Original article:

Predictors of new onset diabetes mellitus in acute coronary syndrome patients

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ABSTRACT

Introduction / Background : The mounting incidence and prevalence of type 2 diabetes, driven by increasing population age, obesity, and physical inactivity, compounded by several other atherosclerotic risk factors which also causes spectrum of diseases like Coronary artery disease (CAD), stroke etc. There is limited information on the incidence of diabetes despite INDIA being the Global capital for Diabetes. Though much of data is available in patients already diagnosed with diabetes but data regarding the new onset diabetes in the subset of Acute coronary syndrome (ACS) is very limited. The present study give insight into the magnitude of New onset diabetes (NOD) in this population subset.

Materials and methods : This was a Cohort study in which 200 consecutive ACS patients were included. A brief history of presenting & past illness, personal & family history; drug & addiction history was taken. Data on several lab & biochemical parameters (i.e. FBS; PPBS; Lipid profile; Hba1c, BP , BMI & Drug intake) was collected at the time of admission, after discharge at 2 weeks, 6 weeks & 3,6 & 12 months post ACS.

Results : In study 85% (n=170) were males. Mean age was 56 years. 37% were hypertensive and dyslipidemic, 42% were smokers, 8.5% had Chronic kidney disease patients, Peripheral Vascular disease was present in 7.5% patients, Family history of premature CAD was present in 36.5% patients, 88.5% had Sedentary lifestyle. 59.5% patients presented as STElevation Myocardial infarction (STEMI), 18.5% patients as Non-STEMI (NSTEMI) and 22% patients as unstable angina.

20% (n=40) developed New onset diabetes (NOD), 2.5% (n=5) developed Impaired Fasting Glucose, 6% (n=12) developed Impaired glucose tolerance in and both 1.5% (n=3) developed Impaired fasting glucose and Impaired Glucose tolerance over a follow up period of 1 year giving a Incidence rate of NOD 0.2 per person per year which is 10 times higher than previous available data on general population.

At the end of 1 year on comparison the new onset diabetics had higher BMI, Waist circumference, Systolic and diastolic blood pressure and deranged lipid profile (Higher Triglycerides, Higher LDL and Low HDL values) which were all statistically significant on analysis. Intake of High dose statins, beta blockers and diuretics were also significantly contributed to the new onset diabetes.

Conclusion : The study highlights two important things, first incidence of new onset diabetes in acute coronary syndrome patients is High, Second the onset of diabetes is very rapid especially in the first six months after acute coronary syndrome thus early and regular screening of blood glucose of Coronary artery disease patients should be done to prevent, detect and treat diabetes mellitus so as morbidity and mortality arising out of new onset diabetes can be decreased.

Keywords: New onset diabetes, Acute coronary syndrome

INTRODUCTION

Diabetes Mellitus

India has more diabetics than any other country in the world, according to the International Diabetes Foundation. The disease currently affects more than 62 million Indians, which is more than 7.1% of India's adult Population. An estimate shows that nearly 1 million Indians die due to Diabetes every year.The average age on onset is 42.5 years. [1]

There is limited information on the incidence of diabetes in India. The high incidence is attributed to a combination of genetic susceptibility plus adoption of a high-calorie, low-activity lifestyle by India's growing middle class.[2]

Coronary artery disease& Diabetes Mellitus

Of the risk factors, diabetes, and its predominant form, type 2 diabetes mellitus (T2DM), has a distinctive association with CHD. Those with diabetes have two- to four-fold higher risk of developing coronary disease than people without diabetes, and CVD accounts for an overwhelming 65-75 per cent of deaths in people with diabetes. [3]

The risk of New Onset Diabetes (NOD) is associated with many factors like diet, physical activity, medical conditions like hypothyroidism, CKD, family history, smoking, dyslipidemia, hypertension and with a wide variety of drugs including statins, thiazide diuretics, beta-blockers, glucocorticoids, niacin etc. [4]

Though much of data is available in patients already diagnosed with diabetes but data regarding the predictors of new onset diabetes in the subset of post PCI patients is very limited. The present study is the opportunity to look at the predictors of NODin this population subset.

The outcomes from this study are expected to enhance our knowledge about the NOD in ACS patients and various measures that can be taken to improve it.

AIMS & OBJECTIVES

1. To study incidence of new onset diabetes mellitus in ACS patients
2. To find association between various diabetic risk factors with new onset
diabetes mellitus.

MATERIALS AND METHODS

This is a Cohort study. 200 consecutive ACS patients in department of cardiology, Government Medical College, Trivandrum were taken up for study after having proper written and informed consent. A brief history including chief complaints; history of presenting & past illness; personal & family history; drug & addiction history was taken. The patients were also studied on several lab & biochemical parameters i.e. FBS; PPBS; Lipid profile; Hba1c, BMI, BP & Drugs prescribed which were studied at the time of admission, after discharge at 2 weeks, 6 weeks, 3,6 & 12 months post ACS.

STUDY DESIGN

Cohort study.

SAMPLE SIZE

With an estimated risk of 7.3% from available previous data and confidence level of 99% calculated sample size for present study is 178.

STUDY PERIOD

April 2016 to March 2017 along with the CATH REGISTRY data of DEPARTMENT OF CARDIOLOGY, GOVERNMENT MEDICAL COLLEGE TRIVANDURM.

STUDY POPULATION

Any ACS patient admitted in the Department of Cardiology, Government Medical College, Trivandrum.

STUDY CENTRE

Department of Cardiology, Government Medical College, Trivandrum.

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INCLUSION CRITERIA

Any ACS Patient.

EXCLUSION CRITERIA

Patients diagnosed to have diabetes mellitus at time of admission (As per standard definition: Hba1c > 6.5, FBS>126 mg/dl, 2 hour PPBS>200 mg/dl or RBS>200 mg/dl with symptoms consistent with diabetes mellitus)

Patients who are already diagnosed or on treatment for diabetes mellitus.

Patients who do not give consent for participation in the study.

RESULTS AND DISCUSSION

The baseline characteristics of study population were comparable to prevalent characteristics of ACS patients quoted in several studies of the region. (**Table 1**)

Table 1 Baseline characteristics of study population

Baseline Characteristics	**N (200)**	**%**
Mean Age	56.2 years	
Males	170	85
Dyslipidemia	84	42
Smoking	42	21
POAD	15	7.5
CKD	17	8.5
Hypothyroidism	71	35.5
F/H of ACS	73	36.5
F/H of DM	120	60
Drugs i.e steroids	0	0
Physically active	23	11.5
ACS -TYPE		
STEMI	119	59.5
NSTEMI	37	18.5
UA	44	22

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INCIDENCE OF NOD IN STUDY POPULATION

In our study New onset diabetes was detected in 20% (n=40) , Impaired Fasting Glucose in 2.5% (n=5) ,Impaired glucose tolerance in 6% (n=12) and both Impaired fasting glucose and Impired Glucose tolerance in 1.5% (n=3) over a follow up period of 1 year out of total study population of 200. **(Table 2)**

TABLE 2 : Number of Patients developed deranged Blood sugars and Hba1c in study population over one year

Impaired Blood Sugar Category	**No.**	**%**
NOD	40	20%
IFG	5	2.50%
IGT	12	6%
IFG+IGT	3	1.50%

The calculated **incidence rate in our study is 0.2 per person per year**, this is very high in comparison to available data on incidence of diabetes.

In our present study after collecting the whole data, for analytic purpose a randomized match sample of 60 patients were taken from the remaining 140 patients who doesn't developed any derangement of blood sugars on follow up and compared with 40 New onset diabetes patients.All baseline characteristics were comparable in both the group i.e. new onset diabetes group and Control group. Mean Age in both the groups were 53.6 years. All Atherosclerotic risk factors were comparable in both the groups with no significant difference.

At the end of 1 year on comparison the new onset diabetics had higher BMI, Waist circumference, Systolic and diastolic blood pressure and deranged lipid profile (Higher Triglycerides, Higher LDL and Low HDL values) which were all statistically significant on univariate analysis. **(Table 3).** Correlation power of different variables were also calculated with Hba1c. **(Table 4).**

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Table 3: Comparison of Follow up characteristics (1 year) in NOD vs Control population

	NOD		**Control**		
	Mean	**sd**	**Mean**	**sd**	
BMI (kg/m^2)	33.86	2	27.74	1.47	<0.001
WAIST CIRCUMFERENCE (cm)	98.08	5.27	87.85	5.28	<0.001
SBP (mm Hg)	159.4	11.18	120.98	12.72	<0.001
DBP (mm Hg)	98.13	5.91	89.55	5.75	<0.001
Hba1C (%)	7.03	0.24	5.38	0.2	<0.001
FBS (mg/dL)	162.25	30.19	79.97	12.15	<0.001
PPBS (mg/dL)	206.5	31.28	122.37	12.98	<0.001
TG (mg/dL)	163.38	21.2	133.48	18.24	<0.001
TC (mg/dL)	225.8	13.4	224.7	8.5	0.633
HDL (mg/dL)	33.75	2.58	50.43	5.78	<0.001
LDL (mg/dL)	120.23	12.79	96.58	8.6	<0.001
VLDL (mg/dL)	24.68	3.19	24.43	6.12	0.819

	NOD (N=40)		**Control (N=60)**		**p**
	N	**%**	**N**	**%**	
Beta Blockers -M50	8	20	28	46.7	0.006
Diuretic	21	52.5	7	11.7	<0.001
Statin high dose	36	90	44	73.3	0.041
Statin low dose	4	10	16	26.7	0.041

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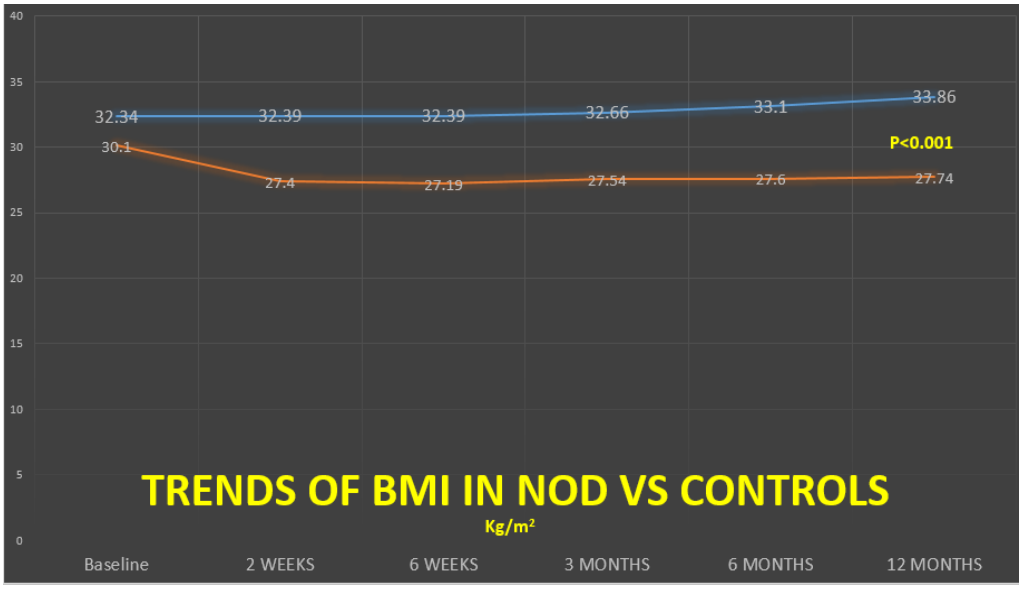
Table 4: Corelation of various Characterestics with Hba1C

Correlation between Hba1C	Pearson Correlation (r)	p
Age	-0.106	0.296
BMI	0.512	0
WAIST CIRC.	0.318	0.001
SBP	0.441	0
DBP	-0.016	0.873
FBS	0.557	0
PPBS	0.511	0
TG	0.42	0
TC	0.136	0.177
HDL	-0.55	0
LDL	0.61	0
VLDL	-0.074	0.465

BMI & NEW ONSET DIABETES

Fig. 1 :BMI In NOD Vs Controls



In present study the patients who developed new onset diabetes on follow up they had significantly higher BMI from the first follow up as compared to control patients who doesn't developed diabetes. The significant difference was present in every follow up of 2weeks, 6 weeks, 3 months, 6 months and 12 months (Fig. 1) suggestive that these patients gained weight rapidly and also they despite of repeated advisory of active lifestyle and healthy diet pattern they keep on

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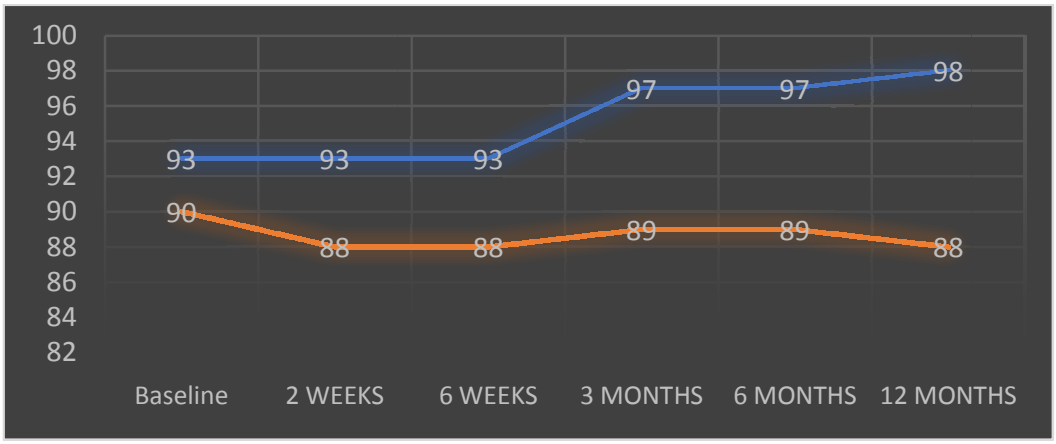
continuing sedentary lifestyle and unhealthy food habits. On an Average the **NOD patients had a BMI of 32.5 kg/m2 and Control patients had BMI of 27.5 kg/m2.**

When correlation strength was analyzed between Hba1c and BMI it came out to be 0.512 showing that both of them were moderately correlated in positive manner i.e. increase in BMI also causes increase in Hba1c.

In a study conducted to find NOD after renal transplant in 2014 founded that the odds of developing NOD after transplantation by discharge or 3 or 6 months post-transplantation increased by a factor of 1.11 (95% confidence interval [CI]: 1.0-1.23), 1.13 (95% CI: 1.03-1.24), and 1.15 (95% CI: 1.05-1.27), respectively, per unit increase in pre-transplantation BMI. [5]

WAISTCIRCUMFERENCE AND NOD

Fig. 2: Waist Circumference in NOD Vs Controls



In present study the patients who developed new onset diabetes on follow up they had significantly higher waist circumference as compared to control patients who doesn't developed diabetes. **The mean waist circumference in NOD was 94.5 cm while control patients had mean waist circumference of 88 cm**. So difference of 2 to 4 inches in abdominal girth puts a heavy impact on the glucose homeostasis of an individual.

Compared with BMI, WC is more true to the biologically well-established mechanism that visceral fat has a greater association with insulin resistance than does subcutaneous fat [6]There are many studies which shows the definite link between Waist circumference and new onset diabetes as in present study. Few of them are as follows:

A metanalysis done by Kodama etal in 2012 concluded that the relative risk of waist circumference with new onset diabetes is 1.63 (95% CI: 1.49, 1.79). [7]

In a population-based cross-sectional study was conducted with 1,000 representative sample among adults aged 20–80 years in Babol, the Northern Iran, and it showed that waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) were significantly higher among diabetic in both sexes (P= 0.001). [7]

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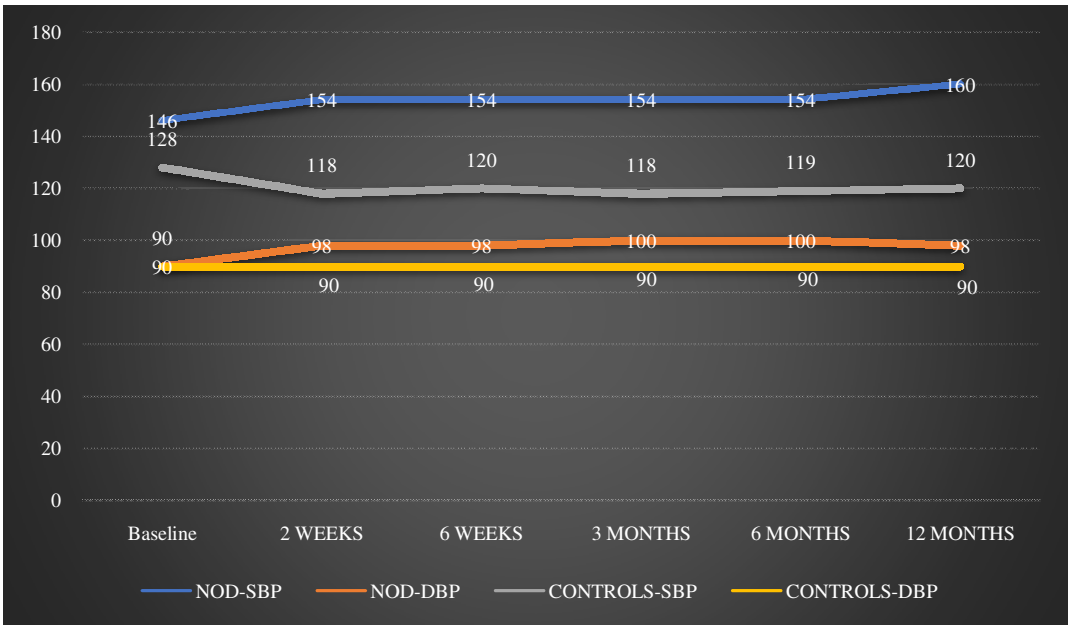
Blood pressure and NOD

Fig. 3: BP in NOD Vs Controls



In present study NOD patients had higher SBP and DBP when compared to controls on every follow up. **The mean BP in NOD patients was 154/98 while in controls was 120/90 mm Hg and it was significantly different**. This may be suggestive of two things either worsening of BP control in these patients accelerated the atherosclerotic process and thus leading to development of diabetes or the NOD patients had developed higher BP with onset of diabetes. But either way round it is the composite of all complex vascular-endocrinological-atherosclerotic process that leads to Higher BP and as well as Higher Blood sugars in these patients.

Our results support the hypothesis that elevated BP is associated with increased risk of diabetes and this corroborates with the largest evidence available yet in the metanalysis performed in 2015 by Connor etal. In this metanalysis a cohort of 4.1 million adults, free of diabetes and cardiovascular disease, was identified using validated linked electronic health records. Among the overall cohort, 20 mm Hg higher SBP and 10 mm Hg higher diastolic BP were associated with a 58% and a 52% higher risk of new-onset diabetes (hazard ratio: 1.58; 95% confidence interval [CI]: 1.56 to 1.59; and hazard ratio: 1.52; 95% confidence interval: 1.51 to 1.54), respectively. [8]

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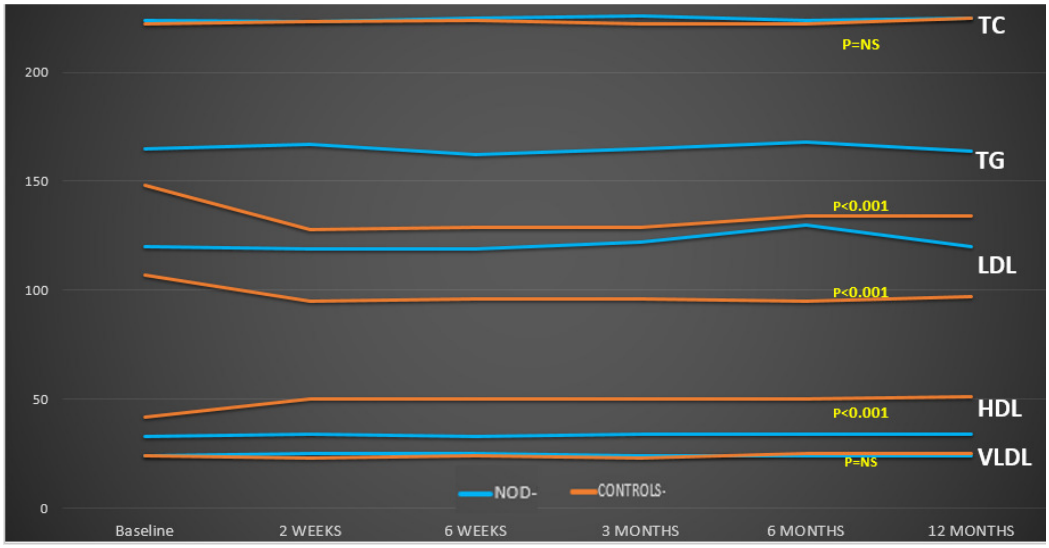
Lipid profile and NOD

Fig. 4 LIPID PROFILE IN NOD VS CONTROL



In present study there was significant difference in the Serum triglyceride, Serum HDL and Serum LDL levels of NOD and control patients at each follow up. **The mean Serum triglyceride, Serum HDL and Serum LDL levels in NOD patients were 167 mg/dl , 119 mg/dl & 33 mg/dl respectively while the same in controls were 129 mg/dl, 96 mg/dl & 50 mg/dl respectively.**

This clearly shows how the deranged Triglyceride, LDL & HDL levels influence the glucose homeostasis. This leads to insulin resistance, depletion of beta cells & raised blood glucose levels which manifests as diabetes.

The correlation strength was strongest between Hba1c and LDL (0.61) followed by Hba1c & HDL (-0.55) and Hba1c and TG (0.42).

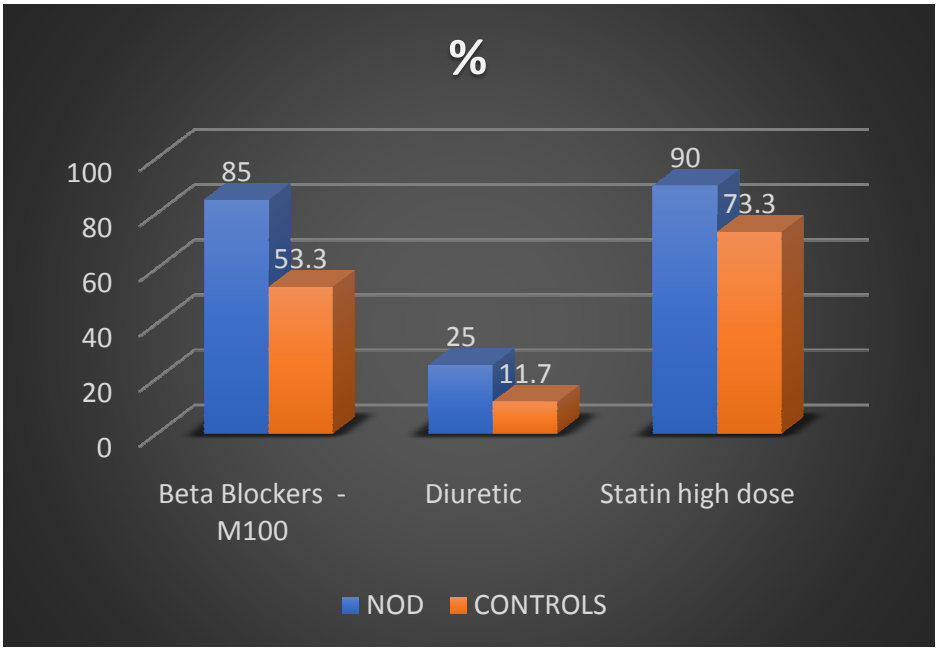
Framingham offspring study founded that HDL <50 mg/dl in women and <40 mg/dl in men has odds ratio of 2.18 and Triglyceride >150 mg/dl had odds ratio of 1.45 in prediction of new onset diabetes. [9]

Out of 19,257 hypertensive patients in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) 1,366 (9.7%) subsequently developed NOD during median follow-up of 5.5 years. NOD was significantly associated with an increase in serum triglyceride level and High HDL levels were protective for NOD[10]

All the above studies strongly prove the association between HDL and Triglyceride level with new onset diabetes.

DRUGS AND NOD

Fig. 6: Baseline Drug therapy in NOD vs Control



STATINS AND NOD

In our present study **90% NOD patients were on High dose statin after ACS while only 75% control group were on high dose statinwhich was significantly different**. This suggests that High dose statin plays a definite role in out-bringing the latent diabetes to reveal as manifest diabetes.

David etal examined the incidence and clinical predictors of new-onset type 2 diabetes mellitus (T2DM) within 3 large randomized trials with atorvastatin. [11] The trials observation on statin induced diabetes is quoted below.

In the TNT trial, a trend toward an increase in new-onset T2DM for the atorvastatin 80 mg group was observed (HR: 1.15, 95% CI: 0.98 to 1.34, p = 0.082; and HR: 1.10, 95% CI: 0.94 to 1.29, p = 0.22, for univariate and multivariate analyses, respectively). [12]

Similarly, in the IDEAL trial a trend toward an increase in new-onset T2DM was observed in the atorvastatin 80 mg group (HR: 1.16, 95% CI: 0.96 to 1.40, p = 0.12; and HR: 1.19, 95% CI: 0.99 to 1.44, p = 0.072, for univariate and multivariate analyses, respectively). [13]

In the SPARCL trial, where the comparator group was placebo, the incidence of new-onset T2DM was higher in the atorvastatin 80 mg group (HR: 1.44, 95% CI: 1.14 to 1.83, p = 0.0024; and HR: 1.34, 95% CI: 1.05 to 1.71, p = 0.018, for univariate and multivariate analyses, respectively). [14]

All the observations in these 3 trials are matching with our study results.

The mechanism underlying the small increase in new-onset T2DM in patients treated with statins is unknown. An increase in cholesterol content of pancreatic beta islet cells has been reported to decrease insulin secretion [142]; however, statin

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treatment would be expected to decrease or have no effect on the cholesterol content of these cells. It is possible that statins decrease insulin sensitivity in liver or muscle, but there is no direct experimental evidence to support this.

BETA BLOCKERS AND NOD

The present study shows clearly how the patients on higher dosage of beta-blockers (i.e 100mg metoprolol or equivalent) were more prone to development of NOD. **85% of NOD patients were on 100mg Metoprolol or equivalent while only 53.3% of Control group were on the same which was significantly different**. Addition of beta blocker on background of patients with metabolic syndrome and clinically proven atherosclerotic vascular disease leads to news onset diabetes.

In the meta-analysis of 6 trials enrolling 55 675 patients with hypertension, β-blockers conferred a 32% increased risk of new-onset diabetes compared with placebo or non-diuretic antihypertensive agents. The risk of new-onset diabetes with β-blockers increased with duration of therapy. [15]

DIURETICS AND NOD

In our study the usage of diuretics also contributed to development of new onset diabetes**. 25% of NOD patients were on thiazide diuretics as compared to 11.3% of control group which was statistically significant**.

There are several studies supporting our result [16] one of them is quoted here.

In the analysis of 6 trials enrolling 30,842 patients with hypertension, diuretics resulted in a 32% increased risk of new-onset diabetes compared with placebo or non–β-blocker antihypertensive agents. Compared with placebo, diuretics resulted in a strong trend toward a 22% increased risk of new-onset diabetes, suggesting that the risk is due to the medication itself. When compared with antihypertensive agents other than β-blockers, diuretics conferred a 35% increased risk of new-onset diabetes. [15]

CONCLUSION

It is well known that diabetes itself is hallmark of complex atherosclerotic process with varying manifestations, causing morbidity and mortality. Coronary artery disease which is an end result of atherosclerotic vascular process has a bad impact on patient health. Presence of diabetes worsens the outcomes in a Coronary artery disease patient by many times. However, the occurrence of new onset diabetes in a coronary artery disease patient has not been studied well till date. With only miniscule data available on this subject, this study is a modest attempt to quantify the new onset diabetes in coronary artery disease patients after acute coronary syndrome.

This study highlights two important things, first incidence of new onset diabetes in acute coronary syndrome patients is High nearly three times more than the general population, Secondnot only the traditional atherosclerotic risk factors butdrugs like beta blockers, statins and diuretics also significantly affect the glucose homeostasis.

Thus early and regular screening of blood glucose of Coronary artery patients should be done to prevent, detect and treat diabetes mellitus so as morbidity and mortality can be decreased.

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