Insulin Resistance Syndrome: Main Villain of Current and Rising Coronary Risk Among Turks

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Turk J Haematol 2002;19(2):203-212

It is a distinction for me, to dedicate this review to Prof. Orhan N. Ulutin, in connection with his retirement from leadership of the Society and from long-standing editorship, who has stayed in the forefront of Turkey's medical scientists throughout the latter half of the 20th century. The collaboration between us started 40 years ago under the same roof in the different sections of the First Medical Clinic of the Istanbul University Medical Faculty Cerrahpa¾a campus. Despite the differing fields of interest, and as a result of our adhering to scientific developments in the ensuing period, the collaboration lasted not only for 30 years until our retirement from the faculty, but persisted in a vivid manner to date in the context of scientific meetings and societies. Ulutin's research activities, which focused on the "joint of the platelet", as some of our teaching staff members designated with half-envy, and half-mischief, led him to be world-renowned among scientific circles. His skill in organizing national and international scientific conventions, made him a true pioneer in this field in our country, prompting other related medical organizers to take him as an example.

The works that Ulutin published in the 1960s an 70s on the relationship between platelet adhesion and aggregability and the atherosclerotic process, had been regarded with a degree of suspicion by some of our cardiologists. Yet, since the demonstration of the cellular dimension of atherosclerosis in the 1980s, the role occupied by thrombogenesis and its therapeutic implications in acute coronary events are currently well recognized. Thus, the following paper on the insulin resistance syndrome, which albeit represents no hematological investigation, nonetheless concerns a multidisciplinary topic involving a disorder of coagulation, I feel honored to dedicate to Ulutin who has been an astute scholar on platelets and thrombosis.

The insulin resistance syndrome, or the metabolic syndrome (MS) is a multidisciplinary disorder which is known to raise the cardiovascular disease risk[1]. It merits growing attention due to its rising prevalence both in the developing and developed societies, probably due to a set of factors including aging, gain in weight and sedentary lifestyle of the populations. Known initially as syndrome X, and later as "deadly quartet" or dysmetabolic syndrome and also designated as "civilization syndrome", it was defined to be composed of hypertension, glucose intolerance, and dyslipidemia comprising hypertriglyceridemia and low HDL-cholesterol levels and insulin resistance or hyperinsulinemia[2-4]. Abdominal obesity is commonly associated, as have subsequent studies shown that other phenotypes such as impaired fibrinolysis, microalbuminuria, small, dense LDL particles and acute phase reactants are associated[5]. Due to the evolving understanding of the risk factor clustering, it is not surprising that an accurate prevalence of this condition and the impact it exerts on the risk of coronary heart disease (CHD) are still not well known. The guidelines of the National Cholesterol Education Program published a year ago designated MS as a secondary target of risk reducing therapy and defined it in the presence of three out of 5 determining components[6]. MS has been described to rival hypercholesterolemia as atherogenic potential[7]. Since in Turkish adults low plasma levels of HDL-cholesterol, hypertension and (in women) obesity is very common, they could be one of the large populations possessing the highest prevalence of IRS in the globe[8,9]. I, therefore, wish to share with the readers the knowledge obtained from the Turkish Adult Risk Factor Study on the prevalence of MS, its standard and other components, its impact on CHD risk and the criteria of high coronary risk in individuals with IRS[10].

Definition of the Insulin Resistance Syndrome

In accordance with the NCEP guidelines, the presence of three of following 5 risk determinants was required for diagnosing IRS: As marker of abdominal obesity a waist circumference > 102 cm in men, > 88 cm in women, low HDL-C levels < 40 mg/dL in men, < 50 mg/dL in women, triglycerides □ 150 mg/dL, blood pressure systolic □ 130 mmHg or diastolic □ 85 mmHg and the presence of diabetes or of glucose intolerance. Applying these criteria identified 391 men (31.3%) and 564 women (43.2%) with IRS[6].

Prevalence of IRS Among Turkish Adults

The prevalence of IRS among adults aged 30 years or over may be estimated to be as high as 9.2 million (of whom 5.3 million women).

The prevalence reaches its peak of 44% in men in the age group 40-49, forming a plateau subsequently (Figure 1). Among women, the prevalence of 24% in the age group 30-39 gradually rises to 56% in the group of 60-69 years. This picture indicates that the syndrome starts in young adulthood in a substantial proportion, in the majority though in middle-aged people. A similar though not identical age distribution has been described very recently in US adults[11]. Age-specific prevalence was very similar after age 50 but was almost double in Turks among younger men. Though no sex difference was observed in the prevalence among US adults, Turkish women exhibited a considerably higher prevalence than Turkish men as well as than US women (by 43%). This feature may help explain the higher rate of coronary morbidity and mortality in our women, the risk approaching that in men.

In the Framingham study when the lowest sex-specific quintile of HDL-C and the highest quintiles of body mass index, systolic blood pressure, triglycerides, glucose and total cholesterol were considered to be matabolically linked, 3 or more risk factors occurred at twice the rate predicted by chance[12]. Clusters of 3 or more risk factors were associated with a CHD risk 2.39-fold in men and 5.9-fold in women.

Incidence of the standard components of IRS: It may be stated that, hypertension and low HDL-C levels existed in the overwhelming majority (90%) of persons with IRS in our population sample, glucose intolerance and/or diabetes was encountered in 1 out of every 7 individuals with IRS. On the other hand, abdominal obesity, while noted in the overwhelming majority of women, was uncommon in men (27%), and hypertriglyceridemia was present in 61% of women and 79% of men.

The distribution of the main components of the IRS differed somewhat from that in American adults. Glucose intolerance, and in men, abdominal obesity had a similar incidence in subjects with IRS in both communities, but the remaining components (high triglyceri-

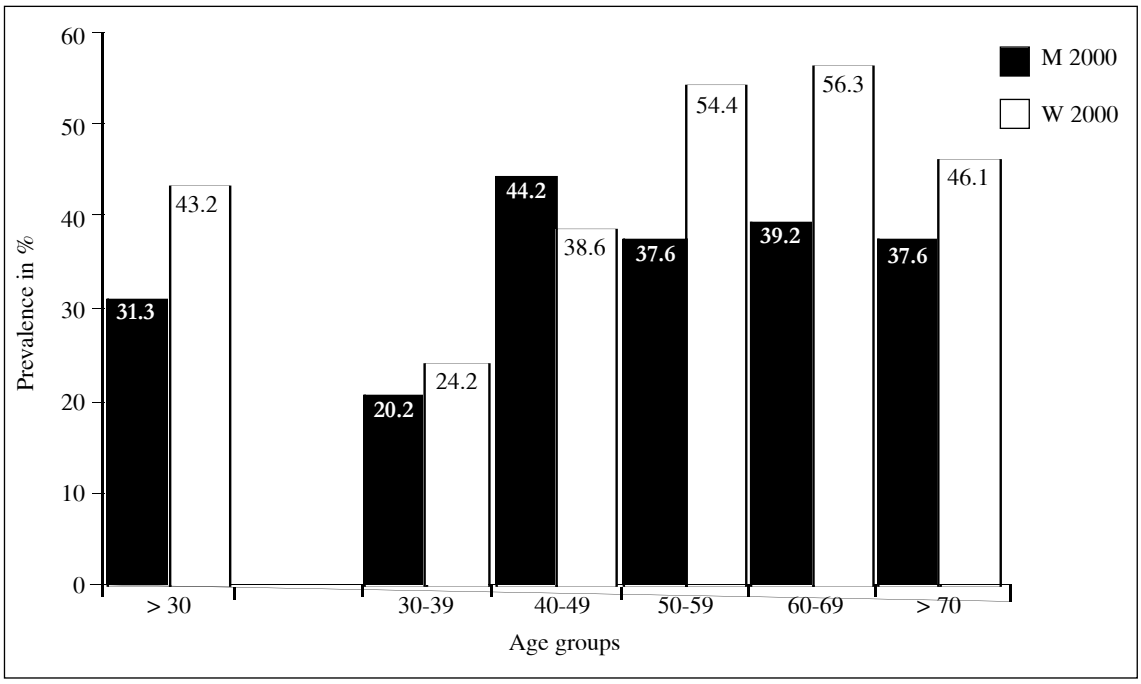

Figure 1. Prevalence of insulin resistance syndrome in Turkish adults, by age groups. A plateau is reached in men after age 40 years, by contrast to women in whom a peak frequency is attained in the age group 60-69 years.

des, low HDL-C and hypertension) were twice as much or more frequent than in Americans in whom these were encountered only at a prevalence of 30-40%[11].

Distinctive Features of Those Having IRS Among Turks

Which characteristics make individuals with IRS differ from the general adult population and to what extent? A good way of assessing this is the comparative use of interquartile ranges, that is the range of values between the 25 and 75 percentiles. Table 1 summarizes these values for 12 parameters. A significant variable is age; namely, those having IRS are older, in men by 3, in women by 6 years. Despite this, 30% of subjects with IRS are 40 years old or younger. Waist circumference is wider by 10 cm, that is they are centrally obese. A critical feature concerns the blood pressure (BP), the systolic BP being 20-25 mmHg higher; it exceeds 140 mmHg in people with IRS in half of men and two-thirds of women.

Serum triglycerides remain 80% higher than in healthy people, levels exceeding 150 mg/dL being encountered in 80% of men and 60% of women. As well known, hypertriglyceridemia is associated with low HDL-cholesterol levels. The latter is, therefore, by 6-8 mg/dL lower in IRS. HDL-C is lower than 36 mg/dL in three-quarters of men and lower than 46 mg/dL in three-quarters of women. The dyslipidemia is limited to triglycerides and HDL-C, whereas LDL-cholesterol is not significantly elevated. I will return later to the exception of Turkish women in this regard.

Noteworthy is that total cholesterol levels are only slightly elevated, compared to those not having the IRS, in men by 11 mg/dL, in women by 15-20 mg/dL. Consequently, the level of 200 mg/dL, considered as the limit of normal, is not exceeded in the majority of subjects with MS (in men even in 62%). This situation results in interpreting serum lipids to be normal, in overlooking the dyslipidemia in millions of individuals with IRS. A total cholesterol range of 180-200 mg/dL should not be regarded as normal in Turkish men, a dyslipidemia consisting of triglyceride and HDL-C abnormalities should be sought in this connection. The concept of non-HDL cholesterol is used for total cholesterol concentrations from which HDL-C is deduced.

Table 1. Interquartile ranges of certain parameters in individuals with insulin resistence syndrome

	n= 391 men				n= 564 women			
	MS		no MS		MS		no MS	
Age	43	62	39	60	44	62	38	56
Waist circumference (cm)	90	103	82	94	92	103	79	92
HDL-cholesterol (mg/dL)	27.4	36	30.7	44.5	34	46	39	56
Triglyceride (mg/dL)	159	272.5	84	155	120	216	65	125
Systolic b. pressure (mmHg)	130	151	111	132	134	166	111	138
Total cholesterol (mg/dL)	167	216	156	205	174	228	159.4	207
non-HDL-cholesterol (mg/dL)	135	183.4	117.7	166	135.3	188	112.6	159
LDL-cholesterol (mg/dL)	96	137	95.6	136.4	105	150	94	139
apo B (mg/dL)	100	142.5	86.4	127	99	149	83	125
CRP (mg/dL)	1.2	4.9	0.8	3.7	1.5	6.3	0.7	3.6
Insulin (mIU/L)	6.6	13.3	4.7	8.4	6.85	11.45	5.0	9.1
Fibrinogen (g/L)	2.34	3.58	2.25	3.45	2.61	3.96	2.47	3.82

Values of non-HDL-cholesterol > 160 mg/dL are abnormal; this limit is exceeded in half of persons with IRS[13]. Likewise, levels of apolipoprotein (apo) B which are contained in LDL, as well as in VLDL, are elevated substantially (by 14-20 mg/dL) in individuals with IRS. A rise in apo B levels without a rise in LDL-cholesterol concentrations, indicates a decline of the cholesterol content of LDL particles, which is a major characteristic for small, dense LDL[14]. This in turn suggests that in Turks having this syndrome, the prevalence of the highly atherogenic small, dense LDL is excessive.

Concentrations of LDL-C behave differently among Turkish men and women. No sex-specific disparity exists in healthy men and women as noted in Table 1, while women having the IRS exhibit levels 11 mg/dL higher than men though men have similar values, regardless of the presence of IRS. I believe this is a significant observation which currently cannot be explained, but which it might possibly be related to the genetic transmission in women of familial combined hiperlipidemia.

It is generally believed that insulin resistance underlies the IRS. Insulin resistance, complex to measure in the laboratory. Is thought to be reflected by levels of fasting insulin[15]. Fasting insulin levels in our society are increased by 1/3 among women, by one-half in men with IRS, as compared to those without. Insulin resistance is considered to represent chronic low-grade inflammation[16]. In a confirmatory manner, serum levels of high-sensitivity C-reactive protein (CRP) in the Turkish population with IRS were 1.5-fold in men and 2-fold higher in women than in the apparently healthy population.

It has also been known in the past decade that a procoagulant state exists in IRS, with elevation in the levels of plasma PAI-1 and fibrinogen. PAI-1 was not measured in this survey's Cohort, in whom plasma fibrinogen values were increased by 4-5% in men and women with this syndrome, without reaching a statistical significance.

Components of IRS by Factor Analysis

More investigation of the key metabolic steps that affect multiple pathways simultaneously will be required in the IRS[7]. We have investigated the clustering of the standard and other components of the syndrome, the relation these components exhibit towards each other and to CHD, in order to identify the main pathways of this syndrome among Turkish adults[17]. For this purpose, we used factor analysis which has been utilized by other investigators as well, a statistical method also designated as "principal component" analysis[18-21]. Based on a Cohort of 1853 subjects with no mis-

sing data, 3 clusters of factors were determined: A glucose intolerance factor, a blood pressure factor and a metabolic factor. The metabolic factor consisted in men of two separate clusters, namely of the adiposity-dislipidemia and the LDL-CRP clusters. These 3 clusters of factors were independent determinants of IRS in a regression analysis (Figure 2). When regression analysis of factor clusters was performed for CHD risk, glucose intolerance and blood pressure factors were strongly associated independently, whereas the metabolic factor, not significantly associated with CHD in men, proved to be an independent determinant (OR 1.52, p= 0.006) in women. The metabolic factor exerted its effects on CHD risk in men apparently by the intermediate of the two factors (glucose, systolic BP). Age and CRP were each considered a significant component of the IRS.

Our findings suggest that at least 3 pathways are operative in Turkish adults for IRS which are partly interrelated. The one represented by the metabolic pathway, comprises central obesity and dyslipidemia, the other two pathways involve glucose intolerance and the age-dependent systolic blood pressure. Abnormality in the latter results probably from endothelial dysfunction mediated by visceral obesity. Evidence is available that a strong adverse effect on endothelium-dependent vasodilation is exerted by obesity rather than by hyperglycemia and that obesity/insulin resistance plays a greater role in the etiology of endothelial dysfunction[22]. Moreover, a synergistic action between serum insulin and glucose or triglycerides in enhancing arterial stiffness has been observed[23].

Striking Rise in the Prevalence of IRS in the 1990s

When patients with coronary disease were excluded from each survey and the cohort was limited to age 30 or over, comparison of the prevalences of the syndrome in 1990 and 2000 would be meaningful in terms of a change therein since the mean age remained similar: 48.2 vs. 49.1 years in 2000. The prevalence which was 24.4% in 1990, had climbed to 36.2% at the end of the decade. The rise was conspicuous in both sexes and all age groups. The 38% rise at an age-standardized population, represents a 3% to 3.5% annual rise in the prevalence of IRS. This change threatening the public health suggests that, though genetic determinants of IRS are not negligible, lifestyle changes have a huge impact on its manifestation.

Share of IRS in CHD

Participants of the population sample receving the diagnosis of CHD in year 2000 numbered 242 of

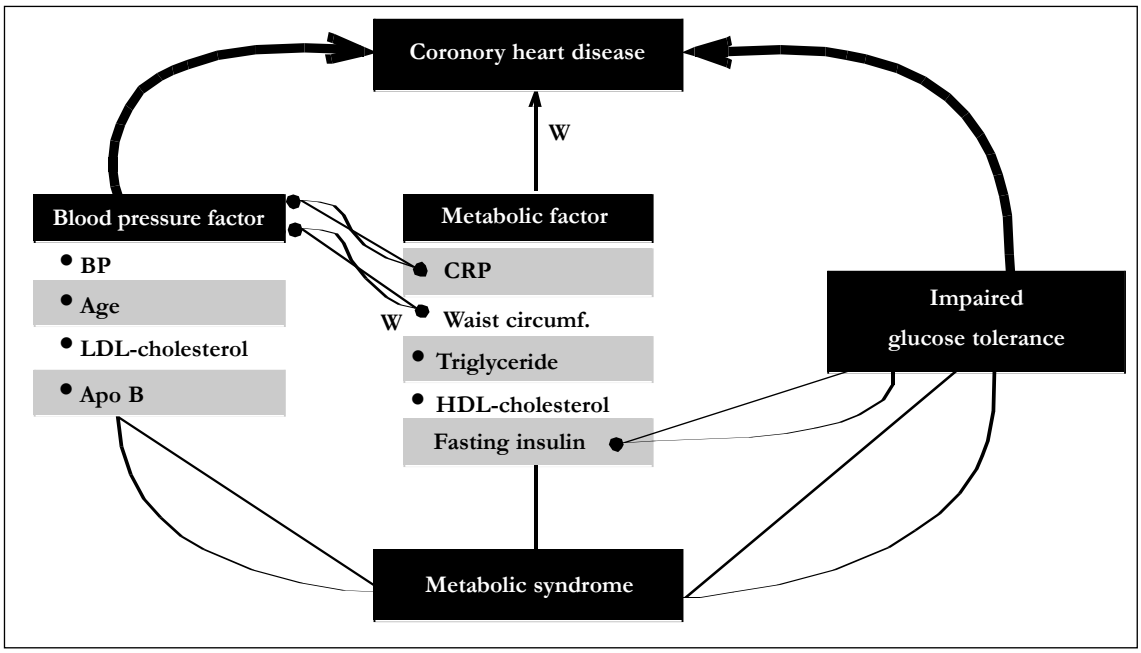

Figure 2. Clustering of factors for the insulin resistance syndrome and coronary heart disease in Turkish adults.

whom 53% were classified to have IRS. Among patients with CHD, those originating from IRS made up 42% (= 54/129) in men, and 66% (= 75/113) in women (Figure 3).

CHD Risk and Its Determinants

In a logistic regression analysis comprising age and IRS, the age-adjusted odds ratio (OR) of IRS for prevalent CHD was 1.56 in men, and 2.27 in women (Figure 4). In another regression model, two factors among the standard components were noted which independently raised the CHD risk of IRS: The presence of glucose intolerance and systolic blood pressure. A 20 mmHg rise in systolic pressure increased the CHD likelihood by 17% in women, and by 37% in men. Triglyceride levels were a further factor that raised the CHD risk independently in men alone.

Of possible components of IRS aside the standard components, when variables such as serum fasting insulin, apo B, LDL-cholesterol, total/HDL-cholesterol ratio, smoking status were tested by multivariate analysis, insulin and apo B levels emerged as significant determinants of CHD risk in both sexes. Furthermore, LDL-cholesterol and CRP in women, and TC/HDL-C ratio and (as a trend) smoking status in men were found to be associated with CHD risk.

Criteria of High CHD Likelihood in the Syndrome

Among the total 391 men with IRS, the median ratio of TC/HDL-C was 6.06. In men aged □ 50 (comprising 56% of men) or men aged □ 45 years and exhibiting a TC/HDL-C ratio □ 6.2 (43% of men), the CHD likelihood was as high as 22%. This represented 2.2-5-fold the likelihood (4-10%) of all the remaining men with IRS. Levels of LDL-C (> 120 mg/dL) and TC (> 190 mg/dL) did not contribute to the information obtained from combining age with the ratio.

Among the 564 women with IRS, the median ratio of TC/HDL-C was 5.01. In 194 women aged □ 50 years and having a TC/HDL-C ratio □ 5 the CHD likelihood was high: 26%; this represented a 3.8-fold likelihood (6.8%) than in all the remaining women with IRS. Levels of LDL-C (□ 130 mg/dL) and TC (□ 200 mg/dL) provided no further information than that obtained by the ratio.

Measures for Intermediate and High Risk Individuals

Intermediate risk: In about 5 million Turks with this subset of IRS (who comprise 350.000 CHD patients) physicians have the obligation to convince their patients (and relatives) to adopt lifestyle changes such as adhering to a healthy nutrition directed to decreasing

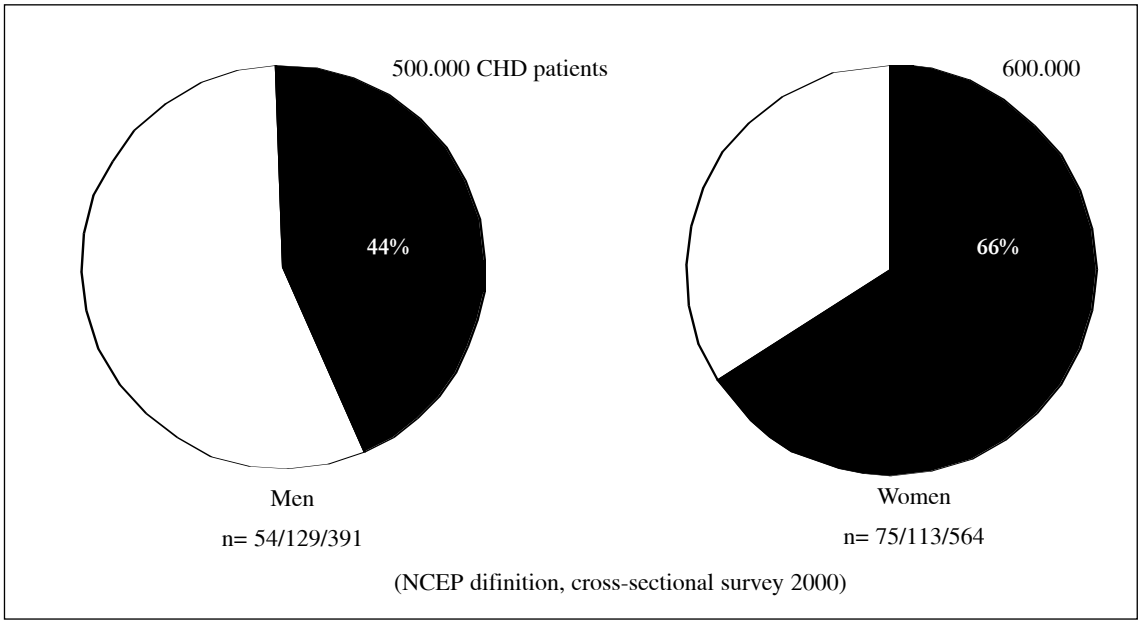

Figure 3. Share held by insulin resistance syndrome among patients with coronary heart disease, by gender.

excess fat and hypertriglyceridemia, increasing physical activity and staying away from smoking.

The high-risk group consists of 4 million Turkish adults harboring 850.000 patients with CHD; in other words, one out of every 6 Turkish adults is a person with IRS at high coronary risk, and they comprise 3 of every 8 coronary patients. It is reasonable to assume that the addition of drug treatment in this subset will likely be cost-effective.

Insulin resistance, the fundamental defect underlying type 2 diabetes and IRS, is linked to a variety of coronary risk factors. Figure 5 illustrates a flow-chart depicting these factors which extend from visceral adiposity to dyslipidemia and hypertension, include hyperinsulinemia and ultimately lead to atherosclerotic vascular disease. Measures that may be taken to help correct this key defect are summarized in Table 2.

Troglitazone lowers serum glucose and insulin levels in type 2 diabetics by improving insulin sensitivity in skeletal muscle, liver and adipose tissue. Troglitazone has been reported to reduce triglycerides by 20% and raise HDL-C levels by about 8%[24]. It is known that insulin sensitivity is lowered by sedentary lifestyle, an increase in body fat mass, a decrease in muscle mass and in emotional stress[25]. Furthermore, a diet rich in carbohydrates and saturated fat, diuretic and beta-blocking agents and menopause also reduce insulin sensitivity.

It has been established in the past 15-20 years that, by effective treatment of high LDL-cholesterol levels which lead to atherosclerosis, it is no longer a feat out of the ordinary to reduce this coronary disease risk. Time has arrived in the West, to better define now the impact of IRS on atherogenesis and to promote CHD prevention by keeping this rival of hypercholesterolemia for atherogenic potential, though less commonly encountered than in Turkey, under control[7]. In Turkey, in which a much greater share of CHD is held by IRS, placing an enormous emphasis on this issue should not be considered an exaggeration. Hematologists, cardiologists, endocrinologists and experts in other fields in Turkey, should embark in a mobilization of research to shed further light on the various aspects of IRS among Turks.

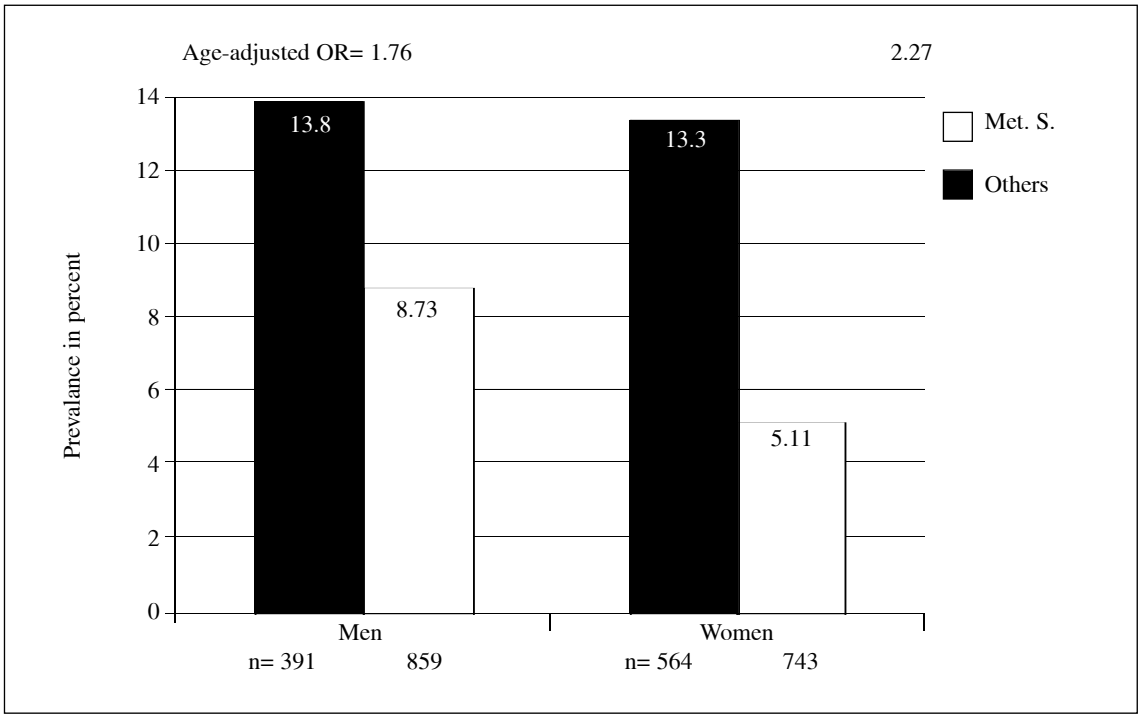

Figure 4. Age-adjusted odds ratio for prevalent coronary heart disease in Turkish men and women with the insulin resistance syndrome.

I wish to conclude that IRS is so common as to be present in three out of every 8 Turkish adults and that low levels of HDL-C, hypertension, and in women, abdominal obesity are the rule. Underlying CHD in the majority of Turkish citizens, the syndrome poses an excess CHD risk of approximately 70%, after adjustment for age. In individuals with IRS, a high-risk subset may be distinguished by using age (50) and the total/HDL cholesterol ratio as criteria.

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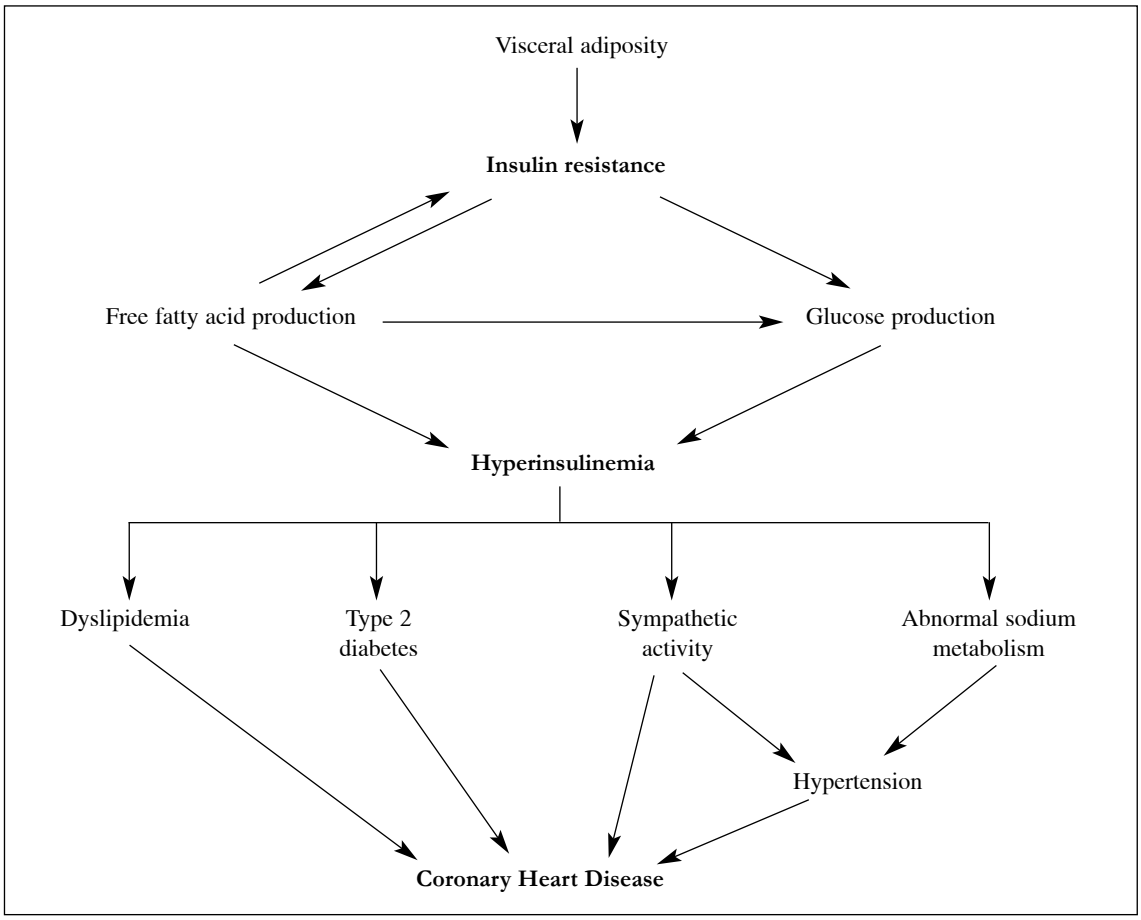

Figure 5. Diagram illustrating relationships between the basic elements of insulin resistance and hyperinsulinemia, and other factors leading to atherosclerotic vascular disease (modified from 25).

Table 2. Measures to improve insulin resistance[25]

1. Exercise (endurance and strength training)
2. Weight reduction (reducing the body fat)
3. Diet rich in fibers, low in fat and simple carbohydrates
4. Metformin (1 g) and troglitazone (400 mg)
5. Estrogen

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