Soumendu Biswas[1], Anindya Mukherjee[1], Subhashis Chakraborty[1], Amit Chaturvedi[1], Biaus Samanta[1], Dibbendhu Khanra[2], Sayantan Ray[3], Ranjan Kumar Sharma[1]

[1] Nilratan Sircar Medical College and Hospital, Department of Cardiology, Kolkata, India

[2] Heart and Lung Centre, Royal Wolverhampton NHS Trust, UK

[3] Jagannath Gupta Institute of Medical Sciences and Hospitals, Kolkata, West Bengal, India

Impact of plasma glucose and duration of type 2 diabetes mellitus on SYNTAX Score II in patients suffering from non ST-elevation myocardial infarction

Aim	The objective was to assess the correlation of fasting plasma glucose (FPG), HbA1c, and the duration of type 2 diabetes mellitus (T2DM) with SYNTAX score (SS) II in patients with non-ST elevation myocardial infarction (NSTEMI).
Material and methods	FPG and HbA1C were measured in 398 patients presenting with NSTEMI at admission. SS II was calculated using an online calculator. Patients were stratified according to SS II (≤21.5, 21.5–30.6, and ≥30.6), defined as SS II low, mid, and high, respectively.
Results	37.7% of subjects were diabetic. Correlations of FPG (R=0.402, R2=0.162, p<0.001) and HbA1c (R=0.359, R2=0.129, p<0.001) with SS II were weak in the overall population. Duration of T2DM showed very strong correlation with SS II (R=0.827, R2=0.347). For the prediction of high SS II in the study population, FPG≥98.5 mg/dl demonstrated a sensitivity of 58% and a specificity of 60%, and HbA1c ≥6.05 demonstrated a sensitivity of 63% and a specificity of 69%. Duration of T2DM (adjusted odds ratio (OR): 1.182; 95% confidence interval (CI): 1.185–2.773) and FPG (OR: 0.987; 95% CI: 0.976–0.9959) were significantly associated with high SS II after controlling for other risk factors. Duration of T2DM (Beta=0.439) contributed strongly to variance of SS II, whereas HbA1c (Beta=0.063) contributed weakly.
Conclusion	Duration of T2DM is a very important risk factor for severity of coronary artery disease.

Keywords	Coronary artery disease; diabetes; fasting plasma glucose; HbA1c; SYNTAX score II
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Corresponding author	Anindya Mukherjee. Email: anindya768@yahoo.co.in

Introduction

India has the second largest number (77 million) of adults with diabetes (DM) worldwide, with a prevalence of 10.4% [1]. In the Asian Indian population, coronary artery disease (CAD) tends to develop a decade or two earlier, and triple vessel disease is more common than the western population [2]. The cardiovascular risk from type 2 diabetes mellitus (T2DM) seems to be 3–4 times higher in Asian Indian individuals compared to their western counterparts, even after adjusting for gender, age, smoking status, hypertension, and obesity [3]. In India, more than 65% of T2DM patients die from cardiovascular disease, and 80% of these deaths are from CAD [4]. Elevated glycated hemoglobin (HbA1c) has been reported to be a risk factor for macrovascular diseases and mortality in patients with CAD [5, 6]. HbA1c is also significantly correlated with the extent of CAD [6]. On the other hand, macrovascular complications have been reported to differ with duration of diabetes in a meta-analysis of four landmark trials:

1) Action to Control Cardiovascular Risk in Diabetes (ACCORD);
2) Action in Diabetes and Vascular Disease Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE);
3) United Kingdom Prospective Diabetes Study (UKPDS);
4) Veterans Affairs Diabetes Trial (VADT) [7].

The SYNTAX Score (SS) was developed to quantify the complexity of CAD. It was followed by SS II which includes two anatomical variables and six clinical variables [8, 9]. DM was not included in the SS II algorithm since it was not found to be an independent predictor of mortality and did not show any interactive effect with revascularisation strategy and long term mortality [9, 10]. SS II 2020 has been recently validated, and it includes medically treated diabetes in the algorithm [11]. None of these scores include glycemic parameters in the form of fasting plasma glucose (FPG), postprandial plasma glucose, or an index

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of long-term blood glucose, such as HbA1c or the duration of DM. Studies have assessed the relation between FPG, HbA1c, and SS II separately in T2DM patients with stable angina and in non-DM populations with non-ST elevation myocardial infarction (NSTEMI) [12, 13]. Srinivasan et al. assessed the association of DM duration and SS in T2DM patients with stable angina [14]. The objective of this study was to assess in patients presenting with NSTEMI, the correlation of FPG and HbA1c with SS II irrespective of DM status, and to assess the correlation of T2DM duration with SS II.

Material and methods

Study oversight and population

This single-center study was conducted in a cross-sectional, observational, analytical design. Patients aged ≥ 18 yrs and presenting with the first episode of NSTEMI, and who were referred from primary or the secondary care centers, were consecutively recruited for this study over a period of 15 mos from May, 2019 to July, 2020. Exclusion criteria: past acute coronary syndrome (ACS); previous computerized tomography or invasive coronary angiography (CAG) showing significant CAD; previous documentation of systolic dysfunction; revascularization; arrhythmias; conduction abnormalities; cardiomyopathy; valvular heart disease; congenital heart disease; newly diagnosed or known type 1 diabetes; significant pulmonary, hepatic or renal dysfunction; bleeding diathesis; abnormal hemoglobin values; history of erythropoietin use or recent blood transfusion; indications for emergency revascularization. Power analysis indicated a sample size of ≥ 385 for 95% confidence that the population values would be within ±5% of measured or surveyed values [15]. All procedures were in accordance with the ethical standards of the responsible institutional and national committees on human experimentation and with the Helsinki Declaration of 1964 and its later revisions. Informed written consent was obtained from all patients included in the study.

Definitions

Tobacco users were defined as those using any form of tobacco in the last 30 days [12]. The diagnosis of NSTEMI was made in patients having acute chest discomfort and with high-sensitivity cardiac troponin suggesting cardiomyocyte necrosis but without persistent ST- segment elevation [16]. T2DM was defined as having prior established T2DM and/or the use of blood glucose controlling medications. The remainder of the population were designated as non-T2DM. The diagnosis of metabolic syndrome (MetS) was based on the criteria defined by the IDF Epidemiology Task Force Consensus Group [17]. Family history (FH) of CAD was defined as first-degree relatives suffering from CAD before the age of 55 yrs in men and 65 yrs in women [18]. The 2018 European Society of Cardiology (ESC) hypertension guidelines were followed in measuring and categorizing blood pressure. Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg [19]. Peripheral arterial disease (PAD) was identified according to the Arterial Revascularisation Therapies Study Part I definition [10]. Chronic obstructive airway disease (COAD) was identified by the EuroSCORE definition [9].

Anthropometric measurements

Body weight was measured with the HBF-516 Body Composition Monitor and Scale (IL, USA). Waist circumference (WC) was measured at the midpoint between the last rib and the iliac crest [19]. Height to the nearest 0.1 cm was measured with a Seca Stadiometer (Hamburg, Germany). Body mass index (BMI) was calculated from height and weight data with categorization according to Asian Indian criteria [20].

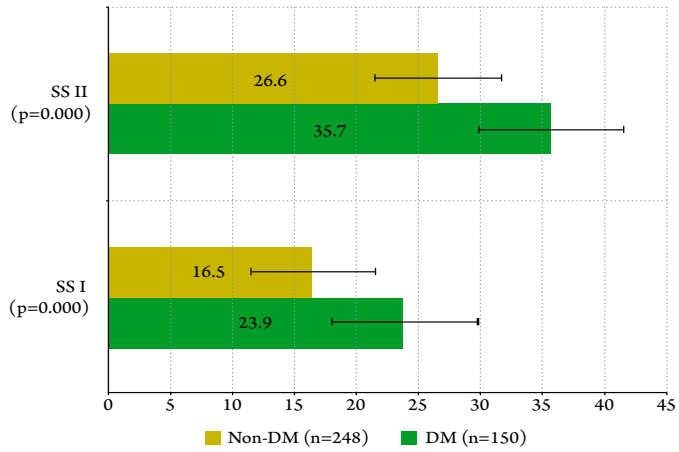
Laboratory parameters

Serum low-density lipoprotein cholesterol (LDL) was computed using Friedewald's equation [21]. Creatinine clearance was computed using the CKD Epidemiology Collaboration creatinine equation [16]. Echocardiography was performed by two experienced operators who were blinded to the clinical and procedural data. Left ventricular ejection fraction (LVEF) was measured with the biplane Simpson method. Final decisions were made by consensus in cases of disagreement.

Risk stratification and management

The latest guideline on NSTEMI at the time of data collection was followed [16]. Risk stratification was done according to the Global Registry of Acute Coronary Events (GRACE) score, and all patients were included, irrespective of risk score [16]. Medical therapy included dual antiplatelets, nitrates, beta blockers, and peri-interventional anticoagulation with unfractionated heparin according to the latest guidelines [16]. Immediate (<2 hrs) coronary angiography was performed for very high-risk patients, while for high-risk patients coronary angiography was performed within 24 hrs of hospital admission [16]. All other patients underwent coronary angiography within 48 hrs of admission. Angiography was performed through a percutaneous radial approach for calculation of the SS II and appropriate management after proper written informed consent. At least two projections were used to obtain angiograms of each coronary artery. A 50% or more reduction of the lumen area of any epicardial artery of >1.5 mm diameter was considered significant. The coronary angiograms were analysed by two experienced operators who were blinded to the results of the clinical and procedural data. In cases of disagreement, final decisions were made by consensus. The SS II were calculated with an online PCI SS II calculator (http://www.syntaxscore.org/calculator/syntaxscore/framesetss2.htm) based on the previously published nomogram [9]. The patients were stratified according to tertiles

Figure 1. Mean and SD of SS I and II for Non-DM and DM patients



DM, type 2 diabetes mellitus; SD, standard deviation; SS, Syntax score.

of SS II (≤21.5, 21.5–30.6, and ≥30.6), defined as SII low, mid, and high, respectively [13, 22].

Statistical analysis

Statistical package for Social Science (SPSS) version 25 (SPSS Inc., Chicago, Il., USA) was used to analyse the data. Mean and standard deviation (SD) for continuous variables and numbers (percentages) for categorical variables were calculated as part of the descriptive analysis. Two independent means were compared by Student's t test. Chi- square test was used to compare categorical variables. A 2-tailed p<0.05 was considered statistically significant. Correlation between the FPG, HbA1c, and duration of T2DM were assessed by Pearson's correlation and graphically represented in scatter plots. Spearman's bivariate correlation followed by multivariate stepwise linear regression was used to determine independent predictors for severity of CAD as assessed by SS II. Multivariate logistic regression was used to assess the extent of independent contribution of variables to high SS II. A receiver-operating characteristic (ROC) analysis was performed to detect the cut-off values of FPG and HbA1c for predicting a high SS II.

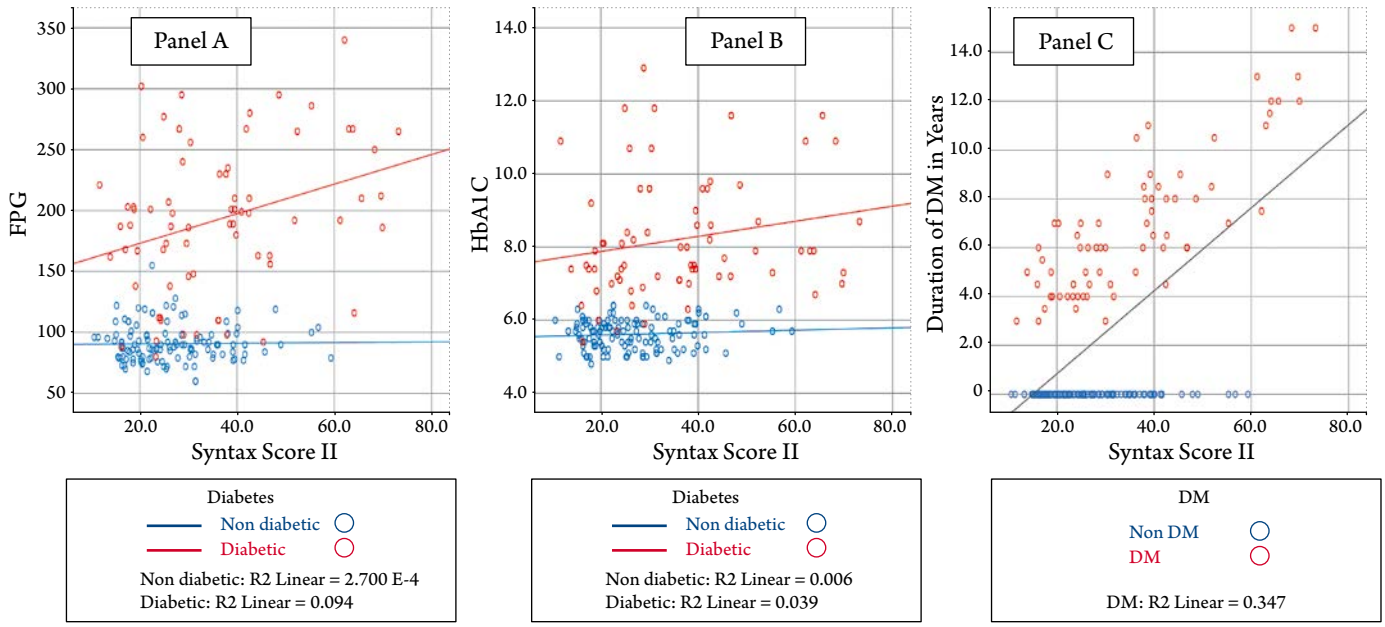
Results

Patient characteristics

398 patients were recruited of whom 150 (37.7%) had T2DM. 20.4% were women. Baseline characteristics of T2DM and non-T2DM patients are shown in Table 1. Mean T2DM WC was 91.7±8.5 cm, and non-T2DM WC was 89.5±9.0 cm (p=0.013). Similarly, mean T2DM BMI (28.7±3.2 kg/m^2) was greater than that of non-T2DM patients (27.8±3.2 kg/m^2) (p=0.005). Mean duration of DM was 6.9±2.9 yrs in T2DM patients (six patients with T2DM could not state the duration of their disease).

Tobacco use was highly prevalent among the patients (65.6%), with the proportion being higher in non-T2DM patients (p<0.001). The prevalence of hypertension (p=0.378), COAD (p=0.356), and mean HDL (p=0.795) did not differ significantly between the groups. All other parameters, namely, prevalence of CAD family history, MetS, multivessel disease, left main coronary artery disease, PAD, lipid parameters, LVEF, and estimated glomerular filtration rate (eGFR) were significantly worse in T2DM patients. As depicted in Figure 1, means of SYNTAX Score I (SS I) and SS II were significantly higher in T2DM patients compared to non-T2DM patients (p<0.001).

Figure 2. Correlation between SS II and FPG (Panel A), HbA1c (Panel B), and duration of DM (Panel C)



DM, type 2 diabetes mellitus; FPG, fasting plasma glucose; SS, Syntax score.

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Table 1. Characteristics T2DM and non-T2DM patients with ACS

Variable	T2DM (n=150)	Non-T2DM (n=248)	Total (n=398)	p value
Women	41 (27.3)	40 (16.1)	81 (20.4)	0.007**
Age (yrs)	56.0±9.5	55.9±10.4	55.9±10.1	0.871
WC (cm)	91.71±8.5	89.49±9.0	90.3±8.8	0.013*
BMI (kg/m²)	28.7±3.2	27.8±3.2	28.1±3.2	0.005**
Duration of DM (yrs) (n=144)	6.9±2.9	-	–	–
Tobacco use	82 (54.7)	179 (72.2)	261 (65.6)	<0.001**
FH of CAD	70 (46.7)	71 (28.6)	141 (35.4)	<0.001**
HTN	66 (44.0)	98 (39.5)	164 (41.2)	0.378
FPG (mg/dl)	192.2±61.9	90.8±15.0	129.0±63.2	<0.001**
HbA1c (%)	8.2±1.6	5.6±0.4	6.6±1.6	<0.001**
MetS	88 (58.7)	56 (22.6)	144 (36.2)	<0.001**
HDL (mg/dl)	36.0±8.5	36.2±7.0	36.2±7.6	0.795
TG (mg/dl)	139.5±45.3	130.5±46.2	133.9±46.0	0.058
LDL (mg/dl)	130.5±38.7	111.6±28.1	118.7±33.7	<0.001**
LVEF (%)	43.0±8.4	50.5±8.2	47.7±9.0	<0.001**
eGFR (ml/min/1.73m²)	78.2±25.6	83.2±18.2	81.3±21.4	0.038*
MVD	98 (65.3)	103 (41.5)	201 (50.5)	<0.001**
LMCA disease	14 (9.3)	6 (2.4)	20 (5.0)	0.002**
COAD	27 (18.0)	36 (14.5)	63 (15.8)	0.356
PAD	27 (18.0)	12 (4.8)	39 (9.8)	<0.001

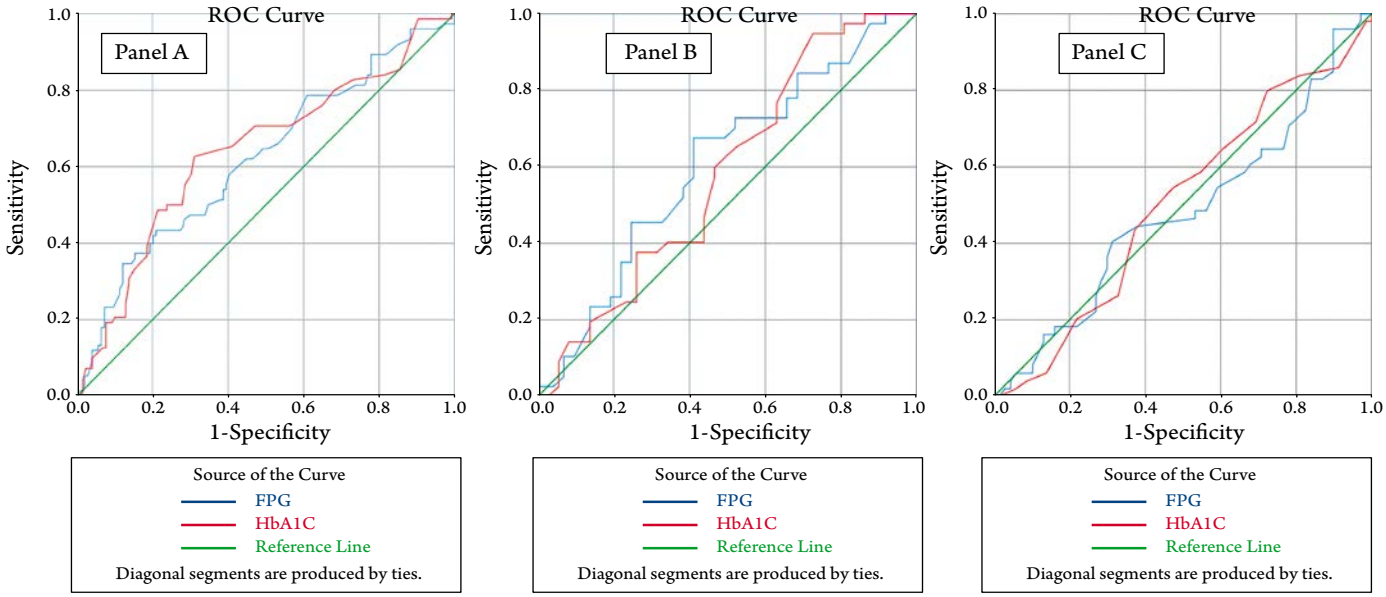
** Data are mean±SD or number (percentage). *p<0.05 (2-tailed). **p<0.01 (2-tailed). BMI, body mass index; COAD, chronic obstructive airway disease; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; FH, family history; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; HTN, hypertension; LDL, low density lipoprotein; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; MetS, metabolic syndrome; MVD, multivessel disease; PAD, peripheral arterial disease; SS, Syntax score; TC, total cholesterol; TG, triglyceride; T2DM, type 2 diabetes mellitus; WC, waist circumference.

Table 2. Logistic regression analyses for prediction of high Syntax score II

Variable	Univariate			Multivariate		
	OR	95% CI	p- value	OR	95% CI	p value
Gender	0.511	0.312–0.837	0.008**	0.473	0.174–1.284	0.142
Age (yrs)	1.236	1.186–1.288	<0.001**	1.174	1.102–1.249	<0.001**
WC (cm)	1.004	0.981–1.028	0.716	–	–	–
BMI (kg/m²)	1.021	0.959–1.088	0.513	–	–	–
Duration of T2DM (yrs)	1.245	1.170–1.325	<0.001**	1.182	1.185–2.773	0.006**
Tobacco use	0.511	0.334–0.780	0.002**	0.802	0.328–1.966	0.630
FH of CAD	0.904	0.591–1.384	0.643	-	-	–
HTN	5.465	3.517–8.492	<0.001**	3.091	1.396–6.846	0.005**
T2DM	2.529	1.660–3.852	<0.001**	0.200	0.013–3.096	0.250
FPG (mg/dl)	1.007	1.004–1.011	<0.001**	0.987	0.976–0.999	0.030*
HbA1c (%)	1.318	1.159–1.499	<0.001**	1.346	0.926–1.956	0.119
MetS	1.636	1.076–2.488	0.02*	1.696	0.634–4.535	0.293
HDL (mg/dl)	1.024	0.997–1.052	0.085	–	–	–
TG (mg/dl)	0.997	0.993–1.002	0.222	–	–	–
LDL (mg/dl)	1.002	0.996–1.009	0.417	–	–	–
eGFR	0.917	0.902–0.933	<0.001**	0.948	0.925–0.972	<0.001**
COAD	17.368	7.972–37.842	<0.001**	7.919	2.641–23.745	<0.001**
PAD	–	–	0.997	–	–	–

* Significant correlation at p<0.05 (2-tailed). ** Significant correlation at p<0.01 (2-tailed). BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; COAD, chronic obstructive airway disease; FH, family history; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; HTN, hypertension; LDL, low density lipoprotein; MetS, metabolic syndrome; OR, odds ratio; PAD, peripheral arterial disease SS, Syntax score; TC, total cholesterol; TG, triglyceride; T2DM, type 2 diabetes mellitus; WC, waist circumference.

Figure 3. Cut-off values of FPG and HbA1c for the prediction of high SS II in the total study population (Panel A), the DM subset (Panel B), and the non-DM subset (Panel C)



DM, type 2 diabetes mellitus; FPG, fasting plasma glucose; SS, Syntax score.

Correlations between SS II and FPG, HbA1c, and duration of DM

Bivariate correlations between these parameters are shown in Figure 2. The correlation between SS II and FPG was significant but weak in the T2DM group (R=0.307, R2=0.094, p<0.001) and in the overall study population (R=0.402, R2=0.162, p<0.001). The correlation between SS II and HbA1c was significant but very weak in the T2DM group (R=0.197, R2=0.039, p=0.016) and significant but weak in the overall study population (R=0.359, R2=0.129, p<0.001). The correlation

Table 3. Spearman correlation and multivariate linear regression analysis for the Syntax Score II

Variable	Spearman Correlation		Multivariate Linear Regression Analysis						
	R	p value	B	Beta	R	Adjusted R2	F	t	p value
Constant	–	–	31.632	–	–	–	–	9.428	<0.001**
Gender	-0.286**	<0.001	-4.307	-0.132	–	–	–	-6.066	<0.001**
Age (yrs)	0.667**	<0.001	0.250	0.193	–	–	–	6.790	<0.001**
WC (cm)	0.014	0.788	–	–	–	–	–	–	–
BMI (kg/ m^2)	0.044	0.386	–	–	–	–	–	–	–
Duration of T2DM (yrs)	0.589**	<0.001	1.523	0.439	–	–	–	7.982	<0.001**
Tobacco use	-0.267**	<0.001	–	–	–	–	–	-0.304	0.761
FH of CAD	-0.039	0.439	–	–	–	–	–	–	–
HTN	0.386**	<0.001	1.649	0.592	–	–	–	2.786	0.006**
T2DM	0.296**	<0.001	-5.644	-0.208	–	–	–	-3.786	<0.001**
FPG (mg/ dl)	0.299**	<0.001	–	–	–	–	–	-0.715	0.475
HbA1c (%)	0.319**	<0.001	0.503	0.063	–	–	–	1.976	0.049*
MetS	0.150**	0.003	–	–	–	–	–	0.678	0.498
HDL (mg/ dl)	0.072	0.152	–	–	–	–	–	–	–
TG (mg/ dl)	-0.127*	0.011	–	–	–	–	–	-1.480	0.140
LDL (mg/ dl)	0.081	0.108	–	–	–	–	–	–	–
eGFR	0.712**	<0.001	-0.190	-0.310	–	–	–	-10.600	<0.001**
COAD	0.418**	<0.001	5.292	0.149	–	–	–	6.608	<0.001**
PAD	0.476**	<0.001	10.078	0.230	–	–	–	9.039	<0.001**
	–	–	–	–	0.919	0.842	231.761	–	–

* Significant correlation at p<0.05 (2-tailed). ** Significant correlation at p<0.01 (2-tailed). BMI, body mass index; CAD, coronary artery disease; FPG, fasting plasma glucose; FH, family history; HDL, high density lipoprotein; HTN, hypertension; LDL, low density lipoprotein; MetS, metabolic syndrome; SS, Syntax score; TC, total cholesterol; TG, triglyceride; T2DM, type 2 diabetes mellitus; WC, waist circumference.

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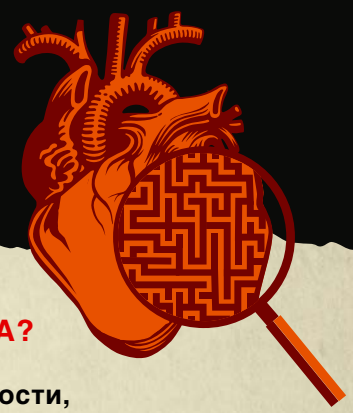
ATTR

ЗАПОДОЗРИТЬ *и* ВЫЯВИТЬ

НАЙТИ КЛЮЧ К ВЕРНОМУ ДИАГНОЗУ



КАК РАСПОЗНАТЬ СИМПТОМЫ ТРАНСТИРЕТИНОВОЙ АМИЛОИДНОЙ КАРДИОМИОПАТИИ (ATTR-КМП) У ВАШЕГО ПАЦИЕНТА?

ATTR-КМП — это зачастую недооцененная причина сердечной недостаточности, в частности сердечной недостаточности с сохраненной фракцией выброса (СНсФВ). Это тяжелое жизнеугрожающее заболевание с медианой выживаемости 2-3,5 года.

ATTR-КМП встречается у 17% пациентов с СНсФВ.[1-5]

ATTR-КМП часто пропускают или диагностируют поздно. Стандартные методы диагностики сердечной недостаточности, эхокардиография (ЭхоКГ) и электрокардиография (ЭКГ) совместно с методами лучевой диагностики могут помочь в поиске правильного диагноза.

ОЗНАКОМЬТЕСЬ С КЛИНИЧЕСКИМИ ПРИЗНАКАМИ, КОТОРЫЕ ПОМОГУТ ОПРЕДЕЛИТЬ ВЕРОЯТНОСТЬ НАЛИЧИЯ ATTR-КМП У ПАЦИЕНТА И НЕОБХОДИМОСТЬ ДАЛЬНЕЙШЕЙ ДИАГНОСТИКИ.

СЕРДЕЧНАЯ НЕДОСТАТОЧНОСТЬ С СОХРАНЕННОЙ ФРАКЦИЕЙ ВЫБРОСА обычно у пациентов старше 60 лет[5]

НЕПЕРЕНОСИМОСТЬ стандартной лекарственной терапии для лечения СН: ингибиторов ангиотензин-превращающего фермента, блокаторов рецепторов ангиотензина и бета-блокаторов[6]

РАСХОЖДЕНИЕ между амплитудой зубцов комплекса QRS и ЭКГ и толщиной стенки левого желудочка при ЭхоКГ[7,8]

КАРПАЛЬНЫЙ ТУННЕЛЬНЫЙ СИНДРОМ или **СТЕНОЗ ПОЗВОНОЧНОГО КАНАЛА**[9,10]

Эхокардиография показывает **УВЕЛИЧЕНИЕ ТОЛЩИНЫ СТЕНКИ ЛЖ**[7]

Дисфункция **ВЕГЕТАТИВНОЙ НЕРВНОЙ СИСТЕМЫ,** включая нарушения со стороны желудочно-кишечного тракта или необъяснимое снижение массы тела[11]

ОТСКАНИРУЙТЕ QR-КОД, ЧТОБЫ ОЗНАКОМИТЬСЯ С КЛИНИЧЕСКИМИ ПОДСКАЗКАМИ, КОТОРЫЕ МОГУТ ПОМОЧЬ РАСКРЫТЬ ПРИЧИНУ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ[12-16]

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Тел.: +7 495 287-50-00. Факс: +7 495 287-53-00

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between SS II and duration of T2DM was very strong (R=0.827, R2=0.347, p<0.001). No correlations existed between these parameters in non-T2DM patients.

ROC curve analysis

Results of the ROC curve analysis are presented in Figure 3. In the total population, irrespective of T2DM status, a FPG value of 98.5 mg/dl yielded an AUC value of 0.621 (95% confidence interval (CI): 0.563–0.679; p<0.001). Furthermore, this FPG value of 98.5 mg/dl demonstrated a sensitivity of 58% and a specificity of 60% for predicting a high SS II. A HbA1c value of 6.05 yielded an AUC value of 0.640 (95% CI: 0.583–0.698; p<0.001). Furthermore, in the total study population, the HbA1c value 6.05 demonstrated a sensitivity of 63% and a specificity of 69% for predicting a high SS II. In the T2DM subset, a FPG value of 188.5 mg/dl yielded an AUC value of 0.605 (95% CI: 0.514–0.696; p=0.027). Furthermore, this FPG value of 188.5 mg/dl demonstrated a sensitivity of 68% and a specificity of 59% for predicting a high SS II in T2DM patients. HbA1c in T2DM subset and both FPG and HbA1c in the non T2DM subset yielded non-significant results.

Regression analysis

Independent risk factors for high SS II were obtained by univariate and multivariate logistic regression analysis (Table 2). 89.5% of the cases could be correctly predicted by this model. Durations of T2DM and FPG were significantly associated with high SS II after controlling for other risk factors, including gender, age, WC, BMI, tobacco use, CAD FH, HTN, MetS, HDL, LDL, TG, eGFR, COAD, and PAD (adjusted odds ratio (OR): 1.182; 95% CI: 1.185–2.773; p=0.006) for duration of T2DM and (OR: 0.987; 95% CI: 0.976–0.9959; p=0.030) for FPG. After controlling for other risk factors, the other independent risk factors associated with high SS II included age, HTN, eGFR and COAD.

We also performed Spearman correlation and multivariate linear stepwise regression analyses for the SS II (Table 3). 84.2% of the variance in SS II could be explained by gender, age, duration of T2DM, HTN, T2DM, HbA1c, eGFR, COAD, and PAD (F=231.761). HTN (Beta=0.592) followed by duration of T2DM (Beta=0.439) contributed the most of the variance in SS II, while HbA1c (Beta=0.063) contributed the least.

Discussion

We found that the duration of T2DM had a very strong correlation with SS II while FPG and HbA1c showed weak correlations with SS II in both the T2DM subset and in the total population. A longer duration of T2DM was an independent risk factor for high SS II, and duration of T2DM contributed significantly to the variance of SS II.

FPG

Yang et al. reported that FPG and HbA1c were independent risk factors for coronary atherosclerosis in prediabetic patients after associating these with 3-vessel disease, SS, and the GENSINI score [18]. Bansilal et al., Karrowni et al., and Mossmann et al. reported that insulin resistance and atherosclerosis were correlated; this provided some evidence for associating FPG with CAD [23–25]. Similarly, Gui et al. studied 906 non-T2DM patients undergoing CAG and found FPG to be an independent risk factor for severity of CAD according to the GENSINI score [26]. Schinner et al. and Qian et al. also reported FPG to be independently correlated with the burden of atherosclerosis [27, 28]. 409 patients from China were studied in another study which also inferred that the coronary artery stenosis score increased with rising FPG [29]. On the other hand, studies by Fu et al. and Jiang et al. denied the association of FPG and CAD severity [30, 31]. We found no correlation of FPG with SS II in non-T2DM patients. Kilic et al. studied 359 non T2DM patients and reported weak correlation between FPG and SS II, and, moreover, FPG was not an independent risk factor for high SS II [13]. Karakoyun et al. reported weak correlation of FPG with SS II in 215 T2DM patients with stable angina similar to our study in patients with NSTEMI [12]. Most of these studies included non-T2DM or pre-T2DM patients, and a few others like Karakoyun et al included only T2DM patients [12]. There are very limited data on the correlation between coronary atherosclerosis and FPG, irrespective of T2DM with a wide range of blood glucose, as we tried to address in this study. Furthermore, the FPG value 98.5 mg/dl demonstrated a sensitivity of 58% and a specificity of 60% for the prediction of high SS II in our study, irrespective of T2DM status, while the FPG value 188.5 mg/dl demonstrated a sensitivity of 68% and a specificity of 59% for the prediction of high SS II in T2DM patients.

HbA1c

Arbel et al. studied 226 non-T2DM patients and concluded that HbA1c is an independent risk factor associated with SS [32]. Similarly, 299 non-T2DM individuals and 480 non-T2DM individuals were studied by Ashraf et al. and Sahal et al., respectively, and increasing HbA1c was found to be associated with the GENSINI score [33, 34]. Yang et al. found similar results with 1006 prediabetic patients [18]. Kilic et al. demonstrated HbA1c to be very strongly correlated to SS II and an independent risk factor of high SS II [13]. Karakoyun et al. studied correlation between HbA1c and SS II in T2DM patients which was found to be good (r=0.535, p<0.001) [12]. Selvin et al., in two separate studies, suggested that HbA1c values were an independent risk factor for CAD in patients with and without T2DM [5]. They also suggested that HbA1c exceeding 6.0% could identify individuals at risk of developing CAD. In our study, a HbA1c value of 6.05% demonstrated a sensitivity of 63% and a specificity of 69% for predicting a high SS II in the total study population. Ayhan et al. found HbA1c values to correlate with the GENSINI score irrespective of T2DM in patients younger than 40 yrs [12]. No study to date had studied the association of HbA1c and SS II,

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irrespective of T2DM status. I n our study, HbA1c and SS II were found to be weakly correlated in T2DM patients, as well as, in the total study population. Strikingly, we found no correlation of HbA1c with SS II in non-T2DM patients, and HbA1c was found not to be an independent factor for prediction of SS II.

Duration of T2DM

Turnbull et al. showed that the spectra of CAD differed with the duration of T2DM [7]. The UKPDS risk calculator did not include events prior to 4 yrs in the risk score [14]. Srinivasan et al. reported a significant increase in the mean SS between 5 and 10 yrs of T2DM when compared to less than 5 yrs of T2DM [14]. The same study from India indicated that coronary profiles of non-T2DM and T2DM<5 yrs were similar, while chronic structural narrowing of coronary arteries took place during 5–10 yrs of T2DM. This raises the possibility of insulin resistance being responsible for generating the macrovascular complications in T2DM. Both functional and structural changes in the blood vessels are caused by hyperinsulinemia. Nitric oxide mediates functional changes by receptor-mediated effects on resistance and maintains vasodilatation, whereas the MAP kinase pathway mediates the proatherogenic changes leading to structural change. This is not affected by insulin resistance. Thus, acting through the MAP kinase pathway, continuous hyperinsulinemia leads to significant structural change over a period of time [35]. In our study, duration of T2DM was very strongly correlated with SS II and was an independent risk factor for SS II. Longer duration of T2DM was independently associated with high SS II. In the earlier cited study, Srinivasan et al. postulated that hyperinsulinemia and insulin resistance likely reaches their peak at 4–5 yrs of T2DM, resulting in increased severity of CAD after 5 yrs. [14]. In our study, mean duration of T2DM was 6.7±2.8 yrs, which probably explains such a strong effect of duration of T2DM on SS II. The SS II nomogram did not include diabetes. SS II 2020 includes medically treated diabetes in the algorithm, but none of the CAD severity scores include duration of T2DM in their analyses. To date, no study has studied the correlation of T2DM duration with SS II. Our analysis found T2DM duration to be a very important factor for predicting the severity of CAD by SS II. Since duration of T2DM is an irreversible factor, intense therapeutic interventions to reduce or prevent cardiovascular complications must be considered early in the diabetic population.

Limitations

Cross-sectional study design and single center data collection are inherent limitations of this study. Evaluation was based on a single set of FPG and HbA1c measurements. A larger study population would have increased the statistical power of the study. SS II 2020 is presently available, but when data collection was started, it had not yet been published. Thus, we could not benefit from using the latest SS algorithm.

Conclusion

Duration of T2DM is a very important factor for assessing the severity of CAD. Unlike earlier studies, FPG and HbA1c did not show significant roles in the non-T2DM population. Keeping in mind the typical Asian Indian phenotype and associated insulin resistance, the duration of T2DM should be given importance apart from T2DM, FPG, and HbA1c when evaluating the burden of cardiovascular disease in this population. Early and intense therapeutic intervention is key to successful reduction and prevention of CAD risk in the T2DM population.

Ethical approval and consent to participate

The ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1964 and later revisions were followed in all steps of research. All the subjects gave informed consent for the study. The Institutional Review Board approved the study.

Author's contribution

Soumendu Biswas and Anindya Mukherjee contributed equally to this work and are joint first authors. DK, SR, RKS: Concept and design; SB, AM, SC, AC, BS: acquisition of data; SB, AM, SC, DK, SR: interpretation of data, drafting the manuscript; SB, AM, SC, DK, AC, BS, SR, RKS: critical review and final approval of the manuscript.

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