Insulin Resistance Syndrome Predicts Coronary Heart Disease Events in Elderly Type 2 Diabetic Men

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OBJECTIVE — To investigate whether cardiovascular risk factors cluster with hyperinsulinemia in elderly type 2 diabetic subjects and, if so, whether this clustering predicts coronary heart disease (CHD) events during a 7-year follow-up.

RESEARCH DESIGN AND METHODS — Clustering of cardiovascular risk factors was analyzed by factor analysis. Cox regression models were used to investigate whether these clusters (factors) predict CHD events (CHD death or nonfatal myocardial infarction) during a 7-year follow-up in 229 type 2 diabetic subjects aged 65–74 years.

RESULTS — There were 70 CHD events (21 in men and 49 in women) during the follow-up period. In diabetic men, components of the insulin resistance syndrome (IRS) loaded on Factor 1 (the insulin resistance factor), which reflected high fasting insulin, obesity (high BMI), central obesity (high waist-to-hip ratio), high total triglycerides, and a short duration of diabetes. Only this IRS factor predicted CHD events in multivariate Cox regression analysis (hazard ratio [HR] 1.71, 95% CI 1.08–2.71, $P = 0.022$). In diabetic women, components of IRS loaded on two factors, none of which predicted CHD events. In women, only Factor 4, characterized by advanced age, left ventricular hypertrophy on electrocardiogram, high alcohol consumption, high systolic blood pressure, and albuminuria, predicted CHD events in multivariate Cox regression analysis (1.34, 1.03–1.74, $P = 0.03$).

CONCLUSIONS — IRS is a risk factor for CHD in elderly type 2 diabetic men.

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Coronary heart disease (CHD) is two- to fourfold more common in subjects with type 2 diabetes than in nondiabetic subjects (1). Conventional risk factors, such as smoking, hypertension, and hypercholesterolemia also predict CHD events in diabetic subjects (2,3). However, at any given level of a risk factor, diabetic subjects have a higher risk of CHD than nondiabetic subjects (2). This indicates that conventional CHD risk factors cannot explain the excess risk of CHD in type 2 diabetes.

The insulin resistance syndrome (IRS), which is characterized by hyperinsulinemia, glucose intolerance, hypertriglyceridemia, low HDL cholesterol level, elevated blood pressure, and central obesity, accompanies the majority of cases of type 2 diabetes and has been suggested to be one of the links between diabetes and an excess risk of CHD. Until recently, IRS has been difficult to investigate because of the lack of generally accepted criteria for the syndrome. Furthermore, intercorrelated risk factors typical of IRS are not readily studied by conventional statistical methods. Recently, factor analysis and principal components analysis, statistical methods for studies of intercorrelating variables, have been applied to investigate the clustering of cardiovascular risk factors in both nondiabetic and diabetic subjects (4–7). Clusterings of cardiovascular risk factors typical of IRS have been identified in all of these study populations. Furthermore, we have previously shown in our studies, which were based on different study cohorts, that this clustering, the IRS factor, predicts CHD events in elderly nondiabetic men (6) and in middle-aged patients with type 2 diabetes (7). Most diabetic subjects are elderly and at a particularly high risk of cardiovascular mortality and morbidity. However, the value of IRS as a predictor of CHD in elderly diabetic subjects has not been previously studied. Therefore, we applied factor analysis and principal component analysis to investigate the clustering of cardiovascular risk factors in a population of elderly men and women with type 2 diabetes and studied if this risk factor clustering predicts CHD during a 7-year follow-up.

RESEARCH DESIGN AND METHODS

Baseline study

The baseline study was carried out in Kuopio, which is located in eastern Finland, from 1986 to 1988. The formation and representativeness of the study population have been previously described in detail (8,9). The study population consisted of 229 elderly subjects who had a previous history of type 2 diabetes or newly diagnosed type 2 diabetes at the baseline study. All subjects with normal or impaired glucose tolerance were excluded from statistical analyses.

Weight, height, waist and hip circumference, and blood pressure were measured as previously reported (8). A subject was defined as having hypertension if systolic blood pressure was ≥160 mmHg, diastolic blood pressure was ≥95 mmHg, or the subject was taking drug treatment for hypertension. With respect

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Abbreviations: ACR, albumin-to-creatinine ratio; CHD, coronary heart disease; ECG, electrocardiogram; HR, hazard ratio; IRS, insulin resistance syndrome; LVH, left ventricular hypertrophy; MI, myocardial infarction; WHO, World Health Organization; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

to alcohol consumption, subjects were classified as alcohol users or nonusers. Smoking status was defined as current smoker.

Chest pain symptoms suggestive of CHD were recorded with the Rose Cardiovascular Questionnaire (10). Electrocardiograms (ECGs) were classified according to the Minnesota Code (11). Verified definite and possible myocardial infarction (MI) were defined according to the World Health Organization (WHO) MONICA project criteria (12), as modified by the FINMONICA Acute Myocardial Infarction (AMI) Register Study Group (13). WHO criteria for definite and possible stroke were used in the ascertainment of a previous stroke (14).

In the classification of subjects without previously known diabetes, the diagnostic criteria of the WHO (1985) were used (15). The criteria for diabetes were fasting venous plasma glucose ≥7.8 mmol/l or 2-h venous plasma glucose ≥11.1 mmol/l in a 75-g oral glucose tolerance test. Previously known diabetes was considered to be present if the diagnosis of diabetes had been made by a physician (15). Insulin-treated subjects whose C-peptide level 6 min after intravenous glucagon (1 mg) stimulation was <0.20 nmol/l were regarded as having type 1 diabetes and excluded from the present study (one male subject). The duration of diabetes was counted from the year of diagnosis; if the diagnosis was made at the baseline study, the duration of diabetes was 0 years.

Blood samples were taken in the morning, after a 12-h overnight fast. All subjects underwent an oral glucose tolerance test (75 g glucose). Plasma glucose and insulin, C-peptide, serum lipids and lipoproteins, urinary albumin (8), and HbA_{1c} (16) were determined as previously described. The urinary albumin-to-creatinine ratio (ACR) (milligrams per liter–to–millimoles per liter) was used as a measure of albumin excretion.

This study was approved by the Ethics Committee of Kuopio University Hospital. All study subjects gave informed consent.

Follow-up study

The 7-year follow-up study was carried out in 1995. A postal questionnaire was sent to every surviving participant of the original study cohort. The questionnaire contained questions about hospital admissions due to chest pain or symptoms suggestive of MI. Of the 229 original diabetic participants of the baseline study, 140 were alive on 30 June 1995; of these subjects, 130 responded to the postal questionnaire (response rate 93%).

Medical records of those who died during the 7-year follow-up (between the baseline study and 30 June 1995) and of those who reported hospitalization due to symptoms suggestive of MI during the 7-year follow-up were reviewed by two of the authors (J.K. and P.L.). In addition, the medical records of all of the nonrespondents to the postal questionnaire were reviewed (J.K. and P.L.) to verify definite or possible MIs and CHD deaths. Copies of death certificates of those who had died during the 7-year follow-up were obtained from the medical records or from the files of the Central Statistical Office in Finland and were reviewed (J.K. and P.L). Thus, all subjects from the original cohort were evaluated for CHD events. All deaths were coded according to the ICD-9 (17).

CHD death during the follow-up was defined as a death resulting from CHD (ICD-9 codes 410–414). A new nonfatal MI during the 7-year follow-up was defined as follows: *1*) a definite or possible MI verified at hospital by the WHO criteria (WHO MONICA project criteria [12], as modified by the FINMONICA AMI Register Study Group [13], based on chest pain symptoms, ECG changes, and enzyme determinations) or *2*) a new major Q-QS change on the ECG (progression from no Minnesota Q-QS code to 1.1 or 1.2 or from 1.3 to 1.1) for those who participated in the 3.5-year follow-up. CHD events included CHD death and definite or possible nonfatal MI. If a subject had more than one CHD event during the follow-up, only the first CHD event was included in statistical analyses.

Statistical methods

Data analyses were conducted with the SPSS/PC+ programs. Fasting and 2-h insulin and triglycerides were log-transformed for statistical analyses. The results for continuous variables are given as means ± SE or percentages. Two-way Student's *t* test for independent samples or the χ^2 test were used in the assessment of differences between the two groups when appropriate. Univariate and multivariate Cox regression models (18) were used to investigate the association of cardiovascular risk factors with the incidence of CHD events. Factor analysis consisted of extraction of initial components by use of principal-component analysis, rotation of components, which resulted in elucidation of factors, and interpretation of factors with loadings >0.40 ($P < 0.05$) and was used to assess the relationship of several intercorrelated variables as previously described in detail (6,7). Principal component analysis identifies a minimum number of components that are transformed (rotated) into interpretable factors. Principal components were rotated using the ortogonal varimax method. Interpretation is based on correlations, known as loadings, between the factors and the original independent variables. Factors represent physiological processes underlying the overall relationship among the original independent variables. The final number of factors was limited to four. Univariate and multivariate Cox regression models were used to investigate the association of these factors, which were identified by factor analysis, with the incidence of CHD events.

RESULTS — Of 229 type 2 diabetic subjects (74 men and 155 women) who had participated in the baseline study, 89 subjects (30 [41%] men and 59 [38%] women) died during the 7-year follow-up. The number of CHD deaths was 43 (19%) in the whole study population (10 [14%] men and 33 [21%] women). CHD events (CHD death or nonfatal MI) occurred in 70 (31%) subjects (21 [28%] men and 49 [32%] women).

The characteristics of the study population at baseline are presented in Table 1. Women were slightly older than men, and fewer women had a previous MI. There was no difference in the duration of diabetes between men and women (5.7 and 5.0 years, respectively). Women were more often hypertensive than men (78.7 and 59.5%, respectively), although the proportion of hypertensive men was also high. There were no statistically significant differences in lipid and lipoprotein levels or in fasting insulin between the sexes, but 2-h insulin was higher in women. Smoking and alcohol consumption were more frequent among men than women. Also, waist-to-hip ratio (WHR) was significantly greater in men than in women.

The association of baseline risk factors with the incidence of CHD events during the 7-year follow-up was assessed

Table 1—*Baseline characteristics of the study subjects by sex*

	Men	Women
n	74	155
Age (years)	68.7 ± 0.3	69.7 ± 0.2*
Duration of clinical diabetes (years)	5.7 ± 0.7	5.0 ± 0.4
Previous MI (%)	24.3	8.4‡
LVH on ECG (%)	16.2	26.5
Hypertension (%)	59.5	78.7†
Current smoker (%)	9.5	1.3†
Consumer of alcohol (%)	45.9	5.8‡
Apolipoprotein c4 allele (%)	35.1	40.1
BMI (kg/m^2)	27.7 ± 0.5	29.8 ± 0.4
WHR	1.00 ± 0.01	0.92 ± 0.01‡
Systolic BP (mmHg)	156 ± 3	167 ± 2†
Diastolic BP (mmHg)	84 ± 1	82 ± 1
Total cholesterol (mmol/l)	6.30 ± 0.16	6.53 ± 0.13
HDL cholesterol (mmol/l)	1.07 ± 0.04	1.15 ± 0.03
Triglycerides (mmol/l)	2.31 ± 0.21	2.75 ± 0.29
Fasting plasma glucose (mmol/l)	10.3 ± 0.5	10.0 ± 0.3
2-h plasma glucose (mmol/l)	17.6 ± 0.8	17.8 ± 0.5
HbA1 (%)	7.2 ± 0.2	7.3 ± 0.2
Fasting plasma insulin (mU/l)	20.7 ± 1.4	24.8 ± 1.3
2-h plasma insulin (mU/l)	82.3 ± 9.3	114.0 ± 10.2*
Urinary ACR (mg/mmol)	8.27 ± 2.29	9.52 ± 1.63

Data are means ± SE unless otherwise indicated. BP, blood pressure. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$ (Student's *t* test or χ^2 test).

by univariate and multivariate Cox regression analyses. Table 2 shows the results of univariate Cox regression analyses by sex. In diabetic men, previous MI, BMI, WHR, and low HDL cholesterol levels were associated with the risk of CHD events. In diabetic women, only systolic blood pressure was a statistically significant predictor of CHD events. Both low HDL cholesterol level and high urinary ACR predicted CHD events, with a borderline significance ($P = 0.055$ and 0.054) in diabetic women.

Multivariate Cox regression analyses were performed to investigate risk factors that were independently associated with the incidence of CHD events. In men, only previous MI predicted CHD events (hazard ratio [HR] 3.16 [1.09–9.15], $P = 0.034$). In women, only systolic blood pressure was associated with CHD events (HR 1.01 [1.00–1.02], $P = 0.039$).

To investigate intercorrelating factors, factor analyses were performed separately for men and women. Varimax rotated factors and their loadings of original variables on these factors by sex are shown in Table 3. In men, components of IRS, such as high fasting insulin level, high BMI, high WHR, high triglycerides, low HDL cholesterol, and a short duration of diabetes had significant (>0.40) loadings on Factor 1. High fasting glucose level and HbA_{1c} loaded on Factor 2. Age, left ventricular hypertrophy (LVH), and systolic blood pressure loaded on Factor 3. Current smoking, alcohol consumption, elevated total cholesterol, and HDL cholesterol levels loaded on Factor 4. Altogether, these four factors accounted for 47.1% of the total variance.

In women, elevated fasting glucose level, low fasting insulin level, and high HbA_{1c} had significant loadings on Factor 1 (Table 3). Elevated fasting insulin level, low HDL cholesterol, and high triglycerides loaded on Factor 2. Current smoking, high WHR and BMI, high fasting insulin level, and low total cholesterol level had significant loadings on Factor 3. Advanced age, LVH on ECG, alcohol consumption, high systolic blood pressure, and high urinary ACR loaded on Factor 4. These four factors accounted for 42.6% of the total variance.

Factors assessed by factor analysis were included in Cox regression model to investigate if they predicted CHD events during the 7-year follow-up. In men, only

Table 2—*Risk factors of CHD events in elderly diabetic men and women during 7 years of follow-up, univariate Cox regression analysis*

	Men			Women		
	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.10	0.93–1.30	0.255	1.02	0.92–1.13	0.697
Previous MI	2.47	1.04–5.86	0.041	1.76	0.75–4.15	0.195
LVH on ECG	1.27	0.42–3.80	0.669	1.20	0.64–2.23	0.570
Current smoker	0.61	0.08–4.56	0.627	0.05	0.02–1.98	0.608
Alcohol consumption	0.75	0.50–1.13	0.164	0.88	0.27–2.83	0.827
BMI	1.16	1.06–1.27	0.001	1.04	0.98–1.09	0.211
WHR (≥1.00)*	2.86	1.15–7.11	0.024	1.20	0.54–2.68	0.657
Hypertension	1.23	0.51–2.96	0.650	1.63	0.76–3.48	0.210
Systolic blood pressure	1.00	0.98–1.02	0.881	1.01	1.00–1.03	0.010
Apolipoprotein e4 allele (no/yes)	0.49	0.18–1.35	0.170	0.79	0.44–1.43	0.441
Total cholesterol (≥6.2 mmol/l)†	0.95	0.40–2.23	0.903	1.04	0.59–1.82	0.894
HDL cholesterol (<1.00 mmol/1)†	2.59	1.07–6.28	0.036	1.74	0.99–3.05	0.055
Triglycerides (2.3 mmol/l)†	1.01	0.41–2.51	0.983	1.14	0.65–2.00	0.647
Fasting glucose	0.99	0.89–1.11	0.910	1.05	0.97–1.13	0.215
2-h glucose	0.98	0.91–1.05	0.526	1.02	0.97–1.06	0.438
Fasting insulin (log)	0.26	0.05–1.48	0.130	0.88	0.27–2.80	0.823
2-h insulin (log)	0.54	0.19–1.49	0.235	0.81	0.39–1.69	0.581
Duration of diabetes	0.92	0.84–1.01	0.075	0.96	0.91–1.02	0.216
HbA_{1c}	1.05	0.85–1.30	0.668	1.12	0.99–1.26	0.071
ACR (≥8.55 mg/mmol)‡	1.71	0.66–4.42	0.268	1.79	0.99–3.22	0.054

Of 74 men, 21 experienced a CHD event, and of 155 women, 49 experienced a CHD event by the time of the 7-year follow-up. Cutoff point is the highest WHR quartile (≥1.00); †cutoff points based on high risk category classification of the National Cholesterol Education Program and the guidelines of the European Atherosclerosis Society; ‡cutoff point is the highest ACR quartile (≥8.55 mg/mmol).

Table 3—*Factors and loadings of different variables (factor analysis) in elderly diabetic men and women*

	Men				Women			
	Factor 1	Factor 2	Factor 3	Factor 4	Factor 1	Factor 2	Factor 3	Factor 4
Age	0.234	−0.002	0.587	0.063	−0.392	−0.044	−0.053	0.456
Previous MI	0.156	−0.000	−0.396	−0.105	−0.229	0.129	0.099	0.081
LVH on ECG	−0.106	0.024	0.458	−0.065	−0.059	0.000	0.162	0.613
Current smoker	−0.117	−0.172	−0.064	0.553	0.149	−0.086	0.434	−0.255
Alcohol consumption	−0.058	−0.116	−0.026	0.747	−0.150	−0.326	0.028	0.459
WHR	0.650	0.217	−0.117	0.276	0.204	−0.021	0.459	0.016
BMI	0.796	0.020	−0.263	0.059	−0.110	0.249	0.676	−0.098
Systolic blood pressure	0.008	−0.097	0.699	−0.134	0.065	0.153	−0.204	0.519
Total cholesterol	0.074	0.202	0.367	0.450	0.078	0.260	−0.616	0.028
HDL cholesterol	−0.641	0.098	−0.054	0.478	−0.025	−0.777	−0.275	−0.051
Triglycerides (log)	0.721	0.253	0.312	−0.015	0.108	0.864	−0.133	−0.080
Fasting glucose	−0.034	0.906	−0.013	−0.040	0.867	0.053	0.147	0.177
Fasting insulin (log)	0.606	−0.379	−0.221	0.060	−0.428	0.478	0.487	−0.136
HbA_{1c}	−0.029	0.920	−0.065	−0.025	0.836	0.069	0.190	0.048
Duration of diabetes	−0.425	0.238	−0.124	0.166	0.369	0.119	−0.320	−0.196
ACR	0.079	0.371	0.378	−0.197	0.251	−0.033	−0.205	0.574
Apo e4	−0.106	−0.021	0.003	−0.368	−0.072	0.340	−0.160	0.049

Apo e4, e4 allele of apolipoprotein E.

Factor 1 (the IRS factor) was significantly associated with the risk of CHD events in both univariate and multivariate Cox regression models (Table 4). In women, only Factor 4 (the hypertension factor) was significantly associated with the risk of CHD events in univariate and multivariate models; Factors 2 and 3, on which fasting insulin had a significant loading, did not predict CHD events. Finally, we performed factor analysis in the whole study population, including both sexes (data not shown). In this analysis, Factor 1 was characterized by a clustering of high fasting insulin level, high BMI, high levels of triglycerides, and low HDL cholesterol levels, but this IRS factor did not quite reach the conventional level of statistical significance to be a predictor of CHD events (HR in multivariate Cox regression model 1.23 [0.98–1.62], $P = 0.066$).

CONCLUSIONS — The present study shows that features of IRS, such as hyperinsulinemia, obesity (particularly central obesity), hypertriglyceridemia, and low HDL cholesterol, clustered in elderly type 2 diabetic men, and this IRS factor predicted CHD events during the 7-year follow-up. In elderly type 2 diabetic women, however, fasting insulin and other components of IRS loaded on two separate factors, none of which predicted CHD events.

Type 2 diabetic subjects have two- to fourfold excess risk for CHD compared with nondiabetic subjects. This excess risk has been shown to be independent of conventional risk factors (1,2). IRS, which is very common in subjects with type 2 diabetes, has been suggested to be one of the factors increasing the cardiovascular risk in diabetic patients. Until recently, however, the role of IRS as a risk factor for CHD in type 2 diabetes has remained controversial. This is because hyperinsulinemia, which has been used as a sole indicator of IRS, correlates weakly with insulin sensitivity in diabetic subjects (19) and because interrelated risk factors typical of IRS are not readily studied by conventional statistical methods. Recently, factor analysis and principal component analysis have been used to show that cardiovascular risk factors, including metabolic, inflammatory, and hemostatic risk factors (21), which are typical of the IRS, cluster in various combinations in Finnish type 2 diabetic middle-aged subjects (7), diabetic Japanese-American men (20), and diabetic tribal members of Arizona, Oklahoma, and North and South Dakota (22). The clustering of the components of IRS in the present study is in accordance with our previous study, which was based on a completely different diabetic cohort (7). Also, in the present study, we could identify a factor characterized by hyperinsulinemia, high BMI, high triglycerides, and low HDL cholesterol. Furthermore, high WHR and a short duration of diabetes had high loadings on this factor. This IRS factor predicted CHD events in both of these Finnish diabetic populations, providing evidence that IRS increases CHD risk in middle-aged (7) and elderly type 2 diabetic subjects, particularly in men.

In the present study, IRS predicted CHD events in elderly diabetic men but not in elderly diabetic women. In women, components of IRS were dispersed among two factors, none of which was predictive of CHD, although the number of CHD events was not smaller in women than in men. Our results support the findings of previous studies that suggest that IRS is probably not as important a risk factor in women as it is in men (6). To our knowledge, there are no studies showing that IRS predicts cardiovascular events in nondiabetic or diabetic women. In the present

Table 4—*Association of four factors derived from factor analysis with CHD events in elderly diabetic men and women, per Cox regression analysis*

	Men			Women		
	HR	95% CI	*P*	HR	95% CI	*P*
Univariate						
Factor 1	1.62	1.03–2.55	0.037	1.09	0.83–1.44	0.539
Factor 2	1.19	0.78–1.81	0.427	1.23	0.91–1.66	0.178
Factor 3	1.01	0.64–1.58	0.982	1.05	0.78–1.41	0.735
Factor 4	1.21	0.77–1.91	0.402	1.31	1.01–1.70	0.038
Multivariate						
Factor 1	1.71	1.08–2.71	0.022	1.11	0.84–1.46	0.481
Factor 2	1.27	0.80–2.02	0.306	1.26	0.94–1.71	0.127
Factor 3	1.12	0.70–1.79	0.640	1.07	0.79–1.44	0.677
Factor 4	1.36	0.82–2.25	0.229	1.34	1.03–1.74	0.030

study, Factor 4, characterized by hypertension, LVH, and albuminuria was the only factor that predicted CHD events in women, which is in accordance with the results of our previous study of nondiabetic elderly women (6).

The present study indicates that IRS also predicts CHD events in elderly type 2 diabetic subjects. The mechanisms by which IRS enhances atherothrombosis are largely unknown, but adverse changes, indirectly through cardiovascular risk or directly through hyperinsulinemia, may accelerate atherothrombosis (23). Insulin resistance may also cause cardiovascular disease by some currently unidentified mechanisms. Although the present study cannot reveal mechanisms via which IRS causes CHD, it suggests that neither hypertension nor hyperglycemia is responsible for the link, since neither of these two loaded on the IRS factor in the present study. Although a short duration of diabetes is not a component of IRS, it loaded on the IRS factor, which suggests that insulin resistance is present and affects CHD risk soon after the onset of diabetes. This is not a surprise because previous studies have suggested that insulin resistance already increases cardiovascular risk in prediabetic subjects (24). On the other hand, our study does not exclude the possibility that insulin resistance is also important in subjects with a long history of diabetes. Plasma insulin concentrations are determined by both insulin resistance and insulin secretion. In type 2 diabetic subjects, defects in both of these components coexist and insulin levels may be low, particularly in those with a long history of diabetes, although subjects are insulin resistant.

The present study included only a limited number of diabetic subjects; thus, more studies are needed to confirm our results. However, our finding that the IRS factor but not conventional cardiovascular risk factors predicted CHD events implies that insulin resistance may be a very important risk factor for CHD also in elderly diabetic subjects. If IRS is an important risk factor for CHD in elderly diabetic subjects, as suggested by the present study, it is possible that decreasing insulin resistance by nonpharmacological (weight reduction and physical activity) or pharmacological therapy might decrease cardiovascular mortality and morbidity in these subjects.

In conclusion, our population-based prospective study on elderly diabetic subjects demonstrates that cardiovascular risk factors typical of the IRS cluster and that this clustering predicts CHD events in type 2 diabetic men. Therefore, in addition to classic risk factors, IRS should be considered as a significant contributor to cardiovascular disease in elderly subjects with type 2 diabetes.

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