

## Review Article

# Profile of acute coronary syndrome in young diabetics: a review

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### ABSTRACT

The clinical presentation and angiographic findings of coronary artery disease (CAD) varies from diabetic and non-diabetic patients and varies with the age of presentation. Coronary artery disease in patients below the age of 45 is a special subset. The objective of this study is to compare the clinical and angiographic profile in patients with the acute coronary syndrome (ACS) with diabetes mellitus (DM) and without DM below the age of 45 years. Clinical Presentation of coronary artery disease in young patients with various risk factors differs, which plays an important role in management strategies. This was conducted through internet search on PubMed and ProQuest database from 2000 to until 2019. Key words used for searching are acute coronary syndrome, young diabetics, and clinical, angiographic profile. An important exclusion criterion is studies which included type one diabetic patients. Totally 35 papers were reviewed. Pattern of involvement of coronary arteries as assessed by the coronary angiographic study is found to be different in younger CAD patients. Atypical clinical presentation and distinct angiographic finding are common in diabetics below the age of 45. In most of the studies single vessel disease (SVD) is the most common angiographic finding in young CAD and non-diabetics. While the diabetics showed the more diffuse pattern of double vessel disease (DVD).

**Keywords:** Acute coronary syndrome, Coronary angiography, Coronary artery disease, Diabetes mellitus

### INTRODUCTION

Coronary artery disease is the major causes of death all over the world. Traditionally Coronary artery disease was considered as the disease of old age group. The incidence of coronary artery disease in the young is in an increasing trend now-a-days possibly secondary to risk factors like stress, sedentary life style, altered food habits, which in turn predisposes to the development of risk factors like DM, Metabolic syndrome obesity which in turn responsible for CAD.<sup>1</sup> Other unidentified noval risk factor like lipoprotein(a), prothrombotic factors also contributes to CAD in young.<sup>2</sup> The clinical presentation and the management strategies are different in younger cardiac patients from its older counterpart.<sup>3</sup> The reason

for the difference in the clinical presentation of CAD in younger age group is because of its varying pathophysiology and nature of coronary involvement and hence the management strategies also differs.<sup>4</sup> More aggressive intervention is required in many of them for improving the morbidity and mortality.<sup>5</sup> At present, the arbitrary age 45 years and below is taken as cutoff age to say young in most of the studies.<sup>6</sup> Among the modifiable and non-modifiable risk factors diabetes mellitus stands first in the list of the modifiable risk factor for coronary artery disease.<sup>7</sup>

In young patients the incidence of CAD is higher in people with DM of relatively new onset. The spectrum of CAD includes stable angina, unstable angina NSTEMI

and STEMI. The clinical presentation varies depending on the spectrum.<sup>8</sup> According to most of the western and Indian literature typical anginal pain and dyspnea before a coronary admission is less common in the younger age group with CAD than in the older age group.<sup>9</sup> This is one reason many of these patients reach hospital very late and hence the increase morbidity and mortality. Hence a high index of suspicion and low threshold for further evaluation is required in these young patients when they present with atypical symptoms especially, when they have risk factor like DM. Single vessel disease and LAD involvement is more common in young individuals.<sup>10</sup>

Economic burden to the country as well as the family is remarkable when a young member of the family suffers from cardiac illness, so studies in this area are very important to identify them at appropriate time and to investigate them properly and to plan a management strategy according to their need to reduce the socioeconomic burden to the country.<sup>5</sup> India is a developing country and the burden of diabetes mellitus and heart disease are increasing. Recently only few studies were published to find the difference between Young diabetic and non-diabetic CAD. Very few data's were available to compare the clinical and angiographic profile of Young CAD.

So tertiary care center like us may be an ideal center to study these young cardiac patients. Which may throw some light especially in taking preventive steps in the community.<sup>11</sup>

### **Search strategy**

This was conducted through internet search on PubMed and ProQuest database from 2000 to until 2019. Key words used for searching are acute coronary syndrome, young diabetics, and clinical, angiographic profile. An important exclusion criterion is studies which included type one diabetic patients. Totally 35 papers were reviewed.

## **REVIEW OF LITRATURE**

### **Demographic profile of young CAD**

Aggarwal et al, state that coronary artery disease occurring below the age of 45 are termed as young coronary artery disease.<sup>12,13</sup> Many spectra of terminology have been used for young coronary artery disease by various authors like Christus et al, proposed that age below 35 as very young coronary artery disease and Gupta et al, uses young coronary artery disease as the age group between 15-19 years.<sup>13</sup> Like young coronary artery disease another term used in various study was premature coronary artery disease, and multiple age limit used to describe early coronary artery disease vary with many studies like van loon et al, did a study in 2012 where he used age limit as below 45 for men and below 55 for female to name them as premature coronary artery

disease, but Genest et al used an age limit as 60 years for premature CAD. Precocious coronary artery disease and early-onset coronary artery disease are the other terms which were used in conjunction with young coronary artery disease.<sup>13</sup> current literature shows incidence and prevalence of coronary artery disease increases which was evidenced by many Indian biographies like in Tammi Raju et al study 1151 patients with a prevalence of 10.42%.<sup>14</sup> T Sekhar et al published a study during December 2014 and gives an incidence of CAD in young as 12-16%, this study also tells family history of CAD were present in 4.4% of men and 6% of women with first degree relatives.<sup>15</sup> The author also comments increased incidence of CAD is because of rapid urbanization and lifestyle changes.<sup>15</sup> On comparing the incidence and prevalence of coronary artery with the western population, the UK has a significantly low amount of Coronary artery disease with a prevalence rate of 0.5% in men and 0.18% in women. The causes for the low incidence in the western population is because of atypical presentation and reluctant to do investigation.<sup>15</sup> A study was conducted among type 1 diabetes mellitus patients by Starkman et al, and showed an incidence of 10.9%.<sup>9</sup>

Yuka Kotka et al, did a study to find the gender difference in young coronary artery disease, which shows 1653 young CAD subjects were studied, in which 70% of subjects were men and 30% of subjects were women.<sup>10</sup> The incidence and prevalence of coronary artery disease in females had a wide range of the spectrum. Literature states that during premenopausal age, women have a comparatively low rate of coronary artery disease, but postmenopausal women had similar incidence for coronary artery disease when compared to their male counterpart.<sup>7</sup> Among young female coronary artery disease patients had a poor prognosis and had a higher prevalence of heart failure when the patient had co-existing diabetes mellitus when compared to the older counterpart. Recently a study was published in the Journal of the American heart association in 2019 with a remarkable result and with a significant impact on present knowledge. This study states 12519 patients have included in the analysis, in which 30% of people were women. On detailed examination of the study, 5.8% of women were between 19-40 years of age, 14% of them were between 41-45 years of age, 29% of them were between 46-50 years of age, and 50% of them were between 51-55 years of age.<sup>16</sup> There are many factors that influence coronary artery disease in females like fertile age, menopause, oral contraceptive pills, hormones metabolic changes during pregnancy, labor, and therapeutic abortion.<sup>17</sup> Another study VIRGO study conducted among 3501 patients between the age group of 15 to 55 years with a mean age 48 years with the total female population of 2349 and males of 1152 and adding controversy to all other literature by having a high female ratio<sup>18</sup>. Family history of coronary artery disease play an essential role in the young coronary artery disease patients, Yuka Otaki et al, extensively discussed the correlation- family history of coronary artery disease and

occurrence of coronary artery disease in the younger population. This study identifies the high prevalence, and severe CAD was associated with patients having positive family history.<sup>19</sup> Bamberg et al. evaluated 195 patients, and he had 44 patients with a positive family history of coronary.<sup>6</sup> On the line, the next study by Sunman et al. evaluated 349 patients and showed above 150 patients a positive correlation with a family history of coronary artery disease, which made a high impact on positive correlation with a family history of Coronary artery disease.<sup>8</sup> But Rivera et al did a study among 1191 patients and conclude that there is no significant relation with family history.<sup>3</sup>

### **Clinical profile of young CAD**

Presenting symptoms of young ACS patients varies from Angina, atypical chest pain, dyspnea, and giddiness. Among multiple symptoms, UN Nagamalesh et al, states that 95% of patients presented with typical chest pain.<sup>4</sup> But another study shows young CAD patients denied any chest pain.<sup>20</sup> On comparing diabetic and, non-diabetic Atypical chest pain is more common in diabetic population.<sup>21</sup> When comparing young and older counterparts, atypical presentation is equally common in younger diabetic when compared to older counterpart.<sup>21</sup> Atypical symptoms include right sided pain, back pain neck pain jaw pain shoulder pain . On looking into the type of presentation STEMI is the most common type of presentation among young adults, and plaque rupture is the most common pathology leading to STEMI.<sup>2</sup> Between the period of 2003 and 2013, a study was conducted among more than 350 patients and conclude STEMI(59%) was the most common type of MI followed by NSTEMI(23%), unstable angina(17%) was the least common type.<sup>22</sup> Another article published in 2016 showed 680 ACS patients, of which 51% had ST-elevation myocardial infarction (STEMI), and 49% had NSTEMI-ACS.<sup>23</sup> On looking into the Thai ACS registry, Young CAD patients below the age group of 45 years had more incidence of STEMI 67%, followed by NSTEMI 19% and unstable angina 14%.<sup>1</sup> Anterior wall MI was most commonly involved in young coronary artery disease patients.<sup>2</sup> This study also states that the inferior wall is the second widely involved wall in young ACS patients. Another study published by Nagamalesh et al, also says that Anterior wall MI is the most common MI in young adults.<sup>4</sup> A survey conducted among young Indians around 2017 and showed that 47% of patients had anterior wall MI, 37% of patients had inferior wall MI, 7.5%, and 5% had inferior with posterior and inferior with RV MI. 10% of patients were presented with Non-ST-T segment MI.<sup>24</sup> Rajeev Bhardwaj et al, did a study in the young population and showed a STEMI of 95.15%, and NSTMI of 4.84% in that 70% had anterior wall involvement, 25% of patients had inferior wall involvement, and only 4% of patients had lateral wall MI.<sup>25</sup> In contrast, another study showed inferior wall was the most commonly involved followed by the anterior wall and lastly lateral wall.<sup>22</sup> Usually, ACS in young

diabetics presented as KILLIP class1(91%), and also most of the patients showed LV function above 55%.<sup>22</sup> Diabetic patients had an increased prevalence of higher Killip class at the time of presentation when compared to nondiabetics.<sup>26</sup> Irrespective of age, when diabetes is associated with CAD for more than four years patient will have low ejection fraction when compared with non-diabetic patients.<sup>27</sup> In young diabetics, LV diastolic function got affected more than the systolic function. Impaired diastolic function because of the deposition of heavily glycosylated protein in the left ventricle and cardiac fibrosis, which increases the cardiac stiffness and causing diastolic dysfunction. Higher HbA1C levels were associated with low LV-EF and diastolic dysfunction by creating altered E'/A'. When left ventricular relaxation and compliance were affected which lead to E'/A' ratio below 127. In MI while comparing KILLIP classification between diabetic and non-diabetic population, there is a significant difference between Killip classification was higher Killip classes are higher in the diabetic group which made them more prone to higher mortality.<sup>28</sup> On comparing the age group below 40 and below 55 there is a significantly worsening LV ejection fraction when age increases that is 8% of severe LV dysfunction case when compared with 48% of LV dysfunction seen in patients below 55 years of age.<sup>5</sup> Mechanical and electrical complications were high in diabetic patients when compared with nondiabetics.<sup>26</sup> Since complications are higher in the diabetic population, overall in hospital mortality is high in diabetic CAD.<sup>26</sup> Thrombolysis was the most common treatment modality of choice in a STEMI patient. Many factors affect the result of thrombolysis in a STEMI patient, diabetes plays an important role, which had caused a higher rate of failed thrombolysis when compared with nondiabetic patients.<sup>11</sup>

### **Coronary involvement of CAD in the young**

Coronary angiogram is the gold standard investigation for coronary artery disease. Significant coronary artery disease is the term which is used when the coronaries had stenosis of 50% in the arterial lumen in arteries like Right and Left main coronaries. In the branches, if the stenosis was more than 70% is called as significant coronary artery disease.<sup>29</sup> Coronary artery disease in young is a special subset. Though STEMI is more common type of MI in younger age group Zimmerman et al, conducted a study among 24000 and concluded that 22% of men and 34% of women participated in the survey shows normal non-obstructing coronary when compared with their older counterpart (18%-22%) and also conclude generally among young adult SVD is more common than double vessel disease.<sup>29</sup> Another study conducted in young Indian CAD patients where Critical stenosis was found in 80% of patients with mild to moderate level of stenosis were found in 8% of patients, On analysing the pattern of involvement of coronaries Single vessel disease predominates with 51% followed by Double vessel disease of 27%, least probability to Triple vessel disease 7%.<sup>25</sup> Next on line Nagamalesh et al, did a study

in Karnataka which also supports the fact that single vessel disease is the most common type of coronary artery involved in which 49% had Left anterior descending involvement and 21% had left circumflex involvement and only 6% had right coronary artery involvement.<sup>4</sup> To create confusion igavarapu et al did a study in the young Indian population were it showed LAD artery was frequently involved artery but on contradicting the above statement left coronary artery is the least involved in this study.<sup>5</sup> To get rid of confusion on looking in to the Tamil nadu literature which was given by Narayanasamy et al, and showed significant proximal LAD stenosis was seen in 37% of patients, 27% had mid LAD lesion and 38% had distal LAD lesion. Diffuse involvement was seen in only a low percentage of patients, followed by RCA and LCX lesion. LCX has more common distal involvement, RCA has more mid involvement.<sup>30</sup> Cardiac involvement in people with diabetes was distinct, many reasons were proposed for distinct cardiac involvement in diabetics, like hyperglycemia, insulin resistance, and hyperinsulinemia. Other mechanism proposed for cardiac abnormalities in people with diabetes were failure of renin-angiotensin-aldosterone system, oxidative stress, coronary endothelial dysfunction and coronary microvascular abnormalities.<sup>31</sup> Cardiac Involvement in people with diabetes varies with male and female. Usually, LV dysfunction is seen in diabetics on looking the difference between the two sex males had higher systolic dysfunction which manifests as a reduction in EF, but females mostly manifest as diastolic dysfunction in the absence of LVH with preserved ejection fraction. On follow up diabetic male were at higher risk of developing heart failure with reduced ejection fraction n contrary females are at higher risk of developing heart failure of preserved ejection fraction.<sup>31</sup> On looking into the angiographic profile of diabetics a study that was published in circulation showed the incidence of triple vessel disease was high in diabetics when compared with nondiabetics. More importantly, diabetics had multiple stenosis, long-segment stenosis, and diffuse lesion.<sup>32</sup> While analyzing the frequency of involvement of coronaries in diabetics and non-diabetics, many studies tell the involvement of the Left anterior descending artery and left circumflex artery is more than other vessels.<sup>32</sup> Another study was conducted in northern Asia, which gives information about the response of the Asian coronary artery to the effect of diabetics which shows multi-vessel involvement is more common in diabetics, that to left anterior descending artery (38%) involvement is more common.

Among various types of LAD involvement, proximal stenosis was the most commonly involved type.<sup>33</sup> Usually, males are a higher risk of development of Coronary artery disease when compared to females but diabetics will reduce the sex difference and put male and female patients in the same risk for CAD.<sup>33</sup> On comparing diabetics and non-diabetics proportion of obstructive CAD was high in diabetic population.<sup>34</sup>

## DISCUSSION

Study showed that atypical presentation was more common in Diabetic patients. STEMI was the most common type of MI In both diabetic and non-diabetic population. Severe LV dysfunction are more common in diabetic population. Anterior wall MI was the commonest type of MI in both the diabetic and non-diabetic population. On analysing the Angiogram SVD was common in both the groups and LAD was the commonest involved vessel. Among Diabetic population patients with higher HBA1C more than 10, had significantly increased proportion of multiple vessel involvement than patients with lower HBA1C.

In the literature studies showed men had higher incidence of CAD at younger age than women, which was similar to our study. Women had cardio protective effect due to estrogen in younger age group.<sup>12</sup> Patients presented with typical chest pain and atypical chest pain in equal proportion. Atypical chest pain was more common among diabetics. Other studies in the literature showed typical chest pain was found to be the most common presenting symptom in both diabetics and non-diabetics.<sup>5</sup> Our study has 62% of STEMI, 25% of unstable angina and 12% of NSTEMI. In the literature most of the patients had higher incidence of STEMI in young CAD which was similar to our study.

Both the World and Indian literature say most commonly affected part of heart in young CAD with STEMI was anterior wall of left ventricle. LV Ejection fraction is studied in all patients admitted with CAD below the age of 45 years, which showed Normal LV function in most of the individuals. This correlates well with the study done by others. Angiographic pattern of Young CAD patients is distinct from angiographic pattern of patients with CAD in older age group.

SVD was the most common type of angiographic pattern in all studies globally, with highest incidence of 67% was seen in a study done by Tammiraju et al and lowest incidence of 39% seen in a study done by Zimmerman et al. One study had an incidence of 48% of SVD ,18% of DVD and 7% of TVD among diabetic population.<sup>17</sup> Others had showed a similar SVD was the most commonly affected vessel followed by DVD and TVD.<sup>15</sup> On comparing the Angiographic pattern of CAD patients below the age of 45 years in various studies, Left anterior descending artery is the most commonly involved artery.

In diabetics LCX, involvement was 18.2% in reference study. RCA involvement in diabetics was 15.4% in reference study. RCA involvement in non- diabetics was 9% in reference study.<sup>19</sup> In studies Patients with HbA1c level between 5-10% had 85% of SVD followed 11% of DVD and 3% of TVD but patients with HbA1c level above 10% had 24% of SVD and 54% of DVD and 20% of TVD. This is also similar to world literature.

Limitations of the study are a smaller sample size. A follow up study is needed to find the long-term outcome of the younger patients with MI, both in the diabetics and non-diabetics; particular emphasis given to the cardiac remodeling.

## CONCLUSION

On reviewing we found asymptomatic status and atypical presentation are more prevalent in young patients with CAD, more so in diabetics. The pattern of coronary artery involvement in young individuals is different from the old age. Single vessel disease is the most common finding which did not differ between diabetics and non-diabetics. Left anterior descending artery is the most commonly involved vessel in most of the study. Among the patients with multiple vessel disease, diabetes mellitus was most commonly seen. In diabetics with higher HbA1C level were associated with multiple vessel involvement.

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