CORRELATION OF ANGIOGRAPHIC SEVERITY OF THE DISEASE AND DIFFERENT GROUPS OF ORAL ANTI-DIABETIC DRUGS (METFORMIN VS METFORMIN PLUS OTHER ANTI-DIABETIC DRUGS VS OTHER DIABETIC DRUGS ONLY) IN PATIENTS WITH TYPE II DIABETES MELLITUS

Nauman Naseer[a], Zeeshan Ghous[b*], Muhammad Hussain[b], Waqar Ahmed[b]

ABSTRACT

BACKGROUND:
Diabetes mellitus is a very important risk factor for coronary artery disease as it accelerates atherosclerosis, endothelial dysfunction and ultimately myocardial infarction or acute coronary syndrome. Different anti-diabetic medications are available for the glycemic control in patients with type II diabetes mellitus.It is not clear which medication is better in terms of its effects on decreasing the angiographic severity. Metformin is the preferred choice for initiating treatment for Diabetes.The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that in obese type 2 diabetic patients metformin reduces the risk of MI more than sulfonylureas or insulin. The vasoprotective role of metformin is largely independent of its hypoglycemic action and has been ascribed to pleiotropic effects.

METHODOLOGY:A total of 163 patients were enrolled in the study. Patients were divided into three major groups. The first group included those patients (total 33 patients) who were taking metformin only, the second group included those patients (41 patients) who were taking metformin with other diabetic medication (sulfonylurea, thiazolidinedione or insulin) while third group included those patients (89 patients) who were taking other diabetic medication (sulfonylurea, thiazolidinedione or insulin) without metformin. The SPSS version 20 was used to evaluate the data.

RESULTS: Out of total 163 patients, the first group which included 33 patients who were taking only metformin there were 7 (21.2%) patients who had left main disease, 19 (57.57%) patients who had LAD disease, 14 (42.42%) patients with LCX disease and 13 (39.4%) patients who had disease in RCA. While in the second group the number and percentage of patients with left main, LAD, LCX and RCA disease 1 patients (2.4%), 28(68.29%) patients, 23 (56.09%) patients and 20 (48.8%) patients respectively while in the third group they were 4 patients (4.5%), 54 (60.67%) patients, 45 (50.56%) patients and 34 (38.2%) patients respectively.

CONCLUSION: Based on the retrospective analysis with limitations as noted, there is no statistical difference for obstructive coronary artery disease among different diabetic treatment groups in our study (Metformin Vs Metformin plus other Diabetes drugs Vs other Diabetes drugs only),apart from left main stem disease patients.

Key words: Angiographic Severity, Type II Diabetes mellitus, Oral Hypoglycemic drugs,ischemic heart disease, coronary artery disease, correlation.

INTRODUCTION:

Diabetes mellitus (DM) has gained the pattern of an epidemic disease worldwide. Both the developed and the developing countries are

[a]Bahria Town Hospital, Lahore.

[b]Punjab Institute of Cardiology, Lahore, Pakistan
* Corresponding author:
Email: zeeshanghouskhan@gmail.com

showing increasing trends of this disease. Diabetes mellitus involves the multiple organs and when it involves the coronary arteries it causes increase in both morbidity and mortality. Prevalence of DM is increasing day by day. The number of Americans with DM is projected to increase 165%, from 11 million people in 2000 to 20 million people in 2025 (prevalence of 4.0%) [1]. Type 2 diabetes mellitus is associated with a marked increase in the risk of coronary heart disease. There has been ongoing debate that those patients who still have not suffered from ischemic heart disease that there should be aggressive treatment towards the modi-

fication of risk factors so that the events to come in future may be prevented. Clinically established coronary heart disease itself is associated with an increase in mortality from coronary heart disease by a factor of three to seven, depending on the mode of presentation.[2]

In recent days it has become more and more complex to manage the glycemic control in type 2 diabetes mellitus because more and more drugs are available due to improvement in the research work. It has mounted concerns about their potential adverse effects and new uncertainties regarding the benets of intensive glycemic control on macrovascular complications [3,4]. Many clinicians find difficulty in which medication for glycemic control should be started. Many drugs can be used for the glycemic control in patients presenting with type 2 DM. Details about the effects of and rationale for available anti-hyperglycemic agents can be found in the 2015 AACE Comprehensive Diabetes Management Algorithm Consensus Statement [5]. According to the AACE recommendations metformin should be initial therapy to be started or a glucagon-like peptide 1 (GLP1) receptor agonist, a dipeptidyl peptidase 4 (DPP-4) inhibitor, a sodium glucose co-transporter 2 (SGLT2) inhibitor, or an-glucosidase. Recent studies have shown that specific Sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP1) receptor agonists have cardiovascular outcome benefits for patients with a history of clinical CVD.[6]

Diabetes is associated with a marked increase (by a factor of two to four) in the risk of coronary heart disease[7]. As we know that diabetes mellitus is major risk factor for coronary artery disease and hyperglycemia may cause endothelial dysfunction, atherosclerosis as well as platelet dysfunction and ultimately causing myocardial infarction or acute coronary syndrome.Diabetic patients with myocardial infarction have a worse prognosis than nondiabetic patients with myocardial infarction[7].

The FINMONICA Myocardial Infarction Register Study Group, concluded that the high mortality rate of diabetic patients after their first myocardial infarction and the high proportion of out-of-hospital deaths in this group imply that vigorous primary and secondary preventive measures should become an integral part of their medical care[8]. Objective of the study was to assess the angiographic severity of the patients who were on different anti-diabetic medications specifically assessing whether metformin has superiority over the other medication group.

MATERIAL METHODS:

This retrospective cross-sectional study was conducted in Bahria international hospital Lahore from 1-1-2016 to 31-12-2016. 163 patients with type 2 DM who underwent cardiac catheterization were included.

Patients with the prior history of coronary artery disease, patients who did not survive their initial coronary event (death occurred within one month of the index coronary angiography), patients who initially presented with cardiogenic shock, cardiac arrest, requiring intubation, or use of inotropic support within a 48 hours period prior to the index coronary angiography, patients with chronic CHF with EF < 30%, patients with documented admissions and creatinine>1.4, patients with history of cirrhosis were excluded from study.

METHODOLOGY:

It was a retrospective study. A total of 163 patients fulfilling the inclusion and exclusion criteria were included in the study. Clinical and pathological data including age, gender, HbA1c, risk factors for ischemic heart disease, indications for coronary angiography and coronary artery disease on angiography was collected from the files available in the hospital.

Patients were divided into three major groups. The First group included those patients (total 33 patients) who were taking metformin only, the second group included those patients (41 patients) who were taking metformin with other diabetic medication (Sulfonylurea, Thiazolidinedione TZD or Insulin) while third group included those patients (89 patients) who were taking other diabetic medication (sulfonylurea, TZD or insulin). All the patients underwent angiography and the severity of disease was assessed by visual assessment as stenosis ≥ 50% was considered significant disease. While in LAD (left anterior descending artery), LCX (left circumflex artery) and RCA (right coronary artery) disease ≥ 70% was considered as severe disease.

Data was computed on statistical package for social sciences (SPSS), version 20. Qualitative variables like gender and indications of coronary angiography like chest pain, unstable angina, NSTEMI, STEMI and chronic stable angina, were described in frequencies and percentage. Quantitative variables like age and HbA1c were presented by mean ± standard deviation.

RESULTS:

Among the 163 patients that fulfilled the inclusion and exclusion criteria there were 93 male patients that made up to 57.1% of total patients and 70 patients were females that made up 42.9% of the total patients. The percentage of male and female patients in metformin group was 57.6% and 42.4% respectively, while in metformin plus other medication group was 70.7% and 29.3% and in third group the ratio was 50.6% and 49.4% respectively(Table 1). The mean age of the patients in metformin group was 54.76 ± 13.01 while the mean age of the patients in metformin combination group 56.73 ± 12.21 and in the other medication only group the mean age of the patients was 58.64 ± 10.86. The mean HbA1c level in three groups was 7.21 ± 0.35, 7.35 ± 0.38 and 7.37 ± 0.38 respectively. (Table 2)

All of the patients underwent coronary angiography while indications of angiography were categorized into chest pain, unstable angina, NSTEMI, STEMI and chronic stable angina. In the metformin only group the percentages of the patients presenting with chest pain, unstable angina, NSTEMI, STEMI and chronic stable anginawere 3%, 24.2%, 39.4%, 3%, 6.1% and 24.2% respectively

Table-1 :Gender of patients.

			Groups			Total
			Met-formin	Metformin Combination (Sulfonylurea, TZD, Insulin)	Sulfo-nylurea, TZD, and Insulin	
Gender of respondents	Male	Count	19	29	45	93
		% within Groups	57.6%	70.7%	50.6%	57.1%
	Female	Count	14	12	44	70
		% within Groups	42.4%	29.3%	49.4%	42.9%
Total		Count	33	41	89	163
		% within Groups	100.0%	100.0%	100.0%	100.0%

Table-2: Data clinical variables: Age and HbA1c

Groups		Age of respondents	HbA1c of subjects
Metformin	N	33	33
	Mean	54.76	7.212
	Std. Deviation	13.010	.3525
	Minimum	29	6.4
	Maximum	81	7.9
Metformin Combination (Sulfonylurea, TZD, Insulin)	N	41	41
	Mean	56.73	7.354
	Std. Deviation	12.211	.3809
	Minimum	36	6.4
	Maximum	81	8.3
Sulfonylurea, TZD, and Insulin	N	89	89
	Mean	58.64	7.366
	Std. Deviation	10.862	.3840
	Minimum	34	6.3
	Maximum	82	8.4
Total	N	163	163
	Mean	57.37	7.332
	Std. Deviation	11.693	.3797
	Minimum	29	6.3
	Maximum	82	8.4

Table-3 :Indications for coronary angiogram

			Groups			Total
			Met-formin	Metformin Combination (Sulfonylurea, TZD, Insulin)	Sulfo-nylurea, TZD, and Insulin	
Indications for coronary angiogram	Chest Pain	Count	1	5	8	14
		% within Groups	3.0%	12.2%	9.0%	8.6%
	Positive Stress test	Count	8	5	11	24
		% within Groups	24.2%	12.2%	12.4%	14.7%
	Unstable angina	Count	13	23	40	76
		% within Groups	39.4%	56.1%	44.9%	46.6%
	NSTEMI	Count	1	4	14	19
		% within Groups	3.0%	9.8%	15.7%	11.7%
	STEMI	Count	2	2	14	18
		% within Groups	6.1%	4.9%	15.7%	11.0%
	Chronic Stable Angina	Count	8	2	2	12
		% within Groups	24.2%	4.9%	2.2%	7.4%
Total		Count	33	41	89	163
		% within Groups	100.0%	100.0%	100.0%	100.0%

Table-4 : Other Risk factors

			Groups			Total
			Met-formin	Metformin Combination (Sulfonylurea, TZD, Insulin)	Sulfo-nylurea, TZD, and Insulin	
Risk factors	Tobacco Use	Count	8	12	21	41
		% within Groups	24.2%	29.3%	23.6%	25.2%
	Hyper-tension	Count	19	20	53	92
		% within Groups	57.6%	48.8%	59.6%	56.4%
	Dyslipi-demia	Count	6	9	15	30
		% within Groups	18.2%	22.0%	16.9%	18.4%
Total		Count	33	41	89	163
		% within Groups	100.0%	100.0%	100.0%	100.0%

Table-5: Angiographic severity

Variables	Metformin (n=33)	Metformin+(Sulfonylurea, TZD, Insulin) (n=41)	Sulfonylurea, TZD, Insulin (n=89)	P-value
Left main	7(21.2%)	1(2.4%)	4(4.491%)	0.0031
LAD	19(57.57%)	28(68.29%)	54(60.67%)	1.029
LCx	14(42.42%)	23(56.09%)	45(50.56%)	1.37
RCA	13(39.4%)	20(48.8%)	34(38.2%)	1.347

while in metformin combination group these were 12.2%, 12.2%, 56.1%, 9.8%, 4.9% and 4.9% respectively and in the third group these were 9%, 12.4% ,44.9%, 15.7%, 15.7% and 2.9% respectively.(Table3)

Smoking, hypertension and dyslipidemia were major risk factors that were found in the patients. In the metformin group there were 24.2 % patients who were smokers, while 57.6% who had hypertension and 18.2 % who had dyslipidemia.Similarly in the second group patients with the tobacco use, hypertension and dyslipidemia had percentages of 29.3%, 48.8% and 22% respectively. While in the third group they had percentages of 23.6%, 59.6% and 16.9% respectively.(Table4).

All the patients underwent coronary angiogra-

phy the results were as follows for each group.

In the first group in which the patients were taking only metformin there were 7 patients (21.2%) who had left main disease, but it was an incidental finding and no clinical significance because this was a very small number of patients. There were 19 patients (57.57%) who had LAD disease, 14 patients (42.42%) with LCX disease and 13 patients (39.4%) who had disease in RCA. While in the second group the number and percentage of patients with left main, LAD, LCX and RCA disease 1 patients (2.4%), 28 patients (68.29%), 23 patients (56.09%) and 20 patients (48.8%) respectively while in the third group they were 4 patients (4.5%), 54 patients (60.67%), 45 patients (50.56%) and 34 patients (38.2%) respectively.(Table 5)

There were 1.6 obstructive lesions per patient in Metformin only group, 1.75 obstructive lesions in second group (Metformin plus other anti-diabetic medication group) and 1.53 in the third group (other anti-diabetic drugs only) but the data was not statistically significant.

DISCUSSION:

Diabetes mellitus affects the multiple organs of the body and it is a major risk factor for coronary artery disease. As it is a well-known fact that the primary cause of death is CVD in most of the patients suffering from DM so a DM comprehensive care plan should include modifications of CVD. Recent guidelines suggest to start treatment with Metformin in newly diagnosed type II diabetic patients. These data from different studies suggest that, in patients with DM[2] treated with Insulin, Metformin may affect glucose metabolism by improving the hepatic responsiveness to insulin and by increasing the release of glucagon-like peptide type 1[9,10]. A 2006 consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), updated in 2009 and 2012, proposed that Metformin therapy be initiated, concurrent with lifestyle intervention, at the time of diabetes diagnosis [11,12].

A recent study done by Hong et al.[13] that compared two major classes of anti-diabetic drugs sulfonylureas and metformin on their effects on the cardiovascular outcome in patients with type 2 diabetes melllitus. At the end of the study both groups achieved a significant in the level of glycated hemoglobin (7.1% in the glipizide group and 7% in metformin group). At the median follow up of 5 years 91 participants had developed 103 primary end points. Intention to treat analysis showed an adjusted hazard ratio of 0.54 (95% Cl 0.30-0.90;

P = 0.026). for the composites of cardiovascular events among the patients that received metformin compared with the glipizide. The secondary end points and adverse events were not significantly different between the two groups.

Another study done by Ravipati et al.[14] threw light on the association of diet alone, insulin, sulfonylureas, metformin and thiazolidinediones with the severity of coronary artery disease on diabetic patients. Coronary angiography was done in 152 men and 163 women who had diabetes mellitus. Of 67 patients with three vessel or four vessel coronary artery disease, 17 (25%) were treated with diet alone, 29 (43%) with insulin, 18 (27%) with sulfonyl ureas, 12 (18%) with metformin and nine percent with thiazolidinediones. Of 76 patients with 2-vessel CAD, twenty six percent were treated with diet alone, fourty seven percent with insulin, twenty eight percent with sulfonylureas, twenty eight percent with metformin and fourteen percent with thiazolidinediones. Of 40 patients with single vessel coronary artery disease, 17 (25%) were treated with diet alone, 29 (43%) with insulin, 18 (27%) with sulfonyl ureas, 12 (18%) with metformin and nine percent with thiazolidinediones. Of 76 patients with 1-vessel CAD, thirty eight percent were treated with diet alone, twenty eight percent with insulin, twenty percent with sulfonylureas, thirty percent with metformin and ten percent with thiazolidinediones. Of 132 patients with zero vessel coronary artery disease, 14% were treated with with diet alone, 16% with insulin, 05% with sulfonylureas, 56% with metformin and 26% with thiazolidinediones. Cochran-Armitage trend tests were used to examine whether the use of treatment significantly increases or decreases number of arteries with the CAD increase. (p=0.036 for diet alone, P<0.0001 for insulin, sulfonylureas and for metformin. P= 0.002 for thiazolidinediones)

Ledru et al.[15] recently compared coronary disease in consecutive diabetic and non-diabetic angiography patients. Angiographic severity was evaluated and compared in both diabetic and non-diabetic patients and it was found that disease was more severe in diabetics than in non-diabetic patients.

As per guidelines Metformin is used as first line drug for the control of blood sugar in patient suffering from type II DM. As we know the fact that increased insulin resistance is the major cause of endothelial dysfunction and ultimately leading to coronary obstruction and ACS. Metformin decreases the insulin resistance, improves endothelial

function, decrease in plasma plasminogen activator inhibitor-1, lipoprotein(a), and immunoreactive insulin levels.[16]

Endothelial function is impaired when patients suffers from Type 2 diabetes mellitus because it affects vasomotor tone, hemostasis, platelet adhesion and fibribolysis. Different studies has been done on endothelial function affected by type 2 DM and the effects of Metformin. Mather et al. reported that Metformin has no effect on endothelium dependent blood flow but has a significant effect on endothelium independent blood flow and insulin resistance reduction[17]. Conversely, Vitale et al. found significant improvement of endothelium dependent flow without a significant effect on endothelium independent response[18].

In order to improve the quality of life and to prevent chronic complications related to diabetes mellitus, intensive lifestyle modification and proper medication are needed from the early stage of diagnosis of type 2 diabetes mellitus (T2DM)[19].

Metformin is also reported to have antioxidant properties as when there is oxidative stress it may cause atherosclerosis,reperfusion injury to endothelium and inflammation resulting in the clot formation and ultimately presenting as acute coronary syndrome. Metformin is believed to reduce the oxidative damage by reducing the oxygen free radicals and by inhibition of mitochondrial respiration.

The results shown in our study did not show any statistical difference of angiographic severity in the threedifferent diabetic treatment group. Metformin use in the patients with type II DM failed to show any statisticaldifference for decreasing angiographic severity of coronary artery disease.

LIMITATIONS:

There were certain limitations of this study such as the total number of patients as well as the group of patients taking Metformin was small and angiographic severity was not assessed on the basis of some scientific scoring method such as syntax score or Euro score. Being a cross sectional study, we could not establish any causality. There was another limitation that the duration of diabetes mellitus was not calculated.

CONCLUSION:

Based on the retrospective analysis with limitations as noted, there is no statistical difference for obstructive coronary artery disease among different diabetic treatment groups in our study (Metformin Vs Metformin plus other Diabetes drugs Vs other Diabetes drugs only), apart from left main stem disease which comprised small number of patients.

Author's Contribution

NN: Collected the data and conducted the study. ZG: Helped in conducting the study.MH: Helped in analysis of data.WA: Data analysis and proof reading.

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