	14(63.6)	0.494 ^{NS}

NS- Statistically non-significant *Statistically significant ($p<0.05$)

TABLE 3: PREVALENCE OF MACROVASCULAR COMPLICATIONS AND SMOKING

Complications	SMOKING		
	Smokers	Non-smokers	p-value
Carotid Artery Disease	14 (66.6)	12(41.4)	0.048*

Peripheral Vascular Disease	11(52.4)	8(27.6)	0.036*
Coronary Artery Disease	13(61.9)	14(48.3)	0.035*
Macrovascular complications	16(76.2)	17(58.6)	0.011*

*- Statistically significant (p<0.05)

TABLE 4: PREVALENCE OF MACRO-VASCULAR COMPLICATIONS AND BMI

Complications	BMI		
	Normal	Abnormal	p-value
Carotid Artery Disease	11(47.8)	13(48.1)	0.603 NS
Peripheral Vascular Disease	7(30.4)	12(44.4)	0.235 NS
Coronary Artery Disease	7(30.4)	16(59.3)	0.039 *
Macrovascular complications	13(56.5)	20(74.1)	0.157 NS

NS- Statistically non-significant
*Statistically significant (p<0.05)

TABLE 5: PREVALENCE OF MACROVASCULAR COMPLICATIONS AND HYPERTENSION

Complications	Hypertension		
	Yes	No	p-value
Carotid Artery Disease	16(47.1)	8(50.0)	0.543 NS
Peripheral Vascular Disease	16(47.1)	3(18.8)	0.049*
Coronary Artery Disease	19(55.9)	4(25.0)	0.040*
Macrovascular complications	24(70.6)	9(56.3)	0.024*

NS- Statistically non-significant
*Statistically significant (p<0.05)

TABLE 6: PREVALENCE OF MACRO-VASCULAR COMPLICATIONS AND HDL

Complications	HDL		
	Normal	Abnormal	p-value
Carotid Artery Disease	16(44.4)	8(57.1)	0.311 NS
Peripheral Vascular Disease	11(30.6)	8(57.1)	0.048*
Coronary Artery Disease	14(38.9)	9(64.3)	0.047*
Macrovascular complications	22(61.1)	11(78.6)	0.203 NS

NS- Statistically non-significant
*Statistically significant (p<0.05)

TABLE 7: PREVALENCE OF MACROVASCULAR COMPLICATIONS AND TRIGLYCERIDES

Complications	Triglycerides		
	Normal	Abnormal	p-value
Carotid Artery Disease	11(45.8)	13(54.2)	0.496 NS
Peripheral Vascular Disease	8(33.3)	11(42.3)	0.359 NS
Coronary Artery Disease	6(25.0)	17(65.4)	0.005*
Macrovascular complications	12(50.0)	21(80.8)	0.022*

NS- Statistically non-significant
*Statistically significant (p<0.05)

TABLE 8: PREVALENCE OF MACROVASCULAR COMPLICATIONS AND DYSLIPIDEMIA

Complications	DYSLIPIDEMIA		
	YES	NO	p-value
Carotid Artery Disease	15(55.6)	9(39.1)	0.049*
Peripheral Vascular Disease	13(48.1)	6(26.1)	0.049*
Coronary Artery Disease	16(59.3)	7(30.4)	0.039*
Macrovascular complications	21(52.2)	12(25.2)	0.040*

NS- Statistically non-significant
*Statistically significant (p<0.05)

TABLE 9: PREVALENCE OF MACROVASCULAR COMPLICATIONS AND HBA1C

Complications	HbA1c		
	Normal	Abnormal	p-value
Carotid Artery Disease	1(20.0)	23(51.1)	0.030*
Peripheral Vascular Disease	0(0.0)	19(42.2)	0.048*
Coronary Artery Disease	2(40.0)	21(46.7)	0.576 NS
Macrovascular complications	2(40.0)	31(68.9)	0.029*

NS- statistically non-significant
*Statistically significant (p<0.05)

TABLE 10: CAROTID ARTERY ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE

Carotid Intima Media Thickness	CAD		Total	P-value
	Yes	No		
> 0.80	15	9	24	0.046
≤ 0.80	8	18	26	
Total	23	27	50	

TABLE 11: CAROTID ARTERY ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE

CAD	Number of patients	C-IMT		P-value
		Mean	SD	
Yes	23	2.43	1.32	0.266
No	27	0.69	0.24	

TABLE 12: ASSOCIATION OF CAROTID INTIMA MEDIA THICKNESS WITH MACROVASCULAR COMPLICATIONS.

	Macrovascular Complications	N	Mean	SD	P-value
Carotid Intima Media Thickness	Present	26	0.86	0.27	< 0.001
	Absent	24	0.60	0.18	

Prevalence of Carotid Artery Disease, Peripheral Vascular Disease and Coronary Artery Disease was 48 %, 38 % and 46 %, respectively. Whereas cumulative prevalence of macrovascular complications was 66 % i.e. 33 patients (out of 50) were having at least one of the three complications reported in above table.

DISCUSSION

The prevalence of smoking in study population was 58%, all of whom were males. The prevalence of macrovascular complications was significantly high (76.2 %) in smokers with significant p value of<0.05. The prevalence of Carotid Artery Disease was significantly high (66.6 %) in smokers. In case of carotid atherosclerosis this pattern is supported by studies done by Diez-Roux et al6 and Fan et al7. Karim et al8 showed that both the frequency and duration of smoking significantly increased the chances of carotid atherosclerosis but Guvener et al9 could not find a significant additional impact on the same. The present study showed a significant association of smoking in diabetics in developing coronary atherosclerosis. The prevalence of coronary atherosclerosis was higher (61.9 %) in smokers. This view was also supported by studies conducted by Vasker et al10 and Richey et al11.Smoking showed statistical significant association with peripheral vascular disease in newly detected diabetics. This association was found significant by Steven et al12, Paul et al13 and Sharon et al14 and the recent study by Maria Teresa Alzamora et al15.

The prevalence of carotid atherosclerosis was 54.5 % in alcoholics. Alcoholism didn't show a significant association with carotid atherosclerosis in this study. Kanters et al64 and Geroulakos et al16 also didn't find any additional significant association of alcoholism in their study. Moreover, Ulf Schminke et al17 showed a inverse relationship to alcoholism with carotid atherosclerosis. Daniel E Cooper et al37 found that in contrary to usual recommendations, moderate alcohol consumption could increase the chances of atherosclerosis in carotids and maybe detrimental before more conclusive evidence about this association is obtained. The prevalence of coronary atherosclerosis was 45.5 % in alcoholics. Alcohol consumption didn't affect outcome of coronary events significantly in the present study. Romana et al18 in their study in 2006 have shown a protective effect of moderate drinking of cardiovascular mortality. The lack of significance may be due to the small sample size under study of which only 44% were alcoholics.

The prevalence of peripheral vascular disease was 50.0 % in alcoholics. Alcohol consumption didn't show significant association with peripheral vascular disease in the present study. Rozemarijn et al19 showed an increase relationship of alcoholism with peripheral vascular disease in both small and moderate amounts, but only in women and not in men. However in no smoking subjects the risk reduction was the same in both men and women. Jepson et al20 found Edinburgh Artery Study that was their is increase in peripheral

vascular disease in subjects both males and females who were heavy drinkers. Kenneth et al21 found a significant risk reduction of PVD with light drinking while this protective effect was not seen in heavy drinking.

Hypertension didn't show a significant association with carotid atherosclerosis in this study with P value>0.05. A study by Mohan et al22 too didn't show a significant association with hypertension and carotid atherosclerosis. While, studies by Pujia et al38, Bonova et al23 and Yamasaki et al 24 showed a significant relationship between hypertension and carotid atherosclerosis. Prevalence of Coronary Artery Disease was significantly more in hypertensive (55.9 %) patients with p value <0.05. Hypertension is a well known individual risk factor for coronary atherosclerosis (Framingham study25), however, there is no additional risk conferred by hypertension (controlled on drugs) in diabetics for the development of the same (Vasker et al10). However, even controlled diabetes was a risk factor for coronary complications.

Prevalence of Peripheral Vascular Disease was 47.1 % in hypertensive subjects while in normotensive subjects it was only 18.8 %, thus the data showed significant association between hypertension and Peripheral Vascular Disease. Although THE UKPDS Study17 showed that tight blood pressure control decrease the cardiovascular mortality, it seldom had any impact on peripheral vascular disease in newly detected diabetics. Hanson et al26 although showed in his study that although tight blood pressure control decrease the vascular complication in diabetes. The latter was also supported in the ABCD Trial 27.

Carotid atherosclerosis showed a significant association with hypertriglyceridemia but not with elevated LDL cholesterol levels in the study. The association of Carotid atherosclerosis with hypertriglyceridemia was found by Shinichi Teno et al28 and Ahmad J et al29. Increased LDL cholesterol and decreased HDL cholesterol is a well known independent risk factor for all types of atherosclerosis and its association with carotid atherosclerosis in those with insulin resistance was demonstrated by Golden et al30.

Increased LDL, decreased HDL is known independent risk factors for coronary atherosclerosis. The present study could demonstrate a highly significant association of hypertriglyceridemia (p=0.005) while it failed to show significant association of raised LDL cholesterol to coronary events. Natalie et al31 also showed a significant association of dyslipidemia while Vasker et al10 did not show a significant increase in coronary events due to dyslipidemia.

There was no significant association between either increased LDL (p=0.399) or triglycertides (p=359) with development of Peripheral Vascular Disease. There were no direct correlation studies in Diabetics between dyslipidemia and Peripheral Vascular Disease except Stevens et al12 which showed a 1.1 relative risk increase with dyslipdemia. Indirect data available from Cannon et al32 and Pederson et al39 showed reduction in PVD in patients on lipid lowering agents. The present study demonstrates a high significant association between HbA1C levels and the development of carotid atherosclerosis (p=0.030). A similar association was found Larsen et al33 although only in women and not in men. Interestingly, Huseyin Doruk et al 34 studied the effect of HbA1C levels on carotid atherosclerosis in geriatric non diabetic patients and found no association among the two. Association between HbA1C and coronary events was not seen in the study with p value of 0.576. Natali et al31 showed that HbA1C values did not correlate well with coronary events. While, Stephen et al35 recently showed a significant association between HbA1C levels and adverse coronary events.

HbA1C showed a significant correlation with development of Peripheral Vascular Disease with p value of 0.048. Elizabeth et al 36 in their study showed a significant association of HbA1C levels with Peripheral Vascular Disease and this association was stronger with symptomatic Peripheral Vascular Disease.

Among all the macrovasular complications in the present study, Carotid complications were highest at 48% followed by Coronary complications at 46% and the peripheral vascular complications at 38%. The cumilative prevalence of all the macrovasular complications in the present study was 66%.

The relatively Small number of subjects studied was a limitation for the application of sophisticated analytical methods in the present study, further investigations in that respect in larger populations will be necessary. In conclusion, our data show that newly detected type 2 diabetic patients exhibit a higher degree of early atherosclerosis than normal glucose tolerance subjects matched for age and sex, suggesting that hyperglycemia together with a clustering of risk factors, particularly dyslipidemia, may cause intimal -medial thickening in the early phases of diabetes.

Declaration:
Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: None declared

ABBREVIATIONS

1) VEGF INHIBITORS: VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS
2) PKC-β INHIBITORS: PROTEIN KINASE C- B INHIBITORS
3) T1 DM –TYPE 1 DIABETES MELLITES
4) T2 DM –TYPE 2 DIABETES MELLITES
5) ESRD-END STAGE RENAL DISEASE
6) CKD-CHORNIC KIDNEY DISEASE
7) HTN-HYPERTENSION
8) CHD-CORONARY HEART DISEASE
9) IDDM-INSULIN DEPENDENT DIABETES MELLITUS
10) NIDDM-NON INSULIN DEPENDENT DIABETES MELLITUS
11) HDL-HIGH DENSITY LIPOPROTEIN
12) LDL-LOW DENSITY LIPOPROTEIN
13) CIMT - CAROTID INTIMAL-MEDIAL THICKNESS
14) CCA- COMMON CAROTID ARTERY
15) RIAD-RISK FACTORS IN IGT FOR ATHEROSCLEROSIS AND DIABETES
16) HDL-HIGH DENSITY LIPOPROTEIN
17) CUPS- THE CHENNAI URBAN POPULATION STUDY
18) CURES- CHENNAI URBAN RURAL EPIDEMIOLOGY STUDY
19) CAD-CORONARY ARTERY DISEASE
20) IGT –IMPAIRED GLUCOSE TOLERANCE
21) BMI- BASAL METABOLIC RATE
22) DR-DIABETIC RETINOPATHY
23) NPDR-Non Proliferative Retinopathy
24) NVE-New Vessels Everywhere
25) IRMA-Intraretinal Microvascular Abnormalities
26) NSC-National Screening Committee
27) US- UNITED STATES
28) ADA-AMERICAN DIABETIC ASSOCIATION
29) HNF4α- HEPATIC NUCLEAR FACTOR 4 α
30) HNF1 α - HEPATIC NUCLEAR FACTOR 1 α
31) IPF1- INSULIN PROMOTING FACTOR 1
32) HNF3β- HEPATIC NUCLEAR FACTOR 3 β
33) MODY-MATURITY ONSET DIABETES OF YOUNG
34) IFG-IMPAIRED FASTING GLUCOSE
35) HbA_{1C} -GLYCOSYLATED HAEMOGLOBIN

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