Pak Heart J

IMPACT OF HYPERINSULINEMIA ON MORBIDITY AND MORTALITY FOLLOWING ACUTE MYOCARDIAL INFARCTION

Syed Farhat Abbas Shah[1], Mohammad Hafizullah[2], Taufiq A. Mufti[3], Abdul Hadi[4], Syed Tahir Shah[5]

[1-5] Department of Cardiology, Lady Reading Hospital & Khyber Medical University, Peshawar - Pakistan

Address for Correspondence:
Dr. Syed Farhat Abbas Shah,
Assistant Professor
Department of Cardiology,
Lady Reading Hospital, Peshawar - Pakistan

E-mail: fashah2010@yahoo.com

Date Received: July, 22 2011
Date Revised: August, 30 2011
Date Accepted: September, 7 2011

Contribution
All the authors contributed significantly to the research that resulted in the submitted manuscript.

All authors declare no conflict of interest.

ABSTRACT

Objective: To study the association of hyperinsulinemia, insulin resistance and its impact on morbidity and mortality following acute myocardial infarction (AMI).

Methodology: This prospective observational study was carried out at cardiology department, Lady Reading Hospital, Peshawar from May to December 2008. A total of 110 patients with first acute myocardial infarction were assessed for fasting insulin and grouped on the basis of normal or high insulin level. The patients were given standard therapy and evaluated for morbidity and in hospital mortality.

Results: More patients in high insulin group were obese (72% vs. 23%, p=0.001), hypertensive (70% vs. 23%, p=0.001), diabetic (70% vs. 16%, p=0.001) and had higher evidence of heart failure i,e Killip class II & III(60% vs. 34%, p=0.04) and Killip class IV(20% vs. 7%, p=0.17). These patients also had higher fasting glucose (158% ± 25 vs. 103 ± 18 mg/dl, p=0.02) and triglyceride (245 ± 40 vs. 165 ± 35 mg/dl, p=0.01). More patients among non survivors had high insulin (80% vs. 38%, p=0.002) in survivor group.

Conclusion: Hyperinsulinemia is positively associated with obesity, diabetes, hypertension and higher morbidity and mortaliy following acute myocardial infarction.

Key Words: Hyperinsulinemia, Acute myocardial infarction, In-hospital Morbidity and Mortality.

INTRODUCTION

The role of raised levels insulin in development of coronary artery disease (CAD) has been debated for many years. Insulin is a vascular growth factor causing smooth muscle cell proliferation and increased lipid uptake by these cells and fibroblasts enhancing their conversion to foam cells posing an additional risk of CAD in patients with diabetes mellitus and hypertension.[1]

A number of studies have suggested a definite role of hyperinsulinemia in the genesis of CAD.[2,3] Some studies[4,5] support the link between insulin level and atherosclerotic lesion while other have questioned it.[6] There is increasing evidence that potentially atherogenic abnormalities are consistently found in subjects with high insulin level including diabetes mellitus, obesity, hypertension, high triglyceride (TG) and low HDL.[7–12] This association has been termed syndrome X by Reaven and it explains the risk of developing diabetes and CAD. Syndrome X is said to be present when 3 of 5 components are present.[13] This syndrome is getting much interest for more than 10 years but data on the syndrome's association with acute myocardial infarction (AMI) & stroke morbidity is limited. In a recently conducted study this syndrome was significantly associated with AMI & stroke both in men & women.[14] Among its component conditions insulin resistance, hypertension & high TG were independently & significantly related to AMI and strokes.[14]

Another study compared the association of low insulin sensitivity (by checking frequently sampled IV glucose tolerance test) with CAD independent of other CAD risk factor and found that low insulin is associated with CAD independently of and stronger than plasma insulin level.[15] Proinsulin is a precursor of insulin and higher concentration of proinsulin in the body is indicative of insulin resistance state. Patients with high proinsulin concentration when treated for hypertension especially with B-blocker and diuretics may worsen their already unfavorable metabolic status thereby increasing the risk of AMI.[16] In one cohort study, it was found that the incidence of AMI significantly increased in patients treated for hypertension as a compared to those who were not.[17]

The Standard technique to identify insulin resistance is through euglycemic clamp; however, that is time consuming, laborious and much complicated. Fasting insulin has been shown to be simple indicator of insulin resistance.[18] Hence we measured fasting insulin in our patients. This short-term study was planned to see the association of hyperinsulinemia in patients with CAD and whether it has any impact on morbidity and mortality following Acute Myocardial infarction (AMI).

METHODOLOGY

This prospective study was carried out at cardiology department, Lady Reading Hospital, Peshawar, from May 2008 to December 2008.Patients of both gender and age less than 70 years, with first acute myocardial infarction were included, using non-probability purposive sampling. Informed consent was taken from the patient. Patients with age more than 70 years, second myocardial infarction, life threatening co-morbidity like strokes, malignancy advanced renal or pulmonary diseases were excluded from study.

The patients were assessed for evidence of heart failure according to Killip classification and their in hospital mortality was observed. Body mass index (BMI) was calculated and patients were declared obese when their BMI was greater than 26kg/m^2. Killip Class was defined as: I; Basilar rales in both the lungs, II; Rales present upto the mid of the chest, III; Rales present in more than mid of the chest and IV; Chest full of rales with cold peripheries and un-recordable blood pressure. Acute Myocardial Infarction (AMI) was defined as ST segment elevation was measured in millimeters at 80msec beyond the J-point, ST elevation of at least 2 mm in 2 or more leads on 12 lead ECG.

Fasting insulin level was checked on two occasions and average level was calculated by HRTF Insulin Assay by CISBIO BIOASSAYS. Patients were divided into two groups according to their fasting insulin level.

Group 1 = Insulin $\leq$ 17 Micro unit/ml

Group 2 = Insulin $>$ 17 Micro unit/ ml

Data was analyzed by SPSS version 12. All categorical variables were described as percentages and continuous variables as mean $\pm$ standard deviation. Difference between categorical variable were tested by chi square test. Continuous variables were compared by student t-test. Statistical significance was defined as $p < 0.05$.

RESULTS

A total of 110 patients with acute myocardial infarction were enrolled for the study out of which 64 had normal insulin level and 46 had high insulin level. They were compared for baseline characteristics, and in hospital morbidity and mortality.

Both the groups were comparable regarding age, sex site of AMI, smoking habits and thrombolytic therapy (Table 1).

High insulin group also had higher fasting glucose (158$\pm$15 vs. 103 $\pm$18 mg/dl, p=0.02), and TG (245$\pm$ vs. 165$\pm$35 mg/dl, p=0.01), however, there was no difference in cholesterol between the two groups (Table 2).

Patients in the non–survivors group were diabetics (80% vs. 34%, p=0.24), hyperinsulinemics (80% vs. 38%, p=0.002)

Table 1: Baseline Characteristics of two groups

Variables	Normal Insulin n=64	High Insulin n=46	P-value
Age	52±8	54±7	0.19
Sex			
Male	54(84%)	38(82%)	0.21
Female	10(16%)	8 (18%)	0.16
Hypertension	15(23%)	32(70%)	0.001
Obesity	15(23%)	33(72%)	0.001
Smokers	20(31%)	9(20%)	0.11
Diabetics	10(16%)	32(70%)	0.001
Non diabetics	54(84%)	14(30%)	0.017
Anterior MI	30(46%)	28(60%)	0.22
Streptokinase	46(72%)	34(74%)	0.13
Killip Class			
I	38(59%)	9(20%)	0.01
II & III	22(34%)	28(60%)	0.04
IV	4(7%)	9(20%)	0.17

Table 2: Comparison of Lab finding in two groups

Variables	Normal Insulin (n=64)	High Insulin (n=46)	P-value
Glucose	103±18mg /dl	158±15 mg/dl	0.02
Insulin	9.8±7.5 micro unit/ml	29.7±7.2(Micro unit/ml	0.02
Triglyceride	165±35mg/dl	245±40mg/dl	0.01
Cholesterol	195±24 mg/dl	192±27mg/dl	0.16

Table 3: Comparison of Survivors and Non-survivors

Variables	Non-survivors n=10	Survivors n=100	P-value
Age	58±7	53±8	0.26
Male	7(70%)	85(85%)	0.29
Hypertension	5(50%)	42(42%)	0.20
Obesity	6(60%)	37(37%)	0.19
Smokers	4(40%)	25(25%)	0.11
Diabetics	8(80%)	34(34%)	0.24
Anterior MI	8(80%)	50(50%)	0.19
Streptokinase	5(50%)	75(75%)	0.30
Hyperinsulenemic	8(80%)	38(38%)	0.002
Killip Class			
I	0	59	0.001
II & III	3	40	0.001
IV	7	1	0.17

and had evidence of cardiac failure i,e Killip class II& III(40% vs. 3%, p=0.001) IV(7% vs. 1%, p=0.17) (Table 3).

DISCUSSION

Epidemiological studies have documented that fasting hyperinsulinemia is a predictor of CAD in non diabetic patients, independent of other risk factors.[19,20] A number of studies confirm that syndrome of insulin resistance is more prevalent in south East Asians (Pakistan, India, Bangladesh) than Western population. [20-23] Established risk factors for CAD including smoking, hypertension, and high cholesterol do not explain the high rates of CAD in South Asians. The prevalence of diabetes mellitus is high in these subjects but this too cannot explain more than a small excess CAD mortality in this group.

Experimental studies suggest that abdominal adipose tissue is a major source of cytokines, including interleukin-6, which is an important determinant of hepatic C-reactive Protein (CRP) syntesis. [24-27] The only known environmental influence on insulin resistance is dietary energy intake,[28] and physical activity.[29] Diabetes and other associated metabolic disturbances associated with insulin resistance in South Asians may be the consequence of low physical activity and non balanced diet.

Our study population belonged to city of Peshawar where meat intake in the form of "Tikka Karahi" is quite popular. Despite this form of food intake the mean cholesterol level was not raised rather it was in the upper range of normal. It is common teaching to recommend vegetable and fish to prevent the genesis of atherosclerosis or delay the progress of atherosclerotic lesions. These preventive measures, however, have not been shown to be useful in Hindus (Vegetarians) and Bengalis (Fish eaters) who equally share the disease profile.[21-23]

The standard technique to identify insulin resistance is through euglycemic clamp; however that is time consuming, laborious and much complicated. Fasting insulin level has been shown to be a simple indicator of insulin resistance. We also studied fasting insulin in our study population to indirectly know about insulin resistance. Hyperinsulinemic patients had a trend towards central obesity, diabetes mellitus hypertension and high TG fitting into what is termed as syndrome "X".

More patients with hyperinsulinemia had left ventricular failure as evidence by their higher killip class. The trend to mortality was higher but it was statistically not significant due to small number of patients.

Nitric oxide regulates endothelial function and is believed to prevent atherogensis. Recent studies suggest that impaired release of nitric oxide might affect cellular insulin activity thereby causing insulin resistance and influencing the development the CAD.[30] Furthermore, insulin resistance and endothelial dysfunction have been found to be independent predictors of early restenosis after coronary stenting. [31]

Smoking has been a definite risk factor for early development of CAD. The number of smokers increasing through out the world in both men and women. Both print and electronic media are playing negative role by showing fascinating advertisements. Smoking alone is a strong risk factor for the genesis of CAD and it particularly does so in the presence of insulin resistance state.[32] Smoking needs to be banned and its sale should be prohibited.

In the presence of AMI and insulin resistance, fatty acids metabolism of myocardium is impaired, delaying the recovery of regional LV wall motion. Patients who underwent primary angioplasty for AMI, presence of insulin resistance negatively influenced recovery of LV wall motion as compared to those who did not have evidence of insulin resistance. [33] Control of obesity and greater physical activity are likely to be the most effective means of preventing or reducing insulin resistance and hence diabetes and CAD in South Asians. Although fish and vegetable are preferable, complete abstinence from meat and dairy products is not recommended as these are the essential constituents of a balanced diet.

CONCLUSION

Hyperinsulinemia is positively associated with obesity, hypertension and diabetes with higher morbidity following acute myocardial infarction. The trend towards mortality is higher but the results are not statistically significant because of small number.

REFERENCES

1. Martínez Candela J, Franch Nadal J, Romero Ortiz J, Cánovas Domínguez C, Gallardo Martín A, López Yepes ML. Predictive capacity of the diagnostic criteria of metabolic syndrome on the insulin-resistance and the coronary risk. Med Clin (Barc) 2007;129:601-6.
2. Black HR. The CAD disease paradox: the role of hyerinsulinemia and insulin resistance and implication for therapy. J Cardiovasc Pharmacol 1990;15:26-38.
3. Reaven GM. Insulin resistance and compensatory hyperinsulinemia: role in hypertension, dyslipidemia and CAD. Am Heart J 1991;121;1283-8.
4. Babić Z, Pavlov M, Bulj N, Heitzler VN, Mitrović V, Hamm C, et al. Metabolic syndrome and outcome in patients with acute myocardial infarction. Acta Clin Croat 2011;50:193-9.
5. Ametov AS, P'ianykh OP, Aslandziia EN. Acute coronary syndrome in patients with type 2 diabetes mellitus. Ter Arkh 2011;83:66-70.

6. Zavaron I, Bonora E, Paglaria M, Dall'Aglio E, Luchetti L, Buonanno G, et al. Risk factor for CAD in healthy person with hyperinsulinemia and normal glucose tolerance. N Eng J Med 1989;320:702-6.
7. Lazzeri C, Valente S, Chiostri M, Picariello C, Attanà P, Gensini GF. Glycated hemoglobin in ST-elevation myocardial infarction without previously known diabetes: it's short and long term prognostic role. Diabetes Res Clin Pract 2012;95:14-6.
8. Larsen J, Goldner W. Approach to the hospitalized patient with severe insulin resistance. J Clin Endocrinol Metab 2011;96:2652-62.
9. Foster DW. Insulin resistance--a secret killer? N Eng J Med 1989;320:733-4.
10. Philips GB, Jing T, Heymsfield SB. Relationship in men of sex hormones, insulin adiposity and risk factors for AMI. Metabolism 2003;52:784-90.
11. Von Eyben FE, Mouritsen E, Holm J, Montvilas P, Dimsevski G, Suciu G, et al. Intra-abdominal obesity and metabolic risk factors: a study of young adults. Int J Obes Relate Metab Disord 2003;27:941-9.
12. Aguilar D. Glycated hemoglobin as a prognostic risk marker in nondiabetic patients after acute myocardial infarction: what now? Circulation 2011;124:666-8.
13. Sawyer A. Syndrome X – the mystery syndrome [Online]. 2010 [cited on 2011 June 12]. Available from URL: http://www.examiner.com/metabolic-syndrome-in-national/syndrome-x-the-mystery-syndrome.
14. Ninomya JK, L'Italian G, Criqui MH, Whyte JL, Gamst A, Chen RS. Association of metabolic syndrome with history of AMI and stroke in the third National Health and Nutrition Examination Survey. Circulation 2004;109:42-6.
15. Rewers M, Zacaro D, Agortino R, Hafner S, Saad MF, Selby JV, et al. Insulin sensitivity, insulinemia and CAD: the insulin resistance atherosclerosis study. Diabetes Care 2004;27:781-7.
16. Dunder K, Lind L, Zethelins B, Berglund L, Lithel H. Increase in blood glucose concentration during antihypertensive treatment as a predictor of AMI: population based cohort study. BMJ 2003;326:681.
17. Al-Rasadi K, Sulaiman K, Panduranga P, Al-Zakwani. Prevalence, characteristics, and in-hospital outcomes of metabolic syndrome among acute coronary syndrome patients from Oman. Angiology 2011;62:381-9.
18. Lakso M. How good a marker is insulin level for insulin resistance? Am J Epidemiol 1993;137:959-65.
19. Korah TE, Ibrahim HH, Badr EA, El Shafie MK. Serum resistin in acute myocardial infarction patients with and without diabetes mellitus. Postgrad Med J 2011;87:463-7.
20. McKeigue PM, Shah B, Marmot MG. Ralation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. Lancet 1991;337:382-6.
21. McKeigue PM, Ferrie JE, Pierpoint T, Marmot MG. Association of early onset CAD in South Asian men with glucose itolerance and hyperinsulinemia. Circulation 1993;87:152-61.
22. Ranjith N, Pegoraro RJ, Shanmugam R. Obesity-associated genetic variants in young Asian Indians with the metabolic syndrome and myocardial infarction. Cardiovasc J Afr 2011;22:25-30.
23. Balarajan R, Bulusu L, Adelstein AM, Shukla V. Patterns of mortality among migrants to England and Wales from Indian subcontinent. Br Med J (Clin Res Ed) 1984;289:1185-7.
24. Hak AE, Stehouwer CD, Bots ML, Polderman KH, Schalkwijk CG, Westendorp IC, et al. Associations of C-reactive protein with measures of obesity, insulin resistance and subclinical atherosclerosis in healthy, middle-aged women. Arterioscler Thromb Vasc Biol 1999;19:1986-91.
25. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 1999;19:972-8.
26. Frohlic M, Imhof A, Berg G, Hutchinson WL, Pepys MB, and Boeing H, et al. Association of C - reactive protein and features of the metabolic syndrome: a population based study. Diabetes Care 2000;23:1835-9.
27. Festa A, D'Agostine R, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000; 102:42-7.
28. Olefsky JM, Reaven GM, Farquhar JW. Effect of weight reduction on obesity: study of carbohydrate and lipid metabolism. J Clin Invest 1974;53:64-76.
29. Kiovisto VA, Yki-jarvinen H, DeFronzo RA. Physical training and insulin sensitivity. Diabetes Matab Rev 1986;1:445-81.
30. Yoshimura T, Hisatomi A, Kajihara S, Yasutake T, Ogawa Y, Mizuta T, et al . The relationship between insulin resistance and polymorphism of endothelial nitric oxide synthase gene in patients with CAD. J Atheroscler Thromb 2003;10:43-7.

31. Piatti P, Di Mario C, Monti LD, Fragasso G, Sgura F, Caumo A, et al. Association of insulin resistance, hyperleptinemia and impaired nitric oxide release with in-stent restenosis in patients undergoing coronary stenting Circulation 2003:108:2074-81.

32. Bennet AM, Brismar K, Hallqvist J, Reuterwall C, De Faire U. The risk of AMI is enhanced by synergistic interaction between serum insulin and smoking. Eur J Endocrinol 2002;147:641-7.

33. Fujino T, Ishil Y, Takeuchi T, Hirasawa K, Tateda K, Kikuchi K, et al. Recovery of BMIPP uptake and regional wall motion in insulin resistance patients following angiography for AMI. Circ J 2003;67:757-62.