CHAPTER 7
Metabolic Syndrome and CAD

7.0. Introduction

Metabolic syndrome (MS) refers to a constellation of metabolic risk factors such as central obesity, hypertension, glucose intolerance (type 2 diabetes, impaired glucose tolerance or fasting glycemia), IR, atherogenic dyslipidemia characterized by low high density lipoproteins (HDL-C) and high triglycerides which predispose the individual to increased risk for development of diabetes mellitus and cardiovascular diseases (Misra and Vikram, 2008; Balkau, Valensi, Eschwege and Slama, 2007; Das and Rao, 2007; Reaven, 1988). It serves as a valuable tool in the identification of individuals at risk for diabetes and CAD. Epidemiological studies have reported a high prevalence of MS and cardiovascular mortality among non-resident Indians settled abroad (Kamath et al. 1999; Enas et al. 1996; McKeigue et al. 1993). Lifestyle factors appear to play an important role as BMI, especially abdominal obesity, and dyslipidaemia worsen with urbanization and migration (Sarkar et al. 2006; Misra and Vikram, 2004).

7.1. Background of the study

The incidence of type 2 diabetes mellitus coupled with CAD is rising worldwide, mostly due to the increasing prevalence of BMI and a longer life expectancy (Mokdad et al. 2001). Insulin resistant patients are at an increased risk of developing MS, a major cause of heart disease and dyslipidaemia (Evans, 2007).
The pathogenesis is still unclear, although environmental factors such as diet and physical activity, coupled with still largely unknown genetic factors, clearly interact to produce this syndrome (Laaksonen, et al. 2002). IR is considered as the chief underlying pathophysiology in MS and is found to be associated with cardiovascular disease, in a family study (Isomaa, et al., 2001), in community based samples (Malik, et al., 2004; Sattar, et al., 2003) and in primary preventive settings (Hunt, et al., 2004; Lakka, et al., 2000). The afore-mentioned observations paved way for the inclusion of MS identification in guidelines for the prevention of cardiovascular diseases in clinical practice (De Baker, 2003). Several organizations have proposed slightly different criteria for MS (Zimmet, Alberti and Shaw, 2005; Expert Panel, 2001; Balkau and Charles, 1999; Alberti and Zimmet, 1998). Different definitions of MS have been framed by the WHO, European Group for the Study of Insulin Resistance (EGIR) ATP III, American Association of Clinical Endocrinologists (AACE), and recently the International Diabetic Federation (IDF). Even though most of these agree on fundamental components namely glucose intolerance, obesity, hypertension and dyslipidemia, they vary with respect to the cut-off points for the criteria of each component of the cluster and the mode of combining them to characterize MS. Moreover, most of the prior reports on MS have been derived from studies on Europeans. Asian Indians have very higher rates of DM (Wild, et al., 2004) and premature CAD with high severity (Anand, et al., 2000a); keeping these distressing observations in mind, special waist cut-off have been proposed for Asians (WHO, 2000). The IDF and WHO have called for more studies employing different criteria for MS in diverse ethnic inhabitants. Hence a
case-control study was proposed to estimate the prevalence of MS in angiographically confirmed CAD and Non-CAD subjects and also to associate the various components of MS with the severity of CAD, family history and smoking, adopting ATP-III guidelines.

7.2. Literature Review

Asian Indians are reported to have high rates of type 2 DM, MS, CAD and related complications in the US, Canada, and UK (Mohanty, Woolhandler, Himmelstein and Bor, 2005; Chandie Shaw, et al., 2002; Anand, et al., 2000b; Hughes, et al., 1997; Enas, et al., 1996; Ramaiya, Denver and Yudkin, 1995; McKeigue, et al., 1993; McKeigue, Pierpoint, Ferrie and Marmot, 1992; Samanta, Burden and Jagger, 1991; Omar, et al., 1985). Moreover, they have the highest ethnic-specific prevalence of CAD, with age-specific mortality two to three times higher than Caucasians (Wild, et al., 1995; Enas, et al., 1996; Enas and Senthilkumar, 2001). IR is highly prevalent in Asian Indians, despite low rates of BMI (Whincup, et al., 2002; McKeigue, 1996; McKeigue, Pierpoint, Ferrie and Marmot, 1992). Long-established risk factors such as hypertension, BMI, and hypercholesterolemia do not account completely for these high rates. Prevalence of DM and related conditions among Indians was assessed by Venkataraman et al. (2004) using a faith-based sample in Atlanta, GA. The overall prevalence of DM was 18.3% (22.5% in men and 13.6% in women). Mohanty, Woolhandler, Himmelstein and Bor, (2005) compared 555 Asian Indians to 87,846 non-Hispanic whites in the NHIS dataset from 1997 to 2000 and reported that the former had significantly higher odds of having diabetes. However, they also reported lower
CAD and hypertension rates, in contrast to prior studies that showed much higher age-standardized CAD rates and related mortality in this ethnic group. Data from national surveys are limited due to small sample sizes or aggregation of ethnic data into a heterogeneous group of “Asian Americans” or “Asian and Pacific Islanders”. Population-based national studies on prevalence and risk factors for DM and CAD among South Indians are currently lacking.

Indians, the third largest and fastest growing Asian group, are hugely diverse, with many languages, religions, racial types, social habits, cultural practices and diets (Gupta, 2000). Indians have marked variations in educational attainment, income, and wealth, and a significant number lack education and job skills (Rangaswamy, 1995). Previous cohorts comprise both highly educated professionals and individuals who lack education and job skills (Rangaswamy, 1995). This investigation makes it imperative to use large, randomized samples to determine disease prevalence and risk factors. Previous studies of Indian health have employed hospital-based or convenience samples (Abate, Garg and Enas, 1995; Enas et al., 1996; Banerji et al., 1999; Raji, Seely, Arky and Simonson, 2001; Venkataraman et al., 2004). Hence a study was carried out in a randomly selected cohort of South Indians to determine the prevalence of MS and its association with CAD risk factors.
7.3. Methodology

This study evaluated the association between the components of MS in patients between the age group of 35-65 years, admitted with a suspicion of CAD, in the cardiac care centre and diagnosed to have CAD or no CAD by angiography. MS was diagnosed based on the modified ATP III guidelines (Expert Panel, 2001), if three or more of the following were present: abdominal obesity (definition of abdominal obesity was modified using Asia-Pacific WHO guidelines as waist circumference ≥ 90 cms for males and ≥ 80 cms for females (World Health Organisation, 2000), hypertension (subjects who were on antihypertensives medication and/or had systolic pressure ≥ 130mmHg and / or ≥ 85mmHg), glucose intolerance (fasting blood glucose ≥110mg/dl), hypertriglyceridemia (fasting TG ≥ 150mg/dl) or low HDL-C levels (males: HDL-C < 40 mg/dl, females: HDL-C < 50 mg/dl).

Statistical analysis:

Descriptive statistics were used to summarise the clinical findings, risk factors, and coronary angiographic findings of patients. Chi-square analysis was used to estimate the prevalence of MS with respect to the severity of CAD, family history of CAD and smoking history. The association between individual risk factor and outcome was estimated using univariate logistic regression. The multivariate logistic regression analysis was used to estimate the components of MS as a risk factor for CAD, controlling the other confounders. The value of P<0.05 was taken as significant.
7.4. Results

The prevalence of components of MS in CAD subjects (n=125) was higher (70.4%) than subjects without CAD (66.4%) (Figure 51). Among the components of MS, waist circumference of >90 cms was found in 67 (67.05%) in males diagnosed with CAD and 36 (34.95%) with no CAD; while in contrast waist circumference of > 80 cms was observed in 21 (25%) in females patients diagnosed with CAD and 63 (75%) patients with no CAD; a blood pressure of ≥ 130/85 mmHg was observed in 75 (63.56%) patients with CAD and 43 (36.44%) patients with no CAD; a fasting blood sugar of ≥ 110mg/dl was found in 75 (53.19%) patients with CAD and 66 (46.81%) patients with no CAD; a triglyceride levels of ≥ 150mg/dl was found in 78 (55.71%) patients with CAD and 62 (44.29%) patients with no CAD; an HDL-C of ≤ 40mg/dl was found in 52 (65.82%) males with CAD and 27 (34.18%) males with no CAD and HDL-C levels of ≤ 50mg/dl was found in 20 (23.81%) females with CAD and 62 (44.29%) females with no CAD.

Diabetic subjects with (88.24%) and without (87.93%) CAD had significantly higher % of MS when compared with non-diabetic subjects without CAD (47.76%) and non-diabetic subjects with CAD (49.12%) (P <0.001) (Figure 52). A mounting trend in level of MS was observed with the increasing severity of CAD: SVD (58.82%) < TVD (73.21%) < DVD (77.14%), when compared with normal coronary arteries (NCA) (No CAD) (66.4%) but was not found to be statistically significant (P=0.176) (Figure 53). Also an attempt was made to correlate the extent of myocardial ischemia in subjects with CAD as
computed by Gensini scoring system with the MS. Among 125 CAD patients, 88 had MS while 37 patients had no MS. The Gensini scores (Mean ± SEM) in patients having MS was higher (47.44±3.22) when compared to patients having no MS (36.62±3.19) (Figure 54).

An additional goal of CAD screening program should be the earlier identification of high-risk individuals with MS, having smoking history (who can be targeted for smoking cessation) and family history of CAD.

![Graph showing percentage of MS in relation to CAD](image1)

**Figure 51: Percentage of MS in relation to CAD**

![Graph showing percentage of MS in relation to CAD and DM](image2)

**Figure 52: Percentage of MS in relation to CAD and DM**
Metabolic Syndrome and CAD

Figure 53: Percentage of MS in relation to angiographic severity of CAD

Figure 54: MS in relation to Gensini scores

Figure 55: Percentage of MS in relation to family history of CAD
Figure 56: Percentage of MS in relation to smoking

In our analysis (Figure 55), in the total study population (n=250) percentage of MS-a strong determinant risk factor of CAD, was higher in patients with family history of CAD (78.18%) in contrast to patients having no family history of CAD (50.86) which was statistically significant (P<0.001). Also our study showed that the percentage of prevalence of MS was comparatively lower in non-smokers (46.7%) and ex-smokers (62.2%) than smokers (65.2%) (Figure 56). These findings suggests that patients having MS coupled with positive family history of CAD and smoking history can become highly vulnerable subjects to develop premature CAD.

Figure 57: Percentage of MS score in relation to CAD
The functional markers to diagnose MS include three or more of the following: dyslipidemia with low serum HDL-C, elevated TG and total cholesterol; higher abdominal obesity (waist circumference), blood pressure, and fasting glucose. In the present study on 125 patients with CAD, 3% patients had no functional markers of MS (0 MS); 11.2% had an expression of one functional marker (1 MS); while 20% had two functional markers of MS. 32% had three (3 MS) and 33.8% had four (4 MS) functional markers of MS respectively. A mounting trend in the percentage of markers of MS occurrence in study population with CAD substantiates the fact that MS is a strong predisposing factor of CAD (Figure 57).

Table 21: Multiple logistic regression analysis using CAD as dependent variable

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio [OR]</th>
<th>95% Confidence Interval [CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent variable: Metabolic syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1: MS - Unadjusted</td>
<td>1.2</td>
<td>0.68 – 2.13</td>
<td>0.49</td>
</tr>
<tr>
<td>Model 2: [Model 1 + adjusted for age and gender]</td>
<td>1.86</td>
<td>1.012 – 3.457</td>
<td>0.045</td>
</tr>
<tr>
<td>Model 3: [Model 2 + FBS]</td>
<td>2.34</td>
<td>1.21 – 4.51</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Multivariate logistic regression analysis was carried out to find the independent association of MS with CAD (Table 21). Areas under the curve of Model 1 (MS – Unadjusted), Model 2 (Model 1 + adjusted for age and gender), and Model 3 (Model 2 + FBS) of regression model were 1.2 (95% CI, 0.68 – 2.13, P = 0.49), 1.86 (95% CI 1.012 – 3.437, P=0.045) and 2.34 (95% CI 1.21 – 4.51, P=0.011), respectively. The logistic regression model incorporating with age,
Metabolic Syndrome and CAD

gender and other major risk factors of atherosclerosis may be useful for screening CAD in patients with type 2 DM. In this case, MS showed a strong association with CAD and diabetes, even after adjusting for age, gender and fasting blood sugar.

7.5. Discussion

The occurrence of MS in various ethnic groups - including Caucasians, Africans, Latin Americans, Asian Indians, Chinese and Aboriginal Australians has been substantiated in numerous epidemiological studies. In developing countries, the lifestyle changes as a result of rapid industrialization and rural-urban migration, is chiefly associated with reduced levels of physical activity and increased intake of energy. The consequent rise in obesity rates has led to a massive increase in prevalence of MS in developing regions. However clear-cut statistics for its prevalence are unavailable. This can be partly explained due to the lack of an internationally accepted definition for MS. Different definitions have been formulated by WHO, US National Cholesterol Education Program Adult Treatment Panel III and IDF (Mohan and Deepa, 2006). People with MS are twice as likely to die from, and three times as likely to develop, MI or stroke when compared to people without MS. The increased risk of CAD which is associated with MS is multifactorial. Blood pressure, BMI, HDL-C, waist circumference, TGL and fasting glucose plays a prominent role in it. Both the MS and type 2 diabetes are commonly associated with an abnormal lipoprotein phenotype which is characterized by increased blood pressure (≥130/85mmHg) and BMI (>30kg/m²), decreased HDL-C and an accumulation of small dense LDL-C.
Metabolic Syndrome and CAD

particles with the levels of LDL-C being often normal (Sinderman, et al., 2002). A number of lipid related parameters have been used to predict the risk of coronary artery disease (CAD). According to Grover, either the evaluation of BMI or fasting glucose is the best related predictor of future cardiovascular events (Grover, Levinton and Paquet, 1999), where as blood pressure and HDL-C were shown to be more accurate predictors of coronary heart disease (Gotto, 1998).

BMI, which is reported to play a key role in the pathogenesis of MS, promotes inflammation, hypertension and dyslipidaemia, thus leading to the development of type 2 DM and atherosclerosis (Ceska, 2007). Moreover, a higher BP is a strong risk factor for CAD (Chobanian, et al., 2003). Abdominal fat which is associated with BMI, a characteristic feature of the MS, is a major source of the excessive flux of free fatty acids which are known to have pro-arrhythmic properties. The prolonged release of free fatty acids is implicated in the development of type 2 DM, since it promotes IR and the associated loss of pancreatic-cell function (Charles, et al. 1997). Patients with type 2 DM are at an increased risk of cardiovascular morbidity and mortality. The significant increase in fasting glucose, BP and the BMI of diabetic patients with MS when compared to the type 2 DM patients without MS, predicts that patients with type 2 DM with MS are at a higher risk level for CAD. This is in agreement with the fact that IR induces several metabolic changes such as hyperglycaemia, dyslipidaemia and perhaps to a lesser extent, hypertension, which all contribute to the development of atherosclerosis (Wassink, et al., 2008). The clinical management should be focused
on multifactorial intervention to address all the associated cardiovascular risk factors.

In the present study, MS was found in 70.4% patients diagnosed with CAD and 66.4% in patients without CAD based on modified ATP III guidelines. This guideline was particularly preferred as it is widely used globally with proven validity (Kahn, Buse, Ferrannini and Stern, 2005). The prevalence of MS was higher in diabetic subjects with and without CAD when compared with non-diabetic subjects. Moreover MS proved to be an independent risk factor for CAD even when adjusted for confounding variables like age, gender and fasting blood sugar. The ICMR task force collaborative study reported the prevalence of MS to be 30 per cent in urban areas of Delhi and 11 per cent in rural Haryana using ATP-III criteria (IC Health, 2008). Mishra, et al. (2001) reported 30 per cent prevalence among the urban slum population in Delhi. Ramachandran et al (1992) reported a prevalence of 41 per cent in urban area of Chennai using modified ATP-III criteria among adults aged 20 to 75 years. They also reported that prevalence was higher in women than men (46.5 vs. 36.4%) and in older people. In contrast, Sarkar, et al. (2006) reported 30-50 per cent prevalence in Bhutia tribe, with no rural-urban difference. Among the Toto tribe, the rural community prevalence was low 4-9 per cent (Sarkar, et al., 2006). The prevalence of MS among Asian Indian males is higher than that reported among African Americans but similar to Non-Hispanic Whites and Mexican Americans (Ford, Giles and Dietz, 2002). The differences may be attributed to the variations in study areas, and the different definitions of MS used. Waist circumference of ≥ 90cms in males and ≥ 80cms in females, a
fasting blood glucose of ≥ 110mg/dL, triglyceride levels of ≥ 150 mg/dL and HDL-C levels of ≤ 40mg/dL in males and ≤ 50mg/dL in females were observed to be major components of MS in patients with CAD and no CAD in the present study. A blood pressure of ≥ 130/85mmHg was found in majority of patients with CAD (63%); whereas 62% of patients with no CAD had a blood pressure of ≤ 130/85 mmHg.

Furthermore, there was a higher prevalence of MS among the smokers (65.2%), in patients having FH-CAD (79.8%, P<0.001) and high degree of coronary artery stenosis (DVD (77.14%); TVD (73.21%)). The causes of the MS are likely to reflect the inter-play of genetic and environmental factors. Current study confirms that genetic factors contribute to the concentration of the MS and its components within family groups. This is in agreement with the statement given by Mohan, Balasubramaniam and Radha, (2005) that there exists a wealth of evidence, revealing a stronger genetic predisposition for diabetes and MS in Asian Indians.

7.6. Conclusion

The higher prevalence of MS in diabetics with and without CAD than non-diabetic patients, predicts that patients with type 2 DM with MS are at a higher risk level for CAD. The magnitude of MS was higher among urban subjects of South India as compared to reported values in rural areas. The findings of this study emphasize the fact that there is a dire need to avert this escalating global epidemic. The most important first-line management is to decrease the risks of cardiovascular
Metabolic Syndrome and CAD

An investigation into the relationship of insulin and other related biochemical parameters with coronary artery disease in a South Indian population

disease and diabetes. Simple life style modifications like regular physical activity and even modest weight loss would lessen the burden of this syndrome. Thus community-wide efforts to improve health awareness are crucial to decrease the morbidity and mortality resulting from MS in developing countries.
Metabolic Syndrome and CAD

References


Metabolic Syndrome and CAD


Metabolic Syndrome and CAD


The Asia Pacific perspective: redefining obesity and its treatment. Regional Office for the Western Pacific of the World Health Organisation. 2000, World Health Organisation International Association for the study of the obesity and
Metabolic Syndrome and CAD

An investigation into the relationship of insulin and other related biochemical parameters with coronary artery disease in a South Indian population


