# Reaven's Quartet (Metabolic Syndrome X): A Potent Predictor Of Coronary Events

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SUMMARY:

**Reaven's syndrome of the deadly quartet (Metabolic Syndrome X) of risk factors for coronary artery disease continues to attract attention. Whether or not insulin is atherogenic and hyperinsulinemia is the major link in this association, it subserves the importance of identifying and treating patients with varying degrees of glucose intolerance. This study confirms the presence of an adverse risk factor profile, and a clustering of risk factors in diabetics. Out of a total of 400 patients with coronary artery disease diabetes was present in 40 patients, hypertension in 120 patients, hypercholestrolemia in 100 patients and obesity in 96 patients. But the incidence of hypertension, dislipidemia and obesity in diabetics ranged from 70% to 90%. A similar profile was seen in the patients with impaired glucose tolerance. This clustering of adverse risk factors suggest that there is a common link accounting for this cluster.**

## INTRODUCTION:

That Diabetes Mellitus is an independent and major risk factor for coronary events is well known[1,2,3,4]. The risk for cardiovascular abnormalities is approximately three times higher in diabetic patients[5]. Acute myocardial infarction represents the most common manifestation of IHD in adult diabetics. Angina, asymptomatic IHD, and congestive cardiac failure account for the remainder. Other manifestations of accelerated atherosclerosis like strokes[6] and peripheral vascular disease also have an increased incidence[7].

Reaven syndrome or the metabolic syndrome X,[8] has highlighted the importance of diabetes, hypertension, increased VLDL, and low HDL cholesterol, in causing the surge of macrovascular disease and suggested hyperinsulinemia as being the causative agent linking this deadly quartet. This view has been supported by[9,10,11].

That this deadly quarter as such, and in varying combinations is the causative factor of the current epidemic of IHD in Pakistani population is very likely. MRFIT and Lifestyle heart trial showing regression of even severe coronary atherosclerosis in as little as one year[12], need highlighting, to improve the adverse risk factor profile in our populations and decrease the epidemic. The suggestion that hyperinsulinemia is the common thread might have important repercussions in the management of diabetes. This study was undertaken to assess the quartet of Reaven syndrome in our population and specially the clustering of adverse risk factors in the diabetics.

## MATERIAL AND METHODS:

400 patients with ischemic heart disease admitted to medical units of Holy Family Hospital between 1989 & 1992 were included in the study. The criteria for selection was patients with angina, clear evidence of acute myocardial infarction at least three months prior to their entry in to the study, and other evidence of ischemic heart disease, congestive cardiac failure or asymptomatic ischemia. All patients had a detailed history, a detailed physical examination and were screened for diabetes according to current WHO recommendations. Lipid estimations were done after an over night fast.

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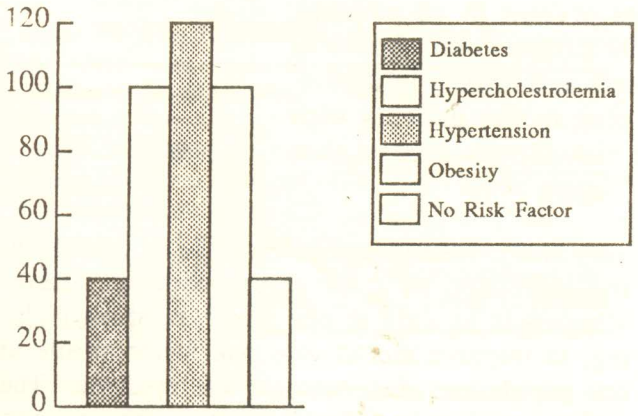
**TABLE I**

**Clustering of individual risk factors in 400 consecutive patients of Coronary Artery Disease**

| Disease | Number of Patients |
|---|---|
| Diabetes | 40 |
| Hypercholestrolemia | 100 |
| Hypertension | 120 |
| Obesity | 96 |
| No Risk Factor | 44 |

*No. of Smokers was 240*




The study was conducted in two parts, in the first part all patients whether known diabetics or proven during screening were included.

In the second part of the study known diabetics were excluded, and 220 patients with all the major complications of macrovascular disease like coronary artery disease and strokes and peripheral vascular disease were screened with an oral glucose lode of 75 gms with fasting and two hours post prandial blood sugars for the presence of impaired glucose tolerance. Exclusion criteria was of patients with acute fevers or who were taking steroids.

## RESULTS:

A total of 400 patients with ischemic heart disease were included in the first part of the study. The frequency of type of ischemic heart disease was infarctions 36%, angina 9%, chronic coronary artery disease 36% Fig I. 36 patients were known diabetics and 4 patients were found to be diabetic on screening. Table I shows the incidence of each risk factor. The total number of diabetics was 40. Out of these 85% had NIDDM and 15% had IDDM. 92% of patients were over 40 years of age. The minimum age was 25 years and the maximum was 80.

73% patients were males. Females were 27%. Out of these 27% females with IHD 76% were diabetics. Fig II.

Obesity was present in 96 patients, i.e., 24%. Obesity with diabetes was concurrently present in

**TABLE II**

**Interrelationship of Obesity with other risk factors**

| Disease | Number of Patients | Percentages |
|---|---|---|
| Obesity with Diabetes | 36(n=136) | 26.47% |
| Obesity with Hypercholestrolemia | 80(n=196) | 40.80% |
| Obesity with Hypercholestrolemia+ Diabetes | 30(n=236) | 12.71% |
| Obesity with Hypertension | 70(n=216) | 32.40% |

36 patients. 41% of the obese patients had hypercholestrolemia > 250 mg. The combination of diabetes, obesity and hypercholestrolemia was seen in 30 patients, i.e., 12.7%. Obesity, hypercholestrolemia and smoking was simultaneously present in 25%. (Table II).

Hypercholestrolemia was present in 100 patients, i.e., 25% but in the subgroup of diabetics with hypercholestrolemia was present in 85% of diabetics. (Table III).

Hypertension with diabetes was seen in 30

**TABLE III**

**Dislipidemia in patients with IHD and in Subgroup of Diabetics with IHD**

| Disease | Number of Patients | Percentages |
|---|---|---|
| Dislipidemia with IHD | 100(n=400) | 25% |
| Dislipidemia in Diabetics | 34(n=40) | 85% |

patients (Table IV) whereas the total incidence of hypertension was 30%, i.e., 120 patients. Out of the total hypertensives 60% were females to 40% males.

Cigarette or Hookah smoking was present in 39% of the patients. 13, i.e., 33% of smokers had diabetes.

The second part of the study in patients with impaired glucose tolerance showed a similar but blunted profile with an incidence of 28.3% of patients showing impaired glucose tolerance. (Table VI). This was significantly higher in women than men 60% Vs. 40%. Obesity was present in 16% (Table VI). Dislipidemia was seen in 40%. 20%

**TABLE IV**

**Percentages of other risk factors in Diabetics with IHD**

| Disease | Number of Patients | Percentages |
|---|---|---|
| Hypertension | 30 | 75% |
| Cholesterol | 34 | 85% |
| Obesity | 36 | 90% |

had raised cholesterol whereas 20% had elevated triglycerides (Table VII). Hypertension was seen in 34%. Incidence of hypertension in subjects with normal glucose level was 26% whereas 39% of patients with IGT were hypertensive. The combination of individual risk factors is given in Fig. III.

As illustrated in (Table III) the incidence of hypertension, dislipidemia and obesity was disproportionately higher in patients with diabetes ranging between 75% to 90%, compared to 20% to 45% for various subsets in the patients with normal glycemia.

## DISCUSSION:

Reaven syndrome[8] has highlighted the previous studies showing clustering of adverse risk

**TABLE V**

**Pattern of Glucose Tolerance**

| | No. of Patients | Median Age | Male | Female | Combined Prevalence/ 100 |
|---|---|---|---|---|---|
| Normal | 110 | 44 | 81 | 29 | 50 |
| IGT | 62 | 56 | 40 | 22 | 28.2 |
| NIDDM | 48 | 58 | 26 | 22 | 21.8 |

factor profile in diabetics. That hyperinsulinemia is the underlying thread in this association has been suggested by[8,9,10,11] and questioned by Jarret[13]. While this would have repercussions in the management of diabetes, here it serves to highlight the importance of diabetes and associated hyperinsulinemia in causation of macroangiopathy and in causing the clustering of adverse risk factors in diabetics. Evidence available to date suggests that more than control of hyperglycemia is required, if cardio vascular sequel of diabetes are to be delayed. Multivariate analysis suggests that the cumulative risk in the diabetics are more than what the individual ones would add upto, suggesting that factors directly associated with the diabetic state like hyperinsulinemia or disorders of homeostasis are significantly involved in the progression of macroangiopathy.

Diabetes both NIDDM and IDDM are associated with insulin resistance and thus hyperinsulinemia. Hyperinsulinemia is directly linked to hypertension[14]. It can also predispose to atheroma and macrovascular disease[15,16].

**TABLE VI**

**Distribution of Body Mass Index with respect to Glucose Tolerance**

| | | Normal n=110 | IGT n=62 | NIDDM n=48 | Combined Prevalence |
|---|---|---|---|---|---|
| Normal weight BMI 20-2; | No | 83 | 38 | 28 | 149 |
| | % | 75 | 62 | 58 | 68 |
| Over weight BMI 25-2; | No | 16 | 11 | 9 | 36 |
| | % | 15 | 17 | 19 | 16 |
| Obese BMI>27 | No | 11 | 13 | 11 | 35 |
| | % | 10 | 21 | 23 | 15.9 |

The presence of hyperinsulinemia in patients with the quartet even in populations at low risk for cardiovascular disease appears to further the importance of glycemic control and hyperinsulinemia[17]. As described by Neel in 1965 diabetes remains a geneticists nightmare. The main ingredients of this nightmare being NIDDM. The genetic component in Pakistani population, for now, remains out of reach of preventive medicine therefore it is the epidemiological risk factors which have commanded the major investigative attention. Since NIDDM and tropical diabetes constitutes the

**TABLE VII**

**Distribution of Hypertension with respect to Glucose Tolerance Status**

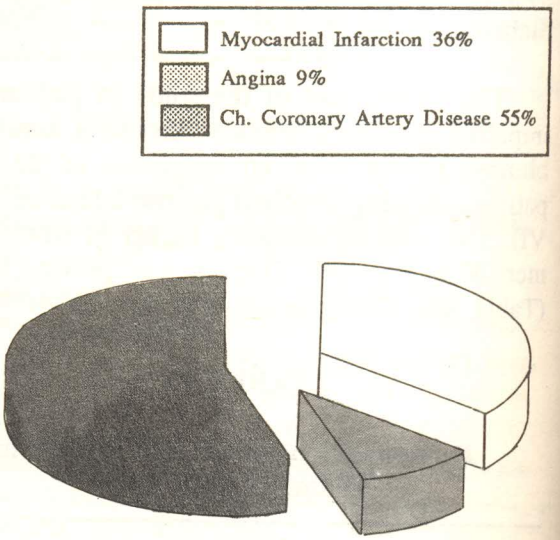
| | | Normal n=110 | IGT n=62 | NIDDM n=48 | Combined Prevalence |
|---|---|---|---|---|---|
| Normotensives (Blood Pressure <160/90mm Hg | No | 81 | 38 | 26 | 145 |
| | % | 74 | 61 | 54 | 66 |
| Hypertensives (Blood Pressure >160/90mm Hg | No | 29 | 24 | 22 | 75 |
| | % | 26 | 39 | 46 | 34 |

bulk of diabetic population in our country, and since significant insulin resistance can exist with even mild degrees of carbohydrate intolerance[8] attention to, and management of, diabetes remains important.

The relative risk of a diabetic having coronary disease is between 2 and 3[5]. In the Joslin clinic[18] 53.3% of deaths were due to coronary artery disease in diabetes compared to 30% of all deaths in the USA for the same period. Framingham studies subsequently conformed both mortality and non fatal events to be more common in diabetics[18], this association being apparently independent of serum cholesterol and blood pressure. In this study coronary heart disease was found in 40 patients 10%, this was more common in patients with NIDDM 85% compared to 14.8% in patients with IDDM. The relative incidence of males to females was 83:17 corrected for the greater incidence in the number of male patient in this series with IHD, it shows a greater risk in the diabetic female to coronary events. 80% of the female with IHD were

**FIGURE I**

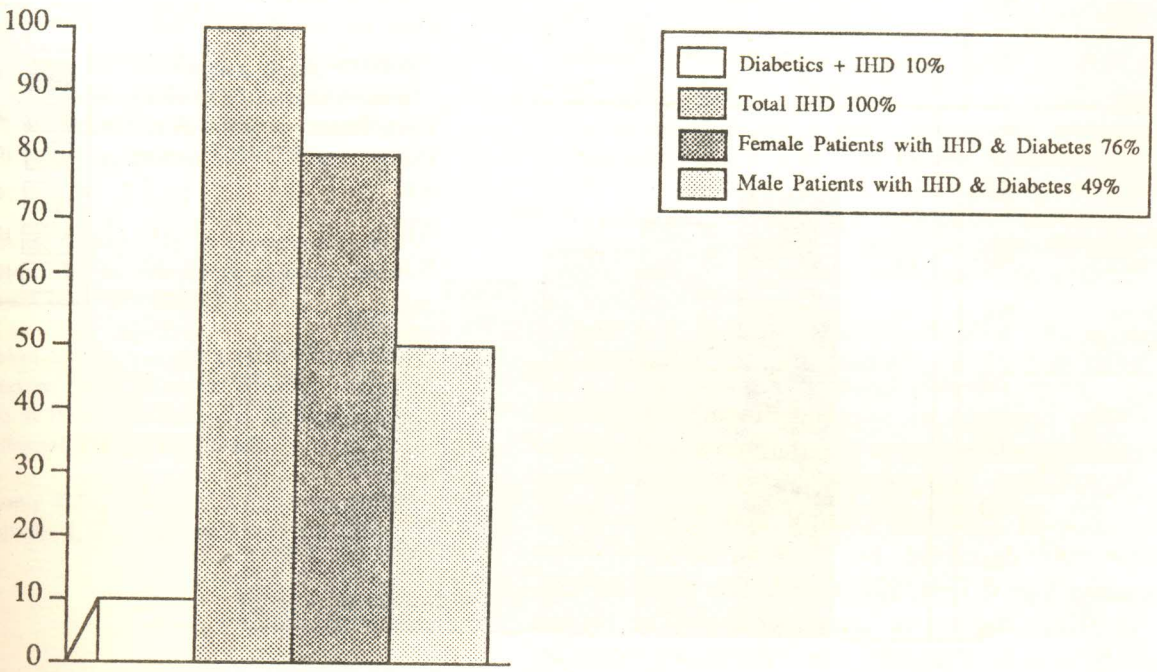
**Distribution of patients according to the Presentation of Ischaemic Heart Disease**




diabetic. This is comparable to the Framingham cohort which showed a relatively greater excess of coronary deaths in diabetic women.

Hyperlipidemia is usually associated with diabetes. The lipid level in diabetics being 20% - 90% higher depending on the degree of diabetic control. The prevalence of hypercholestrolemia in this study was 24%. But in the subgroup of diabetics dislipidemia was disproportionately high, i.e., 85%.

**FIGURE II**
**Total incidence of Diabetes in patients with Ischaemic Heart Disease**



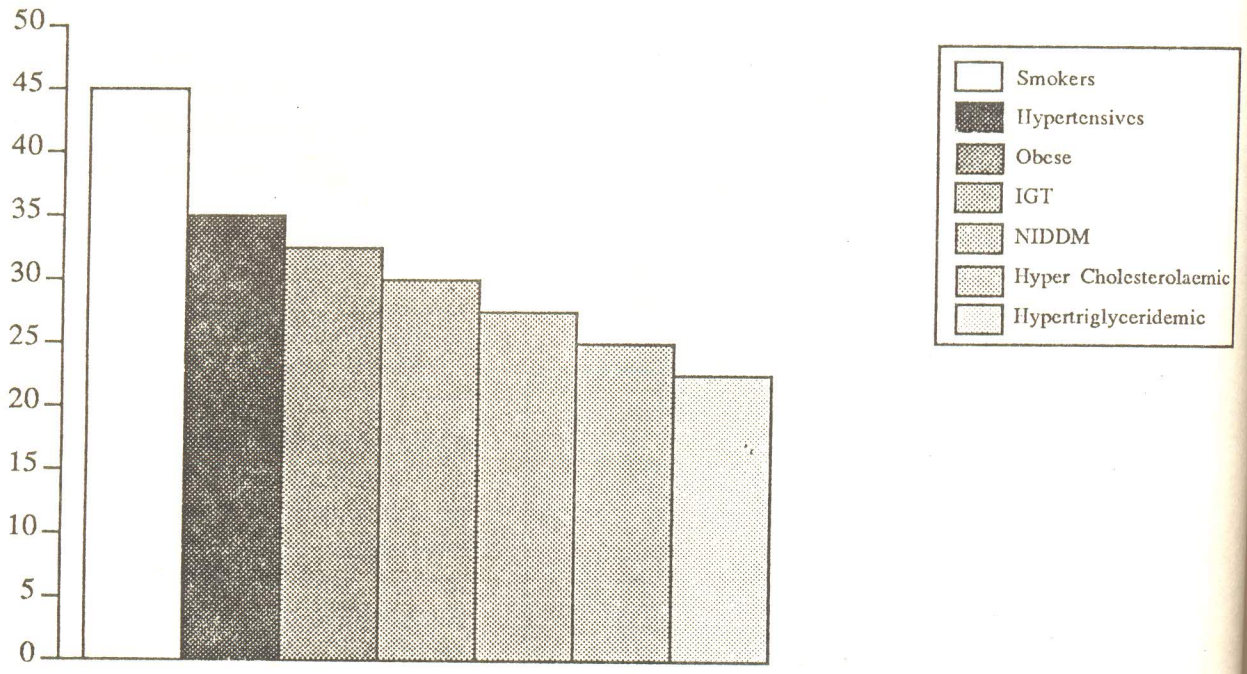

Hypertension in diabetes appeared to be the risk factor most useful in predicting cardiovascular events. The process leading to CAD, CCF, peripheral vascular disease and stroke are all further accelerated in the hypertensive diabetic. According to[19] the prevalence of hypertension was 54% high in diabetics. This study shows an incidence of hypertension of 75% in the diabetics with IHD of which 60% were females and 40% males. In part the increased incidence in this study is explained due to the presence of associated risk factors like obesity and hypercholestrolemia making this a special high risk subset.

Obesity is related with both IHD and diabetes[20]. Obese patients with IHD in this study were 96 patients, i.e., 24% out of these 36 patients, i.e., 9% had obesity with diabetes but in the subgroup of diabetes with IHD 36 patients, i.e., 90% had diabetes. Obesity with dislipidemia was present in 80 patients, i.e., 41%. The combination of obesity, diabetes and hypercholestrolemia was present in 12.71% of patients. This is similar to[20] how have found fasting insulin levels to be related to decreased HDL, increased triglycerides, NIDDM and obesity.

The influence of cigarette smoking upon vascular disease has not been studied as extensively as other risk factors. No general conclusions can be reached about cigarettes smoking and diabetes. Cigarette smoking in this study was present in 39% of the cases. Out of these 33% were diabetic and 25% of these had associated hypertension.

In the second part of the study patients with impaired glucose tolerance. The incidence of impaired glucose tolerance in patients with macrovascular disease was 28.3%. The majority of patients were women compared to 40% women. Hypercholestrolemia was present in 20%. 20% had elevated serum triglyceride. In patients with IGT the incidence of hypertriglyceridemia was double that of subjects of normal glucose tolerance. 15% were obese, again in patients with IGT obesity was 62%. Combination of obesity with dislipidemia was 75%. Combination of IGT, obesity and dislipidemia was 38%. IGT has been shown to have a

**FIGURE III**
**Prevalence of Individual Risk Factors in the Study**




risk factor profile for coronary events inbetween diabetics and normal populations[21,22].

## CONCLUSION:

This study emphasizes the importance of identifying the clustering of risk factors in the diabetics with coronary artery disease and confirms the presence of Reaven's Syndrome's Quartet.

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