HbA_1c: Future Diabetic And Cardiovascular Risk In First Degree Relatives Of Type 2 Diabetes Mellitus

Asha Shrivastava*, Namit Garg, Rashmi Dave*****

* Professor, ,*** JR-II,Gandhi Medical college, Bhopal,**Tutor, RD Gardi Medical college, Ujjain

Abstract: Background:The patients withtype 2 diabetes mellitus(T2DM) are at high risk for future cardiovascular events. The present study was aimed to assess the future 8 year diabetic and 10 year cardiovascular risk in first degree relatives of T2DMand association with glycemic status as measured by Fasting plasma glucose (FPG) and glycosylated haemoglobin (A1c) levels. Method: Out of 230 first degree relatives of T2DM patients attending the diabetic clinic of Hamidia hospital ,60 subjects having FPG in prediabetic rangeand 60 age and sex matched (30-60 yrs) normoglycemics healthy controls were selected . FPG, A1cand lipid profile were measured as per the standard laboratory Method. Prediabetes and T2DM was defined as per American Diabetes Association criteria (2011) and dyslipidemia was defined as per NCEP ATP III guidelines (2004). Future diabetic and cardiovascular risk were assessed by using Framingham Risk Score (2007) and Framinghamcardiovascular risk score (2008) Result: Dyslipidemia was identified in 32 % of prediabetics.Overall diabetic and cardiovascular risk in prediabetic group was found to be 23.13 ± 9.85 % and 10.85± 9.19 % respectively. Dyslipidemia was associated with 26.28 ±8.65% diabetic and 12.88±9.98% cardiovascular risk.FPG and A1c showed positive correlation with future diabetic risk(r=0.55,0.61) and cardiovascular risk(r=0.49,0.73).Conclusion:It is concluded that A1c levels below the threshold for diagnosis of diabetes(<6.5%) associated with dyslipidemia carry high future diabetes and cardiovascular risk.

Key Words:HbA1c,dyslipidemia,diabetic risk,cardiovascular risk.

Author for correspondence: Dr.Asha Shrivastava, Department of Physiology, Gandhi Medical College, Bhopal–462003.e- mail: drashashrivastava@gmail.com

Introduction: Epidemiological evidences suggest that the complications of diabetes begin early in the progression from normal glucose tolerance to frank diabetes. Prediabetes raises short-term absolute risk of T2DM by 3-to 10-fold [1,2]. Early identification and efforts to improve glycemia in persons with prediabetes have the potential to reduce or delay the progression to diabetes and related cardiovascular diseases [3-7,8].

Acknowledging these challenges, present study aimed to identify existence of prediabetes in first degree relatives of T2DM patients and to assess their future 8 year diabetic and 10 year cardiovascular risk.

Material and Method: The study was carried out in the Department of Physiology, Gandhi Medical College, Bhopal (M.P.) in collaboration with the Department of Medicine. The study was approved by the Ethics Committee of Gandhi Medical College, Bhopal (Letter No. 1666-67/MC/7/2013). Informed consent was obtained from the each participant.

Study Design: Sample Selection: Sample sizebased on the reported prevalence of 3.6% of prediabetes in India, the sample size (53) was calculated by using the formula[9].230 first degree relatives (117 males, 113 females) of T2DM patients attending the Diabetic Clinic who gave consent to participate in the study were selected. On the basis of fasting plasma glucose (FPG) 60 subjects were identified as prediabetes as per ADA 2011 criteria. Mean age was 45.2±8.9 years. 60 age and sex matched healthy normoglycemic employees of the Gandhi Medical College and Hamidia Hospital served as control.All the subjects included in study had no known endocrinal, renal and cardiovascular disorder.

Subjects having FPG >126 mg/dl, abnormal ECG and taking hormonal therapy, hormonal contraceptive, lipid lowering drugs or drugs to control blood sugar level were excluded from the study.

Method: Baseline clinical characteristics, anthropometric measurements and biochemical data were recorded as per the standard

procedures. Subjects underwent clinical examination under standardized conditions.

Biochemical Analysis: 5 ml of the fasting blood samples were collected for further analysis of FPG, HbA1c, total cholesterol (TC), triglyceride, high density cholesterol (HDL) and low density cholesterol (LDL) .

All analytes were measured in Auto analyzer (Merck 300) using Kits supplied by Aggappe Diagnostics, Kerela. A1c was measured by Microcolumn method at recommended temperature range (21 – 26˚C). Plasma glucose was measured by glucose oxidase – peroxidase method.

Serum total cholesterol and triglycerides were measured by CHOD-PAP method and GPO-PAP method Serum HDL-C was measured by precipitation method. LDL-C was calculated using Friedewald's Formula (TC-(VLDL+HDL).

Dyslipidemia was defined based on National Cholesterol Education Programme NCEP-ATP III(2004) criteria.

The 8 Year Diabetic Risk was assessed using Framingham Risk Score(basedon: The Framingham Offspring Study, 2007)

10 years general cardiovascular risk was assessed by using Framingham risk score based on a general cardiovascular risk profile for use in primary care: The Framingham Heart study (2008).

Statistical Analysis: All values were expressed as mean ± standard deviation. Comparison of means between the two groups was done using a student t test. Bivariate correlations between variables were evaluated by Pearson's correlation. Statistical analysis was done using SPSS version 16.00 (Statistical package for Social science)

Result: Prediabetics exhibited both central and generalised obesity. The blood pressure values were in the prehypertensive range(Table 1).

Table 1 : Comparison Of Baseline Physical Characteristics Of The Study Population

Parameters	Control Group (N = 60)	Prediabetic Group (N = 60)	P-Value
Age (Years)	45.3 ± 9.1	45.2 ± 8.9	N.S.
WC (cm)	83.1 ± 6.6	92.3 ± 9.7	< 0.0001
BMI (kg/m²)	22.1 ± 1.4	26.1 ± 2.8	< 0.0001
SBP (mm Hg)	116.9 ± 8.7	131.5 ± 8.2	< 0.0001
DBP (mm Hg)	76.6 ± 5.5	87.1 ± 6.8	< 0.0001
Pulse Rate (RPM)	81.2 ± 8.1	82.2 ± 7.7	N.S.

Table 2 : Biochemical Parameters Of The Study Population

Parameters	Control (n = 60)	Prediabetic (n = 60)	P- value
FPG (mg/dL)	84.6 ± 8.1	113.2 ± 7.1	< 0.0001*
A1C (%)	4.8 ± 0.5	5.7 ± 0.5	< 0.0001*
TC (mg/dL)	150.1 ± 27.1	179.4 ± 25.2	< 0.0001*
TG (mg/dL)	116.7 ± 27.2	158.1 ± 21.8	< 0.0001*
HDL-C (mg/dl)	44.4 ± 6.8	34.9 ± 6.3	< 0.0001*
LDL-C (mg/dl)	82.70±23.6	111.66 ± 23.13	< 0.0001*

The A1c values in the range of 5.7-6.4(%) confirmed the presence of prediabetes in first degree relatives of T2DM patients. Central obesity and dyslipidemia confirmed the coexistence of metabolic syndrome in prediabetics.

Table 3: Comparison of 8 - year diabetic risk and 10 - year general cv risk

Prediabetics	8-Yr diabetic risk (%)	10-Yr CV risk (%)
Without metabolic Syndrome(n = 17)	13.6 ± 5.3	5.6 ± 3.2
With Metabolic Syndrome(n = 43)	26.2 ± 8.6	12.8 ± 9.9
Overall	23.1 ±9.8	10.8 ± 9.1
Controls (n=60)	-	4.5 ± 3.1

As evident from the observation, coexistence of metabolic syndrome and prediabetes has increased the future diabetic and CV risk significantly.

Strong Positive correlation of FPG ,A1c level and dyslipidemia could be established with future CV and diabetic risk(Table- 4).

Table 4: Correlation of biochemical parameters with 8-yr diabetic risk and 10-year CV risk in the prediabetic group

Parameter	Correlation with8-Yr Diabetic Risk (r)	Correlation with 10-YrGeneral CV Risk (r)
FPG (mg/dL)	0.55*	0.49*
A1C (%)	0.61*	0.73*
TC (mg/dL)	0.40*	0.34*
TG (mg/dL)	0.65*	0.37*
HDL- C (mg/dL)	-0.59*	-0.53*
LDL- C (mg/dL)	0.39*	0.34*

*Significant at 95% confidence interval

Discussion: According to Das et al. (2001)[10] T2DM has a strong genetic component. T2DM often exhibits familiar aggregation, in their siblings nearly 4 fold increased risk for future T2DM compared with general population has been reported.

Tilburg et al. (2005)[11] suggested that the genetic contribution to T2DM arise from genetic variations in several genes, each confirm a small increase in the risk. These gene variations do not cause diabetes but increase its risk by interacting with other diabetes susceptibility genes,the metabolic environment of the body.

The present study investigated the existence of prediabetes in the first degree relatives of T2DM . Out of a total of 230 first degree relatives of T2DM, 60 subjects (29.5 %) were identified as prediabetic on the basis of Impaired FPG and A1c.Ma H et al (2011)[12] investigated the prevalence of prediabetes in the first-degree relatives (FDR) of patients with T2DM and reported that FDR of T2DM patients had greater standardized prevalence of diabetes than those without a family history of diabetes (26.6% vs. 9.2%).

In the present study, diabetic risk was assessed using Framingham Scoring as a Tool. Overall 8-year diabetic risk in prediabetic group was 23.1 ± 9.8 %.A highly significant positive correlation ($p< 0.0001$) was found between FPG and A1c levels and diabetic risk (r= 0.55,0.61)

Stephen M et al (2007)[13] reported that about 3%–10% of people per year with prediabetes develop T2DM. Prediabetes confers about a six fold increased risk of T2DM compared with normal glucose tolerance. They reported that in most populations studied, the rates of conversion from IFG and IGT to diabetes were similar, with IGT having greater sensitivity but less specificity than IFG in predicting diabetes risk.[12]

The 10-year general cardiovascular (CV) risk in prediabetic group (mean 10.85 ± 9.19 %) was significantly higher than the control group (mean 4.51 ± 3.15 %). Numerous research studies indicated that the risk of CV disease maintains a linear association with glycemia well below the present diagnostic threshold for T2DM.Stephen et al (2007)[13] reported that people with prediabetes have an increased risk of developing cardiovascular disease (CVD) and all-cause mortality. There was two- to three fold increased prospective risk of cardiovascular events.

They alsoreported that increased serum TG levels, decreased HDL-C levels were more common in adults with prediabetes compared with those with normal glucose tolerance.In the present study, a positive correlation was found between TC, TG and LDL-C levels and CV risk(r=0.34,0.37,0.34).A strong negative correlation was found between HDL-C levels and CV risk(r=-0.53).Based on Updated NCEP ATP III Criteria (2004), existence of metabolic syndrome was identified in 7 % of the control and 72 % of the prediabetics.

Conclusion: Before people develop T2DM, they almost always have "Prediabetes"—blood glucose levels that are higher than normal but not yet high enough to be diagnosed as diabetes. The study recognized that the prediabetic state involves the presence of other cardiometabolic risk factors in addition to the elevated blood glucose.Strong correlation of

A1c could be established with 8- year diabetic Risk (r =0.61)and 10-Year general CV risk (r= 0.73) suggesting use of A1c estimation to evaluate future risk . It is concluded that A1c levels below the threshold for diagnosis of diabetes(<6.5%) associated with dyslipidemia carry high future T2DM and cardiovascular risk. The study emphasises the need to lower A1c in prediabetics to avoid future long term complications

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