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Clinical Outcomes of Patients with Type II Diabetes Mellitus and Hypothyroidism undergoing Percutaneous Coronary Revascularization

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Diabetes mellitus (DM) and hypothyroidism are independently associated with coronary artery disease (CAD) severity with poor percutaneous revascularization outcomes. However, the influence of Type 2 diabetes mellitus (T2DM) with hypothyroidism on the clinical outcomes of patients undergoing percutaneous coronary intervention (PCI) has not been evaluated. The aim of the study is to assess the clinical outcomes of CAD patients with T2DM and hypothyroidism undergoing PCI. Consecutive patients who underwent PCI from September 2020 to March 2021 at our institution were enrolled in the study. Patients were categorized into four groups: Group I-Patients with euglycemia and euthyroid, Group II- patients with T2DM and euthyroid, Group III- patients with hypothyroidism and euglycemic, and Group IV- Patients with T2DM and hypothyroidism. Baseline demographics, laboratory investigations, procedural details, and in-hospital major adverse cardiovascular events were assessed. The continuous and normally distributed data were presented as mean ± standard deviation and were analysed using ANOVA. Categorical data were presented as the frequency with percentages and analysed using the Chi-square test. In the total of 605 patients, 36% (n=220), 54% (n=325), 3% (n=19), and 7% (n=41) were in Group I, Group II, Group III, and Group IV respectively. The mean age of the population was 56.1 ± 11.6 vs 59.6 ± 9.8 vs 60.4 ± 9.9 vs 56.9 ± 12.1 (p = 0.002). Males were predominant 89.5% (n=197) in Group I and females were predominant 47.4% (n=9) in Group III. The prevalence of hypertension and dyslipidemia were high in Group II and Group IV respectively. Higher triglyceride levels (159.6 ± 109.6 Vs 166.2 ± 83.2 Vs 136.7 ± 72.3 Vs 222.2 ± 161.9, p = 0.03) and glycosylated hemoglobin A1c (HbA1C) levels (6.2 ± 1.2 Vs 8.5 ± 1.9 Vs 6.6 ± 2.1 Vs 9.2 ± 1.8, p<0.001) were noted in Group IV. Single vessel disease was high (59.1% Vs 45.5% Vs 57.8% Vs 48.7%, p=0.02) among Group I patients whereas left anterior descending (LAD) artery involvement was more in Group IV (64.5% Vs 57.8% Vs 36.8% Vs 70.7%, p=0.03) and in-stent restenosis was high among Group III (0.9% Vs 3.7% Vs 10.5%, p=0.02). Incidence of bleeding was high in Group III (0.5% Vs 1.2% Vs 10.5%, p= 0.001). There was no significant difference in In-hospital mortality between groups. Patients with T2DM and hypothyroidism had significantly higher levels of triglycerides, HbA1C and more LAD involvement but there was no significant difference in in- hospital mortality.

Keywords: Percutaneous coronary intervention, Type 2 diabetes mellitus, Hypothyroidism.

In both developed and developing countries Coronary artery disease (CAD) is still the major cause of morbidity and mortality[1]. Type 2 diabetes mellitus(T2DM) is an established risk factor for atherosclerosis[2]. High blood glucose levels accelerate the atherosclerotic process through different mechanisms[3] hence diabetic patients are more prone in developing CAD than non-diabetics.[4] Patients with T2DM account for more than a quarter of all patients undergoing percutaneous coronary intervention (PCI)[5]. Studies consistently showed increased disease complexity, poor PCI outcomes, increased Major adverse cardiovascular events (MACE), and mortality in T2DM compared to non-diabetic patients[6,7]. The other endocrine disorder which is closely associated with cardiovascular disease is hypothyroidism[8]. Patients with hypothyroidism have an increased risk of CAD[9]. In acute coronary syndrome (ACS) patients, low T_3 levels have been associated with increased severity of CAD, large thrombus burden, and extensive myocardial injury post PCI[10]. The co-existence of both T2DM and thyroid disease further increases the risk of CAD[11]. Although many studies have evaluated the PCI outcomes in patients with T2DM and hypothyroidism individually, no major studies so far evaluated the effect of the combination of these two diseases. This study was intended to assess the impact of T2DM and hypothyroidism on the outcomes of patients with CAD undergoing PCI.

MATERIALS AND METHODS

This is a single-center, prospective observational study. Consecutive patients who are above 18 years of age and underwent PCI between September 2020 to March 2021 at Madras Medical Mission Hospital, Chennai, and were willing to provide informed consent were enrolled in this study. Patients with Type 1 diabetes mellitus, hyperthyroidism, other endocrine disorders such as pheochromocytoma, and unwillingness to participate were excluded from the study. Overall, 605 patients' data were analyzed and were categorized into four groups based on the history of T2DM and hypothyroid. Group I- Patients with euglycemia and euthyroid, Group II- Patients with T2DM and euthyroid, Group III- patients with hypothyroidism and euglycemic, and Group IV- Patients with T2DM and hypothyroidism. Incomplete data at the baseline were excluded from the analysis. Baseline demographics, laboratory investigations, procedural details, and in-hospital clinical outcomes were assessed. The study was approved by the institutional ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki (Reg No: ECR/140/Inst/TN/2013/RR-20).

Statistical Analysis

The continuous and normally distributed data were presented as mean ± standard deviation and were analyzed using ANOVA. Categorical data were presented as the frequency with percentages and analysed using the Chi-square test. Statistical analysis was performed using the SPSS statistical package, version 25.0 (IBM Corp., Armonk, NY, USA). A two-sided P value <0.05 was considered to indicate statistical significance.

RESULTS

In the total of 605 patients, 36% (n=220), 54% (n=325), 3% (n=19), and 7% (n=41) were in Group I, Group II, Group III, and Group IV respectively. The baseline characteristics are summarized in Table 1. Patients in Group III were older (56.1 ± 11.6 Vs 59.6 ± 9.8 Vs 60.4 ± 9.9 Vs 56.9 ± 12.1, p = 0.002) when compared with the other three groups. Males were predominant 89.5% (n=197) in Group I and females were predominant 47.4% (n=9) in Group III. The prevalence of hypertension (35% Vs 55.7% Vs 42.1% Vs 51.2%, p=0.004) and dyslipidemia (7.7% Vs 12% Vs 10.5% Vs 12.2%, p=0.012) were high in Group II and Group IV respectively. The laboratory investigations are summarized in Table 2. Higher triglyceride levels (159.6 ± 109.6 Vs 166.2 ± 83.2 Vs 136.7 ± 72.3 Vs 222.2 ± 161.9, p = 0.03) and glycosylated hemoglobin A1c (HbA1C) levels (6.2 ± 1.2 Vs 8.5 ± 1.9 Vs 6.6 ± 2.1 Vs 9.2 ± 1.8, $p<0.001$) were noted in Group IV. The procedural characteristics are summarized in Table 3. Single vessel disease was commonly noted (59.1% Vs 45.5% Vs 57.8% Vs 48.7%, p=0.02) among Group I patients. Left main disease (0.9% Vs.1.8% Vs.10.5%, p=0.01), In-stent restenosis (0.9% Vs. 3.7% Vs. 10.5%, p=0.02) and requirement of Intra-aortic balloon pump (2.7% Vs. 3.1% Vs 10.5% Vs 9.8%, p=0.05) were high in Group III

patients, whereas left anterior descending (LAD) artery involvement was more in Group IV (64.5% Vs. 57.8% Vs. 36.8% Vs. 70.7%, p=0.03). The post-PCI laboratory investigations and in-hospital clinical outcomes were summarized in Table 4 and Table 5 respectively. Group III patients had increased bleeding events (0.5% Vs.1.2% Vs.10.5%, p=0.001) and hence had significantly lower hemoglobin levels post-procedure (13.1 ± 1.8 Vs 12.6 ± 1.9 Vs 11.8 ± 1.2 Vs 12.2 ± 1.9, p=0.003). There was no significant difference in mortality between groups.

DISCUSSION

The present study evaluated the impact of T2DM and hypothyroidism on the outcomes of patients undergoing PCI. The main observations of the study were that patients with T2DM and hypothyroidism have significantly higher levels of triglycerides, HbA1C, and more LAD involvement with no significant difference in clinical outcomes. The risk of CAD increases in patients with T2DM and hypothyroidism. DM has always been shown to be a predictor of adverse outcomes after PCI[12,13]. Hypothyroidism also accelerates atherosclerosis and increases the risk of CAD[14] and congestive heart failure[15] and post-PCI. It is associated with a higher incidence of all-cause and cardiac mortality, MACE.[9,10]

The first main observation of the study was a significant elevation of triglyceride levels (159.6 ± 109.6 Vs. 166.2 ± 83.2 Vs. 136.7 ± 72.3 Vs. 222.2 ± 161.9, p = 0.03) in Group IV compared with other three groups. In patients with DM, insulin deficiency or resistance activates intracellular hormone-sensitive lipase which increases non-essential fatty acids (NEFA) that in turn increases hepatic triglyceride production.

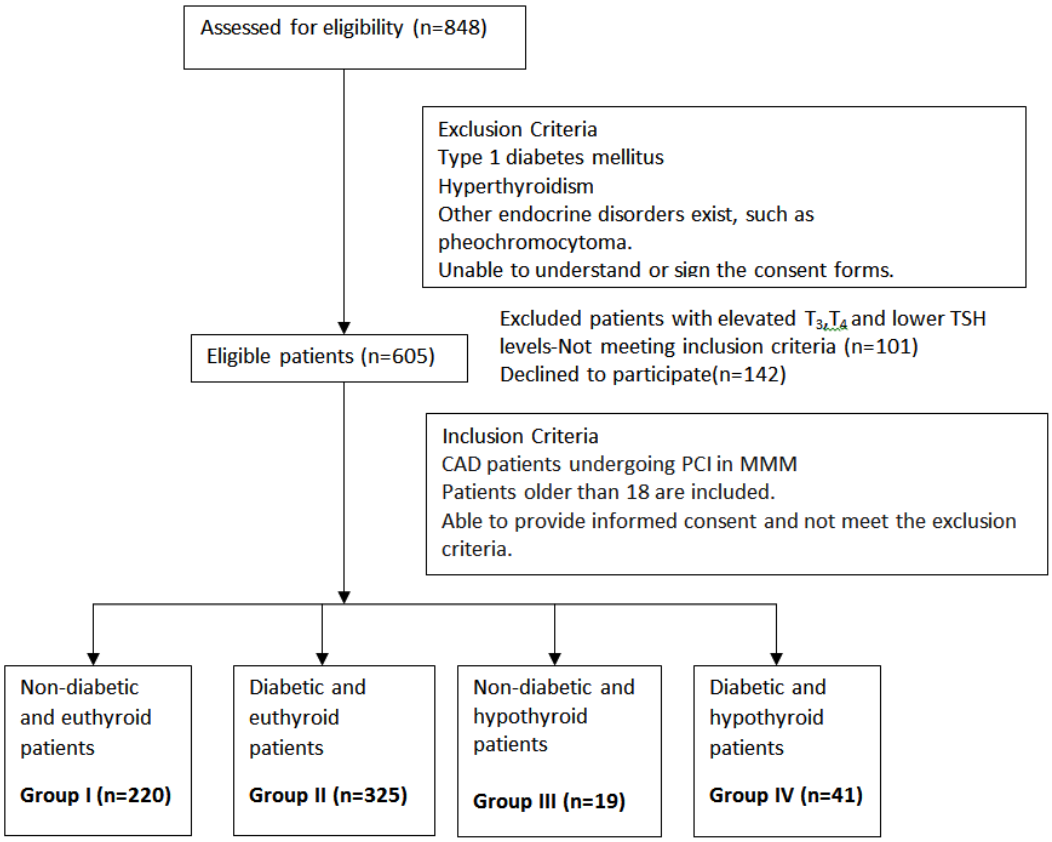

Fig. 1. Flow diagram of patient enrollment: A total of 848 consecutive patients who underwent PCI between 22nd September 2020 and 31st March 2021 in MMM hospital were assessed for eligibility

In addition, there is a delay in the passage of triglyceride-rich lipoprotein through the lipolytic cascade due to the shortage of catalytic sites on lipoprotein lipase, and the overproduction of triglycerides rapidly saturates available sites, which further promotes hypertriglyceridemia[16]. Hypothyroidism leads to decreased lipid oxidation rates and elevated triglyceride levels. Impaired hepatic lipase activity in hypothyroid patients may also be related to the accumulation of triglyceride-enriched lipoproteins[17]. Mason RL et al., reported a significant increase in triglyceride levels in DM with subclinical or clinical hypothyroid patients as insulin sensitivity act as a mediator of thyroid-induced lipid changes[18]. Biondi B et al., noted that hypothyroidism with T2DM was associated with an increased level of triglyceride[19]. The HbA1C levels (6.2 ± 1.2 Vs. 8.5 ± 1.9 Vs. 6.6 ± 2.1 Vs. 9.2 ± 1.8, p<0.001) were higher in Group IV patients. Some studies showed increased thyroid dysfunction with the rise of HbA1c. The poor glycemic control in T2DM patients may be associated with thyroid dysfunction as the effect of hyperglycemia on hypothalamic–pituitary–thyroid axis in turn leads to low T_3 levels in DM patients or due to the hyperglycemia-induced inhibition of peripheral deiodination of T_4 to T_3, causing a low T_3 level[20].

The third important finding of the study was more involvement of LAD (64.5% Vs. 57.8% Vs. 36.8% Vs. 70.7%, p=0.03) in Group IV patients. Dhawan J, et al studied that in patients with T2DM is associated with increased severity of CAD and a higher incidence of LAD disease[21] and poor PCI outcomes when compared to non- diabetic patients[22,23]. Similarly, greater LAD involvement was noted in patients with subclinical hypothyroidism in previous studies[24,25]. The CAD involving LAD is

Table 1. Baseline characteristics

Parameters	Group I n=220	Group II n=325	Group III n=19	Group IV n=41	p value
Age (years)	56.1 ± 11.6	59.6 ± 9.8	60.4 ± 9.9	56.9 ± 12.1	0.002*
Male	197(89.5%)	263(80.9%)	10(52.6%)	33(80.5%)	<0.001*
Female	23(10.5%)	62(19.1%)	9(47.4%)	8(19.5%)	
Height (cm)	164.4 ± 8.2	16.2 ± 7.7	163.7 ± 7.6	160.8 ± 5.1	0.2
Weight (kg)	70.1 ± 11.3	68.4 ± 10.1	67.5 ± 8.3	68.8 ± 9.6	0.5
BMI	25.9 ± 4.6	26.1 ± 3.7	24.7 ± 1.9	27.2 ± 4.9	0.6
HTN	77 (35%)	181 (55.7%)	8 (42.1%)	21(51.2%)	0.004*
Dyslipidemia	17 (7.7%)	39 (12%)	2 (10.5%)	5(12.2 %)	0.012*
Smoker	4(1.8%)	5 (1.5%)	0	2(4.8%)	0.5
Prior CVA	4(1.8%)	9 (2.8%)	1 (5.3%)	1 (2.4%)	0.8
Prior COPD	1(0.5 %)	5 (1.5%)	0	0	0.5
Prior CKD	7(3.2%)	10 (3.1%)	0	1(2.4%)	0.8
Prior PVD	0	2 (0.6%)	0	0	0.6
UA	31 (14%)	61 (18.7%)	5 (26.3%)	8 (19.5%)	0.3
STEMI	5(2.3%)	7 (2.2%)	0	1(2.4%)	0.7
NSTEMI	57 (25.9%)	60 (18.4%)	3 (15.7%)	7(17%)	0.4
MI < 90 days	127 (57.7%)	197 (60.6%)	11(57.8%)	25(60.1%)	0.9
Thrombolysis	51 (23.2%)	78 (24%)	6(31.6%)	14(34.1%)	0.5
CS	2 (0.9%)	7 (2.2%)	0	1 (2.4%)	0.6
Prior CAD	30 (13.6%)	70 (21.5%)	4 (21.1%)	9 (21.9%)	0.2
Prior PCI	15(6.8%)	39 (12%)	2 (10.5%)	0	0.03*
Prior CABG	7(3.2%)	19 (5.8%)	0	2 (4.8%)	0.4
LVEF	43.2 ± 9.9	43.1 ± 9.3	43.9± 11.1	41.4 ± 11.6	0.7

Abbreviations: BMI- Body Mass Index, HTN – Hypertension, CVA – cerebrovascular accident, CKD – Chronic Kidney Disease, PVD – Peripheral Vascular Disease, UA – Unstable Angina, STEMI – ST- Elevation Myocardial Infarction, NSTEMI – Non ST-elevation Myocardial Infarction, MI- Myocardial Infarction, CS – cardiogenic shock, CAD – Coronary Artery Disease, PCI – Percutaneous Coronary Intervention, CABG – Coronary Artery Bypass Graft, CAD- Coronary Artery Disease , Coronary Vascular Accident, LVEF-Left Ventricular Ejection Fraction.

prognostically important as it supplies significant major proportion of left ventricular myocardium compared with the other two vessels[26]. A higher incidence of involvement of LAD may be an adverse prognostic marker in patients with T2DM and hypothyroidism undergoing PCI. Group III patients had increased bleeding events (0.5% Vs.1.2% Vs.10.5%, p=0.001). de Matos Soeiro, et al investigated that in 505 ACS patients having TSH >4 mlU/L had worse prognosis in terms of in-hospital events and bleeding[27]. L.P.B Elbers, et al studied that in patients undergoing invasive procedures, hypothyroidism is at increased risk of developing bleeding complications. He proved the

Table 2. Laboratory investigations

Parameters	Group I n=220	Group II n=325	Group III n=19	Group IV n=41	p value
Hb (g/dl)	13.6 ± 2.1	13.1 ± 2.1	12.1 ± 1.3	13.2 ± 2.1	0.006*
Platelets (lak/Cmm)	2.8 ± 2.3	3.2 ± 0.6	2.9 ± 0.9	2.7 ± 0.8	0.8
Urea (mg/dl)	25.8 ± 14.9	27.9 ± 15.7	26.9 ± 10.1	29.9 ± 26.1	0.3
Creatinine (mg/dl)	1.1 ± 3.8	1.2 ± 5	0.7 ± 0.2	0.8 ± 0.5	0.9
CK NAC (IU/L)	555.5 ± 150	610.9 ± 147	146.6 ± 209.8	998.9 ± 216	0.7
CK MB(ng/ml)	44.8 ± 83.8	56.8 ± 170	1.27 ± 0.3	45.8 ± 115	0.9
Troponin I (ng/ml)	10.8 ± 18.2	8.6 ± 16.3	2.9 ± 6.8	8 ± 16.1	0.5
TGL (mg/dl)	159.6 ± 109.6	166.2 ± 83.2	136.7 ± 72.3	222.2 ± 161.9	0.03*
TC (mg/dl)	163.2 ± 44.3	164.1 ± 52.8	164 ± 67.8	176.3 ± 59	0.7
HDL (mg/dl)	36.9 ± 10.9	37.8 ± 13.3	38.4 ± 10.1	35.6 ± 11.8	0.8
LDL (mg/dl)	111.9 ± 40.6	108.4 ± 44.4	123 ± 54.9	109.4 ± 53.7	0.7
HbA1C (%)	6.2 ± 1.2	8.5 ± 1.9	6.6 ± 2.1	9.2 ± 1.8	<0.001*

Abbreviations: Hb – Hemoglobin, CK NAC – Creatinine Kinase N-acetyl-cystein, CKMB – Creatinine phosphokinase MB, TGL – triglycerides, TC – total cholesterol, HDL- High Density Lipoprotein, LDL – Low Density Lipoprotein, HbA1C – Glycosylated Hemoglobin.

Table 3. Procedural Details

Parameters	Group I n=220	Group II n=325	Group III n=19	Group IV n=41	p value
HR (bpm)	79.2 ± 13.8	81.4 ± 11.4	79.6 ± 13.5	80.8 ± 11.2	0.2
Systolic BP (mmHg)	133.3 ± 21.9	138.5 ± 22.7	130.4 ± 14.8	133.9 ± 22.5	0.03*
Diastolic BP (mmHg)	77.5 ± 12.2	77.3 ± 11.2	79.7 ± 8.4	75.7 ± 13.1	0.6
Mean BP (mmHg)	99 ± 14.5	100.8 ± 16.2	98.7 ± 11.6	97.1 ± 14.5	0.3
SVD	130(59.1%)	148(45.5%)	11(57.8%)	20(48.7%)	0.02*
DVD	62(28.2%)	108(33.2%)	3(15.8%)	13(31.7 %)	0.3
TVD	26(11.8%)	63(19.4%)	3(15.8%)	8(19.5%)	0.1
LEFT MAIN	2(0.9%)	6(1.8%)	2(10.5%)	0	0.01*
LAD	142(64.5%)	188(57.8%)	7(36.8%)	29(70.7%)	0.03*
LCX	54(24.5%)	81(24.9%)	6 (31.6%)	7(17.1%)	0.6
RCA	72(32.8%)	116(35.7%)	10(52.6%)	13 (31.7%)	0.3
ISR	2(0.9%)	12(3.7%)	2(10.5%)	0	0.02*
SVG	3(1.4%)	9(2.8%)	0	0	0.4
IABP	6(2.7%)	10(3.1%)	2 (10.5%)	4(9.8%)	0.05*
TPI	3(1.4%)	7(2.2%)	0	1(2.4%)	0.8

Abbreviations: HR – Heart rate, BP – systolic blood pressure, SVD – Single Vessel Disease, DVD – Double Vessel Disease, TVD – Triple Vessel Disease, LAD – Left Anterior Descending Artery, LCX – Left Circumflex Artery, RCA – Right Coronary Artery, LM – Left Main, ISR –In-stent Restenosis, SVG – Saphenous Vein Graft, IABP – Intra Aortic Balloon Pump, TPI – Temporary pacemaker implantation

Table 4. Post PCI laboratory Investigations

Parameters	Group I n=220	Group II n=325	Group III n=19	Group IV n=41	P value
Post Hb (gm/dl)	13.1 ± 1.8	12.6 ± 1.9	11.8 ± 1.2	12.2 ± 1.9	0.003*
Post Ur (mg/dl)	25.9 ± 16	27.5 ± 13.1	24.7 ± 11.9	31 ± 29.3	0.3
Post Cr (mg/dl)	0.9 ± 0.8	0.8 ± 0.4	0.7 ± 0.2	0.8 ± 0.4	0.1

PCI – Percutaneous Coronary Intervention, Hb –hemoglobin, Ur –Urea, Cr –Creatinine

Table 5. In-Hospital Clinical Outcomes

Parameters	Group I n=220	Group II n=325	Group III n=19	Group IV n=41	p value
Bleeding	1(0.5%)	4(1.2%)	2(10.5%)	0	0.001*
CVA	0	2(0.6%)	0	0	0.6
MI	0	1(0.3%)	0	0	0.8
Repeat revascularization	0	1(0.3%)	0	0	0.8
Death	2(0.9%)	2(0.6%)	0	1(2.4%)	0.6

CVA-Cerebrovascular accident, MI-Myocardial infarction

effect of thyroid hormone on the hemostatic system and the associated risk of bleeding[28].

T2DM and hypothyroidism have been shown to be associated with poor outcomes in patients undergoing PCI, the current study did not show a difference in the in-hospital outcomes with its small sample size and no long term follow up. However, this is one of first studies assessed the outcome of patients with combination of T2DM and hypothyroidism, showing some important observations.

Limitation

The current study has some important limitations: (1) This is a single center study with small population size, (2) It assessed only the in-hospital event rate. The event rates were very low to derive any definite conclusion, (3) No long term follow up were assessed. Thus, large sample size will be required to understand better.

CONCLUSION

Patients with T2DM and hypothyroidism had significantly higher triglycerides, HbA1C levels and more LAD involvement with no significant change in clinical outcomes compared to other groups. A larger study with adequate sized population and longer follow-up is needed to further evaluate the current findings.

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