Clustering of Dyslipidemia, Hyperuricemia, Diabetes, and Hypertension and Its Association With Fasting Insulin and Central and Overall Obesity in a General Population

Maria Inês Schmidt, Robert L. Watson, Bruce B. Duncan, Patricia Metcalf, Frederick L. Brancati, A. Richey Sharrett, C.E. Davis, and Gerardo Heiss, for the Atherosclerosis Risk in Communities Study Investigators

Clustering of elevated triglycerides, decreased high-density lipoprotein cholesterol (HDL-C), hyperuricemia, diabetes, and hypertension has been related to insulin resistance/high insulin levels and central and/or overall obesity. The extent to which these abnormalities cluster and whether hyperinsulinemia, central adiposity, and overall obesity each independently associate with this clustering were evaluated in 14,481 US whites and African-Americans 45 to 64 years of age. With the exception of hypertension, abnormalities rarely existed in isolated form. Clustering greatly exceeded chance association ($P < .001$). Although this clustering was greater in relative terms (ratio of observed to expected cluster frequency) in the lean and less centrally obese, it was greater in absolute terms (observed minus expected cluster frequency as a percent of total population) in the more centrally and more generally obese. The greatest excesses were found for clusters that included both hypertriglyceridemia and low HDL-C. Multiple logistic regression models showed strong and independent graded relationships of clusters with quintiles of fasting insulin (fifth quintile odds ratio, 10 to 54, $P < .001$) and to a lesser degree with quintiles of the waist to hip ratio (2.2 to 5.4, $P < .001$ for most) and of body mass index (1.6 to 4.5, $P < .05$ for most). In conclusion, all abnormalities cluster in excess of that predicted by chance, with clusters showing remarkable and graded independent associations with fasting hyperinsulinemia and to a lesser extent with central and overall obesity. Thus, a metabolic syndrome occurs in both lean and obese middle-aged US adults.

HYPERTRIGLYCERIDEMIA, low high-density lipoprotein cholesterol (HDL-C), hyperuricemia, hypertension, and diabetes are each common conditions in adult life and frequently coexist. However, it has been shown that they cluster within individuals more often than predicted by chance.[1-3]

Traditionally, obesity has been viewed as the link for such nonrandom clustering. In the 1950s, android obesity was proposed by Vague[4] to be the factor determining predisposition to diabetes, hypertension, atherosclerosis, gout, and uric calculous disease. Empirical evidence, although based on measurements different from those used by Vague, has now accumulated in support of his ideas,[5-12] and pathogenic mechanisms have been recently described.[13,14]

The relations of insulin to cardiovascular disease[15-19] and risk factors[8,20-24] have been extensively studied, raising the hypothesis that hyperinsulinemia is the link between these abnormalities. More recently, the characterization of this clustering as syndrome X[25] or the insulin resistance syndrome[26] attributes the aggregation primarily to insulin resistance. Proposed pathogenic mechanisms related to insulin resistance have been recently summarized[27-29] and the relative roles of hyperinsulinemia and insulin resistance[30-32] debated.

Generally greater associations between insulin levels and cardiovascular disease risk factors in the lean versus the obese have been recently described,[33] but the degree of clustering at different levels of central and overall obesity has not been well characterized.

The large population sample of middle-aged adults examined by the Atherosclerosis Risk in Communities (ARIC) Study permits a broad assessment of this clustering and its association with putative underlying causes. Thus, the purposes of this report are (1) to investigate the extent to which clustering of hypertriglyceridemia, low HDL-C, diabetes, hypertension, and hyperuricemia exceeds chance in middle-aged adults; (2) to examine the degree to which excess clustering occurs in different categories of obesity; and (3) to assess the independent associations of fasting insulin level, central body fat, and overall obesity with this clustering.

SUBJECTS AND METHODS

The ARIC Study investigated 15,800 men and women aged 45 to 64 years selected by probability sampling from four US communities from 1987 to 1989, as described elsewhere[34]: Forsyth County, NC, Jackson, MS, the suburbs of Minneapolis, MN, and Washington County, MD. After excluding American Indian and Asian individuals, persons who fasted less than 12 hours, or those who had missing information on laboratory values, 14,481 individuals remained for analysis.

From the Departmento de Medicina Social Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil; Departments of Epidemiology and Biostatistics, School of Public Health, University of North Carolina, Chapel Hill, NC; Division of Epidemiology, Department of Preventive Medicine, University of Mississippi Medical Center, Jackson, MS; Welch Center for Prevention, Epidemiology and Clinical Research, The Johns Hopkins Medical Institutions, Baltimore; and the National Heart, Lung, and Blood Institute, Bethesda, MD.

Submitted July 18, 1994; accepted November 13, 1995.

Supported by National Heart, Lung, and Blood Institute Contracts No. N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022, and in part by a fellowship from the Brazilian Conselho Nacional de Desenvolvimento Científico e Technológico (M.I.S.), a fellowship from the Brazilian Ministry of Education (B.B.D.), an Overseas Research Fellowship from the Health Research Council of New Zealand (P.M.), and a Career Development Award from the American Diabetes Association (F.L.B.).

Address reprint requests to Robert L. Watson, DVM, PhD, Division of Epidemiology, Department of Preventive Medicine, University of Mississippi Medical Center, 2500 N State St, Jackson, MS 39216-4505.

0026-0495/96/4506-0006$03.00/0

Glucose level was measured by a hexokinase/glucose-6-phosphate dehydrogenase method. Insulin was determined by a radioimmunoassay (^{125}I-insulin Kit; Cambridge Medical Diagnostics, Billerica, MA) with a lower limit of sensitivity of 1 μU/mL, interassay coefficient of variation of 9.3% at a mean of 26 μU/mL, and cross-reactivity with proinsulin of 33%. Uric acid was assayed by the method of Haeckel.[35] Total triglycerides[36] and HDL-C were determined by enzymatic methods.[37]

Physical measures were obtained with participants in the fasting state, after voiding. Waist circumference at the umbilicus and maximum hip circumference were measured. Sitting systolic and diastolic blood pressure were taken three times after a 5-minute rest using a random-zero sphygmomanometer.

Prevalent diabetes mellitus was defined as a fasting (12 hours) serum glucose of at least 140 mg/dL[38] and/or a previous diagnosis of diabetes (a report of the medical diagnosis and/or of the use of hypoglycemic medications); hypertension as blood pressure of at least 140/90 mm Hg[39] and/or use of antihypertension medication; low HDL-C as HDL-C less than 35 mg/dL; hypertriglyceridemia as triglycerides of at least 200 mg/dL[40]; and hyperuricemia as uric acid of at least 8 mg/dL.[41] High body mass index was defined as at least 27.3 for women and 27.8 for men, and a high waist to hip ratio as a value above the sex-specific medians of the sample (0.896 for women and 0.963 for men).

Clusters of abnormalities were defined by pairs of specified abnormalities regardless of the presence of additional abnormalities. Combination beyond chance of these pair-defined clusters was assessed by comparing observed with expected frequencies, assuming independent distributions of the individual abnormalities. The expected relative frequency of a cluster was calculated as the product of the relative overall frequency of each of its two defining abnormalities. For example, the expected relative frequency of the cluster of low HDL-C with diabetes is equal to the relative frequency of low HDL-C times the relative frequency of diabetes. The statistical significance of the association beyond chance of combinations was evaluated through chi-square testing.

The occurrence of clusters was studied in relation to quintiles of serum insulin, waist to hip ratio, and body mass index with multiple logistic regression[42] controlling for the effects of age, ethnicity, gender, and ethnicity/gender interaction. The reference group in these models was composed of individuals presenting no more than one abnormality. Colinearity between the independent variables of the models was examined in a multiple linear regression model through evaluation of their variance inflation factors.[43]

RESULTS

Table 1 presents the frequency of each of five metabolic abnormalities according to the study definition. Hypertension was the most frequent condition, especially in its isolated form. The presence of the other four abnormalities in isolated form was much less common.

Table 2 compares observed and expected frequencies of the 10 possible clusters defined by distinct pairs of abnormalities. An excess of observed pairs above that expected by chance was seen in every case ($P < .001$). The excess was most notable for the cluster of high triglycerides with low HDL-C. In relative terms, its observed frequency was three times as great as that expected by chance alone (column 3). In absolute terms, 576 (866 − 290) more individuals presented with this cluster than were expected by chance, representing 4% of all individuals studied (column 4). Thus, 66% of all observed clusters of HDL-C with hypertriglyceridemia occurred in excess of chance (column 5). Other clusters often occurring in excess of chance were those defined by the presence of high triglycerides, low HDL-C, or hypertension with diabetes or with high uric acid. The three pairs with a lesser degree of excess clustering were hypertension with either high triglycerides or low HDL-C, and diabetes with high uric acid.

Table 1. Frequency of Metabolic Abnormalities in the Study Sample of 14,481 Men and Women Aged 45 to 64 Years: ARIC Baseline Survey, 1987 to 1989

Abnormality	No.	%	% Isolated*
High triglycerides	1,929	13.3	2.8
Low HDL-C	2,180	15.1	4.9
Diabetes	1,208	8.3	1.8
High uric acid	1,627	11.2	2.3
Hypertension	4,919	34.0	18.3

*Present in the absence of any of the other 4 abnormalities.

To assess the extent to which clustering of abnormalities was due to diabetes, analyses were repeated excluding diabetic individuals. Similar results were found for all remaining pair-defined clusters (data not shown).

Excess clustering was also seen after stratification by categories of overall and central obesity. Although there was a statistically significant excess ($P < .001$) for most pair-defined clusters in all strata, the excess of the cluster of HDL-C with high triglycerides was again notable in all strata (Table 3). An overall pattern contrasting greater relative (observed/expected) excess clustering with lesser absolute ([observed − expected]/total) excess clustering was generally seen in lean subjects and in those with lower waist to hip ratios.

Next, associations of these abnormalities with fasting insulin levels, the waist to hip ratio, and body mass index—three purported factors underlying the nonrandom clusterings—were examined. This was done first for the abnormalities individually, and then for their clusters.

The prevalence of each abnormality increases monotonically along the quintile gradient of each of the three factors, with the increase being remarkably similar for each of these factors. However, of note is the high prevalence of hypertension at the low quintiles of the purported underlying factors (Fig 1).

To assess whether these three factors associated independently with the presence of clusters, logistic regression models were fitted for each of 10 possible pair-defined clusters. The reference category consisted of individuals presenting no more than one abnormality. Dummy variables for quintiles of insulin, waist to hip ratio, and body mass index, the main predictor variables, were included together in all models. Age, ethnicity, gender, and ethnicity/gender interaction were treated as control variables. Diabetic individuals receiving insulin treatment were excluded from these analyses.

The odds for the occurrence of a cluster increased markedly with increasing insulin level (quintile 1 being the reference category), beginning at the second quintile and reaching high and statistically significant values at the fourth and fifth quintiles (varying from 10.0 to 54.4 for the fifth quintile, $P < .001$; Table 4). This effect was indepen-

Table 2. Comparison of Observed and Expected Frequencies of Clusters in 14,481 Men and Women Aged 45 to 64 Years: ARIC Baseline Survey, 1987 to 1989

Clusters	Observed	Expected	Observed/ Expected Ratio*	(Observed − Expected)/Total (%)*	(Observed − Expected)/Observed (%)
Hypertriglyceridemia with					
Low HDL-C	866	290	3.0	4.0	66
Diabetes	384	161	2.4	1.5	58
Hyperuricemia	469	217	2.2	1.7	54
Hypertension	932	655	1.4	1.9	30
Low HDL-C with					
Diabetes	349	182	1.9	1.2	48
Hyperuricemia	471	245	1.9	1.6	48
Hypertension	840	741	1.1	0.7	12
Diabetes with					
Hyperuricemia	181	136	1.3	0.3	25
Hypertension	715	410	1.7	2.1	43
Hyperuricemia with					
Hypertension	988	553	1.8	3.0	44

NOTE. Clusters were defined by the presence of 2 specified abnormalities regardless of whether accompanied by additional abnormalities.
*All clusters were observed in frequencies statistically significantly greater than expected ($P < .001$).

dent of waist to hip ratio and body mass index. Although a similar pattern was observed with the quintiles of waist to hip ratio, the odds ratios were of smaller magnitude (varying from 2.2 to 5.4 for the fifth quintile) and not always statistically significant. With body mass index, the odds ratios were generally even smaller (varying from 1.6 to 4.5 for the fifth quintile) and also not always statistically significant. No important colinearity between these three independent variables was found, since the variance inflation factor for each variable was less than 3. Large and statistically significant associations were also seen when the relationship between insulin quintiles and clustering was examined separately in the lean and in the obese using similar logistic regression models (data not shown).

To assess whether clustering due to diabetes could be responsible for these large associations, we repeated the analyses excluding diabetic individuals. The results were similar for all clusters that remained (Table 5).

DISCUSSION

A significant excess frequency existed for all 10 possible pair-defined clusters ($P < .001$). Clusters composed of high triglycerides with low HDL-C were the most notable in both relative and absolute terms, consistent with the current understanding of the intimate relationship between triglyceride and HDL metabolism.[27] Hypertriglyceridemia with diabetes was the next most prominent pair in relative terms, and hyperuricemia with hypertension in absolute terms. The least prominent clusters were defined by the pairs of hypertension with low HDL-C and diabetes with hyperuricemia. The low degree of clustering of this latter pair is probably explained by the increased renal excretion of uric

Table 3. Variation of Observed and Expected Frequencies of Clusters Across Levels of Body Mass Index and Waist to Hip Ratio in 14,481 Subjects Aged 45 to 64 Years: ARIC Baseline Survey, 1987 to 1989

	Observed/Expected Ratio				(Observed − Expected)/Total (%)			
	Body Mass Index		Waist to Hip Ratio		Body Mass Index		Waist to Hip Ratio	
Clusters	Low	High	Low	High	Low	High	Low	High
Hypertriglyceridemia with								
Low HDL-C	3.6	2.4	4.1	2.3	2.6	5.3	2.2	5.1
Diabetes	2.6	1.9	2.5	1.8	0.6	2.2	0.4	2.1
Hyperuricemia	2.9	1.6	3.2	1.6	1.1	1.9	1.1	1.9
Hypertension	1.6	1.2	1.5	1.2	1.3	1.5	1.0	1.9
Low HDL-C with								
Diabetes	2.5	1.5	2.2	1.5	0.7	1.3	0.4	1.4
Hyperuricemia	2.2	1.6	2.4	1.6	0.9	1.9	1.0	1.7
Hypertension	1.1	1.0	1.2	1.0	0.4	0.1	0.5	0.1
Diabetes with								
Hyperuricemia	1.6	1.0	1.8	1.0	0.2	−0.1	0.2	0
Hypertension	1.9	1.4	2.0	1.5	1.0	2.5	1.0	2.5
Hyperuricemia with								
Hypertension	2.2	1.4	2.3	1.5	2.0	3.1	2.4	3.0

NOTE. All clusters were observed in frequencies statistically significantly greater than expected ($P < .001$), with the exception of the clusters of low HDL-C with hypertension and diabetes with hyperuricemia. In the obese and in individuals with a high waist to hip ratio, these latter clusters were not statistically significant ($P > .05$), whereas in the lean and in individuals with a low waist to hip ratio, they were ($P < .05$).

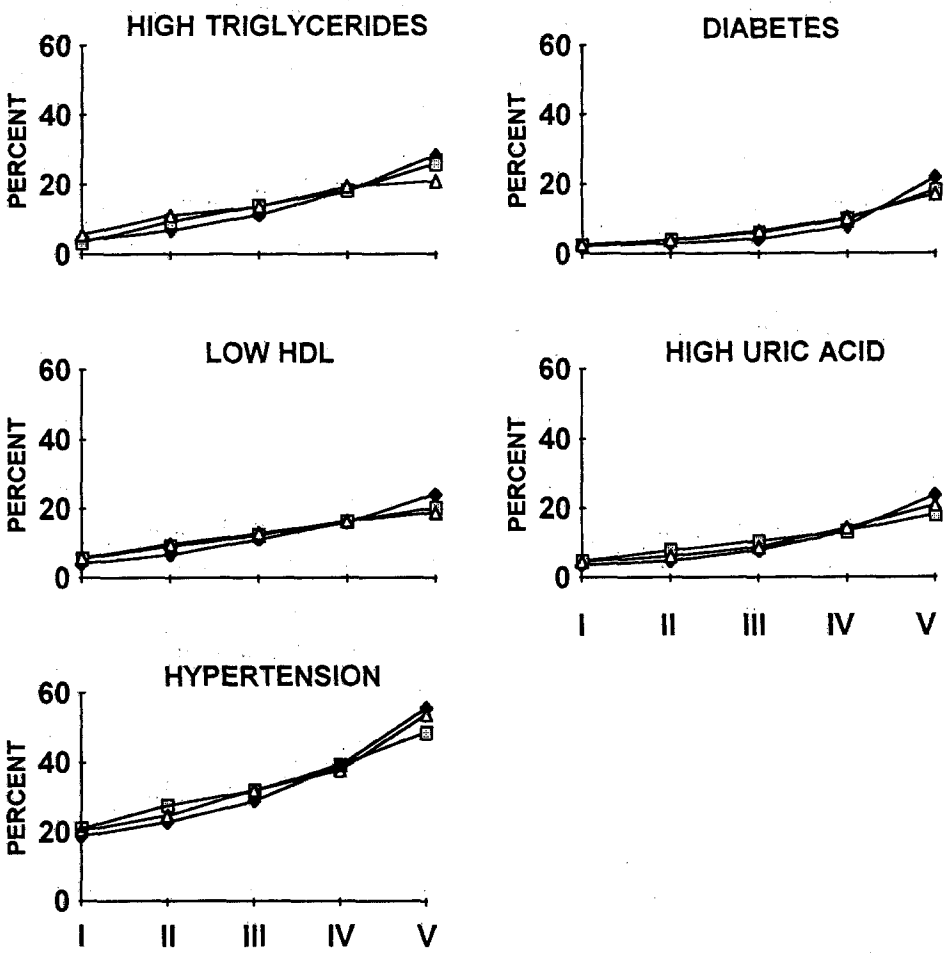

Fig 1. Prevalence of selected metabolic abnormalities in 14,481 men and women aged 45 to 64 years across quintiles of insulin, waist to hip ratio, and body mass index (ARIC Baseline Survey, 1987 to 1989). Insulin, ◆; waist to hip ratio, □; body mass index, △.

Table 4. Odds Ratios for the Independent Associations of Insulin, Waist to Hip Ratio, and Body Mass Index With Clustering in Men and Women Aged 45 to 64 Years: ARIC Baseline Survey, 1987 to 1989

	Insulin Quintiles				Waist to Hip Ratio Quintiles				Body Mass Index Quintiles			
Clusters	II	III	IV	V	II	III	IV	V	II	III	IV	V
Hypertriglyceridemia with												
Low HDL-C	1.6	3.0‡	5.9‡	15.5‡	1.8*	2.4‡	2.5‡	3.6‡	1.9†	1.6*	1.9†	2.1‡
Diabetes	1.4	2.5	5.1‡	22.2‡	1.2	1.9	2.9†	5.4‡	1.6	1.1	2.0	2.4*
Hyperuricemia	2.1	3.2†	6.7‡	25.1‡	1.8	2.9‡	3.0‡	4.1‡	1.4	1.6	2.0*	1.8
Hypertension	1.8*	3.3‡	5.5‡	17.8‡	1.3	2.0‡	2.3‡	3.6‡	1.4	1.5*	1.8†	1.6*
Low HDL-C with												
Diabetes	0.9	2.1	2.7*	15.6‡	1.2	2.6*	2.9*	5.2‡	1.6	1.6	1.7	2.6*
Hyperuricemia	2.5	4.4‡	10.5‡	31.6‡	1.3	1.6	1.8*	2.3†	1.8	2.6†	3.2‡	3.3‡
Hypertension	1.9*	3.2‡	5.4‡	15.6‡	1.4	1.8†	2.0‡	2.6‡	1.4	1.8†	2.2‡	2.6‡
Diabetes with												
Hyperuricemia	3.8	6.4	11.4*	54.4‡	0.6	1.0	1.0	2.2	0.5	3.3	3.6*	4.5*
Hypertension	1.3	1.9*	3.2‡	10.0‡	1.2	1.8*	2.1†	3.9‡	1.2	1.3	1.7*	2.5‡
Hyperuricemia with												
Hypertension	1.5	2.4‡	4.4‡	11.1‡	1.3	1.9‡	1.9‡	2.3‡	1.1	1.4	1.6†	2.2‡

NOTE. Odds ratios obtained from 10 logistic regression models wherein the dependent variables are the presence of 1 given cluster; the exposure variables quintiles of insulin, waist to hip ratio, and body mass index; and the control variables age, ethnicity, sex, and ethnicity/sex interaction. The reference exposure category is always the first quintile of each factor; the reference end-point category is composed of individuals presenting no more than 1 abnormality. Individuals receiving insulin treatment are excluded from these analyses. The lowest values (cutoff points) for insulin quintiles 2 through 5 were 6, 8, 11, and 16 μU/mL; for waist to hip ratio, 0.918, 0.950, 0.979, and 1.01 for men and 0.822, 0.874, 0.919, and 0.968 for women; for body mass index, 24.1, 26.1, 27.9, and 30.5 for men and 22.6, 25.2, 28.1, and 32.3 for women.

*$P < .05$.

†$P < .01$.

‡$P < .001$.

Table 5. Odds Ratios for Independent Associations of Insulin With Clustering in Nondiabetic Men and Women Aged 45 to 64 Years: ARIC Baseline Survey, 1987 to 1989

Clusters	Insulin Quintiles			
	II	III	IV	V
Hypertriglyceridemia with				
Low HDL-C	1.6	2.8‡	6.1‡	14.1‡
Hyperuricemia	2.1	3.1†	6.5‡	22.9‡
Hypertension	1.9*	3.4‡	5.8‡	17.5‡
Low HDL-C with				
Hyperuricemia	2.3	4.0†	10.4‡	27.7‡
Hypertension	1.9*	3.1‡	5.3‡	13.2‡
Hyperuricemia with				
Hypertension	1.5	2.4‡	4.4‡	10.7‡

NOTE. Odds ratios obtained from 6 logistic models wherein the dependent variables are the presence of 1 given cluster; the exposure variables, quintiles of insulin, waist to hip ratio, and body mass index; and the control variables, age, ethnicity, sex, and ethnicity/sex interaction. The reference exposure category is always the first quintile of insulin; the reference end-point category is composed of individuals presenting no more than 1 abnormality. Individuals with diabetes are excluded from these analyses. The lowest values (cutoff points) for insulin quintiles 2 through 5 were 6, 8, 11, and 16 μU/mL, respectively.

*$P < .05$.

†$P < .01$.

‡$P < .001$.

acid in the presence of hyperglycemia.[44] We have no explanation for the lack of clustering of the former pair.

Excess clustering was seen in both the lean and the obese and in those with or without a high waist to hip ratio. In the less centrally and generally obese, the excess clustering was statistically significant for all 10 pairs, and in relative terms was consistently more pronounced than in the more obese. To our knowledge, these observations have not been previously reported. They are consistent with previous reports of weaker correlations of insulin with hypertension and other cardiovascular risk factors in the obese.[33,45] However, the greater absolute excess of clusters of nearly all types in persons generally and centrally obese emphasizes the greater impact, and thus the greater public health implications, of this clustering for the obese.

Independent graded associations with clustering were seen across quintiles of fasting insulin, waist to hip ratio, and body mass index (Table 5). In this sample of US whites and African-Americans, unlike the sample composed of Mauritians,[3] the independent association of fasting insulin with clustering was considerably stronger than the independent associations of measures of central or overall obesity. The prominence of insulin associations was also observed in the San Antonio Heart Study.[1,2] A determination of whether these differences reflect genetic differences between the populations must await further study.

Hypertriglyceridemia, low HDL-C, hyperuricemia, and diabetes appear to be more specific to the syndrome, since all were uncommon in isolation, clustered in excess of expectation with each other, and showed strong positive associations with fasting insulin and the waist to hip ratio. By contrast, hypertension appears to be least specific to the syndrome, since it was more prevalent than the above four abnormalities in the lowest quintiles of insulin, waist to hip ratio, and body mass index (Fig 1), was more common in isolation, and showed a generally lesser degree of aggregation with other abnormalities, and since clusters defined by its presence were generally less associated with fasting insulin, waist to hip ratio, and body mass index. Thus, although these analyses support the inclusion of hypertension as a syndrome component, they also suggest that pathways unrelated to the syndrome are relatively more important in the development of hypertension than in the development of the other abnormalities. Nevertheless, accumulating data suggest that a link between hypertension and the syndrome may result from hemodynamic alterations that, by producing skeletal muscle vasoconstriction, generate a hemodynamically mediated insulin resistance.[46-49]

Although there is little room for doubt that uric acid is part of the syndrome, the biological basis for its clustering has barely been investigated. The hyperuricemia accompanying the syndrome may be a metabolic by-product of syndrome-induced alterations in free fatty acid metabolism,[50] or is perhaps due to decreased renal clearance of uric acid in the face of hyperinsulinemia.[44]

The independent, statistically significant, and often large odds ratios for insulin, waist to hip ratio, and body mass index in the multivariable analyses suggest that each may make an independent contribution to the pathogenic processes underlying this clustering. The prominence of cluster associations with fasting insulin may in fact result from its relatively high correlation with insulin resistance in nondiabetic individuals.[51] However, the issue of temporality cannot be addressed here, and hyperinsulinemia and central or overall obesity may all cause the syndrome and, to some extent, result from it. Once insulin resistance and excess adiposity, especially in visceral deposits, are present, a pathologic metabolic state involving hyperinsulinemia and central and overall obesity is established that may tend to be self-perpetuating. Variations in the expression of this state (the specific cluster of abnormalities presented) may be principally a function of genetic and environmental factors that causally influence the individual abnormalities.

Although it appears legitimate to consider this clustering a metabolic syndrome,[25,26,52,53] the graded nature of the associations across quintiles of the three purported factors suggests that the basic causes of the syndrome are not limited to a special category of individuals, for instance, those with insulin levels in the fifth quintile ($\geq$16 μU/mL), or even in the fourth quintile ($\geq$11 μU/mL). These individuals are the extreme of a population distribution rather than a categorically distinct group. In fact, a major association with clusters was seen even for those in the third quintile of insulin ($\geq$9 μU/mL). Additionally, calling this aggregation a metabolic syndrome does not remove the importance of behavioral factors in its determination in populations.[25] Factors such as dietary and alcohol intake, physical activity, and smoking may act through increasing the frequency of central obesity,[28,54-57] as well as through altering insulin levels/insulin resistance.[58]

These findings have evident clinical implications. They point to a clustering of common, clinically important

metabolic and hemodynamic abnormalities. The 20% of this population presenting the highest fasting insulin levels ($\geq$16 μU/mL) had 10 to 54 times the odds of presenting a cluster as the 20% with the lowest insulin levels ($\leq$5 μU/mL). Additionally, the clustering of such factors as hypertension and diabetes, the therapies for which are among the mainstays of clinical cardiovascular disease prevention, presents a therapeutic dilemma of unknown proportions to be explored. As calculated from the data in Table 1, only 22% of diabetic individuals and only 54% of hypertensive individuals had none of the additional abnormalities. The long-term effects of therapies for these conditions on the other abnormalities of the metabolic syndrome are only now receiving due attention.[59-63]

The major strengths of this investigation include the community-based sampling strategy, concern with measurement quality-control, and large sample size in an age range wherein many participants have developed these abnormalities but not so many have died as to produce an important survival bias. The large number of individuals in the sample permits detailed categorical analysis of clustering. This approach minimizes bias due to medication use—avoiding analysis of variables such as blood pressure or glucose that are altered by medication use, and obviating the necessity of exclusion of medication users, who may be exactly those most affected by the syndrome.

Potential limitations of this study need to be considered. Although the prevalence of abnormalities is dependent on the cutoff points chosen to define the abnormalities, it is unlikely that different cutoff points would change the general pattern of the associations. The inclusion of some mildly diabetic individuals (due to the absence of glucose tolerance test evaluation in the ARIC Study) in these analyses somewhat limits the capacity of fasting insulin levels to reflect an insulin-resistant state: a correlation between insulin sensitivity and fasting insulin level is acceptable only in the state of normal glucose tolerance.[51] Additionally, proinsulin, which cross-reacts with insulin in the assay used here, appears to have an independent association with clustering.[64] However, the categorization of insulin into quintiles in our analyses appears to have minimized these problems, since logistic models including (Table 4) and excluding (Table 5) known diabetic individuals had similar results.

In conclusion, these findings are consistent with the occurrence of a metabolic syndrome involving hypertriglyceridemia, low HDL-C, diabetes, hyperuricemia, and hypertension in a large proportion of US middle-aged adults. Morbid processes associated especially with high fasting insulin, but also with high waist to hip ratio and to a lesser extent with high body mass index, appear to underlie this clustering. There is a higher relative excess clustering in lean individuals. However, the much higher absolute excess clustering in the obese testifies to the large impact of the syndrome in these individuals.

ACKNOWLEDGMENT

The authors wish to acknowledge the valuable contributions made by the ARIC staff at the collaborating institutions: Carol Summers, Catherine Burke, Deanna Horwitz, and Carmen Woody (University of North Carolina, Chapel Hill); Agnes L. Hayes, Roberta J. Howell, Jane G. Johnson, and Patricia F. Martin (University of Mississippi Medical Center, Jackson); Nancy MacLennan, Cheryl Swanson, Mary Fowler, and Jean Bucksa (University of Minnesota, Minneapolis); Carol Christman, Melissa Minotti, Dorrie Costa, and Joan Nelling (The Johns Hopkins University, Baltimore); Valerie Stinson, Pam Pfile, Hoang Pham, and Teri Trevino (University of Texas Medical School, Houston); Julita Samoro, Wanda Wright, Karima Ghazzaly, and Sandra Sanders (The Methodist Hospital, Houston); Regina deLacy, Delilah Cook, Carolyn Bell, Teresa Crotts, and Suzanne Pillsbury (Bowman-Gray School of Medicine, Winston-Salem); and Ming Zhong, Jeff Abolafia, Ernestine Bland, and Hope Bryan (University of North Carolina, Chapel Hill [Coordinating Center]).

REFERENCES

1. Ferrannini E, Haffner SM, Mitchell BD, et al: Hyperinsulinaemia: A key feature of a cardiovascular and metabolic syndrome. Diabetologia 34:416-422, 1991

2. Haffner SM, Valdez RA, Hazuda HP, et al: Prospective analysis of the insulin-resistance syndrome (syndrome X). Diabetes 41:714-722, 1992

3. Zimmet PZ, Collins VR, Dowse GK, et al: Is hyperinsulinaemia a central characteristic of a chronic cardiovascular risk factor clustering syndrome? Mixed findings in Asian Indian, Creole and Chinese Mauritians. Diabetic Med 11:388-396, 1994

4. Vague J: The degree of masculine differentiation of obesities: A factor determining predisposition to diabetes, atherosclerosis, gout and uric calculous disease. Am J Clin Nutr 4:20-34, 1956

5. Larsson B, Svardsudd K, Welin L, et al: Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. Br Med J 288:1401-1404, 1984

6. Lapidus L, Bengtsson C, Larsson B, et al: Distribution of adipose tissue and risk of cardiovascular disease and death: A 12 year follow up of participants in the population study of women in Gothenburg, Sweden. Br Med J 289:1257-1261, 1984

7. Bjorntorp P: The associations between obesity, adipose tissue distribution and disease. Acta Med Scand [Suppl] 723:121-134, 1988

8. Folsom AR, Burke GL, Ballew C, et al: Relation of body fatness and its distribution to cardiovascular risk factors in young blacks and whites. The role of insulin. Am J Epidemiol 130:911-924, 1989

9. Terry RB, Page WF, Haskell WL: Waist/hip ratio, body mass index and premature cardiovascular disease mortality in US Army veterans during a twenty-three year follow-up study. Int J Obes 16:417-423, 1992

10. Prineas RJ, Folsom AR, Kaye SA: Central adiposity and increased risk of coronary artery disease mortality in older women. Ann Epidemiol 3:35-41, 1993

11. Folsom AR, Kaye SA, Sellers TA, et al: Body fat distribution and 5-year risk of death in older women. JAMA 269:483-487, 1993

12. Kaplan N: The deadly quartet—Upper body obesity, glucose intolerance, hypertriglyceridemia and hypertension. Arch Intern Med 149:1514-1520, 1989

13. Bjorntorp P: "Portal" adipose tissue as a generator of risk factors for cardiovascular disease and diabetes. Arteriosclerosis 10:493-496, 1990

14. Kissebah AH: Insulin resistance in visceral obesity. Int J Obes 15:109-115, 1991

15. Peters N, Hales CN: Plasma insulin after myocardial infarction. Lancet 1:1144-1145, 1965

16. Nikkilä EA, Miettinen TA, Vesenne MR, et al: Plasma insulin in coronary heart disease. Response to oral and intravenous glucose and tolbutamide. Lancet 2:500-511, 1965

17. Welborn TA, Wearne K: Coronary heart disease incidence and cardiovascular mortality in Busselton with reference to glucose and insulin concentration. Diabetes Care 2:154-160, 1979

18. Pyörälä K: Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: Results from two population studies in Finland. Diabetes Care 2:131-141, 1979

19. Ducimetiere P, Eschwege E, Papoz L, et al: Relationship of plasma insulin levels to the incidence of myocardial infarction and coronary heart disease mortality in a middle-aged population. Diabetologia 19:205-210, 1980

20. Olefsky JM, Farquahar JW, Reaven GM: Reappraisal of the role of insulin in hypertriglyceridemia. Am J Med 57:551-560, 1974

21. Orchard TJ, Becker DJ, Bates M: Plasma insulin and lipoprotein concentrations: An atherogenic association? Am J Epidemiol 118:326-337, 1983

22. Modan M, Halkin H, Almog S, et al: Hyperinsulinemia—A link between hypertension, obesity and glucose intolerance. J Clin Invest 75:809-817, 1985

23. Hunt SC, Wu LL, Hopkins PN, et al: Apolipoprotein, low-density lipoprotein subfraction and insulin associations with familial combined hyperlipidemia: Study of Utah patients with familial dyslipidemic hypertension. Arteriosclerosis 9:335-344, 1989

24. Modan M, Halkin H, Karasik A, et al: Elevated serum uric acid—A facet of hyperinsulinemia. Diabetologia 30:713-718, 1987

25. Reaven GM: Banting Lecture 1988: Role of insulin resistance in human disease. Diabetes 37:1595-1607, 1988

26. DeFronzo RA, Ferranini E: Insulin resistance—A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and other atherosclerotic cardiovascular disease. Diabetes Care 14:173-194, 1991

27. Deprés J-P, Marette A: Relation of components of insulin resistance syndrome to coronary disease risk. Curr Opin Lipidol 5:274-289, 1994

28. Taskinen M-R: Insulin resistance and lipoprotein metabolism. Curr Opin Lipidol 6:153-160, 1995

29. Reaven GM: Role of insulin resistance in human disease (syndrome X): An expanded definition. Annu Rev Med 44:121-131, 1993

30. Lindahl B, Asplund K, Hallmans G: High serum insulin, insulin resistance and their associations with cardiovascular risk factors: The Northern Sweden MONICA Population Study. J Intern Med 234:263-270, 1993

31. Lind L, Lithell H, Pollare T: Is it hyperinsulinemia or insulin resistance that is related to hypertension and other metabolic cardiovascular risk factors? J Hypertens 11:S11-S16, 1993 (suppl 4)

32. Mykännen L, Rönnemaa T, Laakso M: Low insulin sensitivity is associated with a clustering of cardiovascular risk factors. Diabetes 43:150A, 1994 (suppl 1, abstr)

33. Nabulsi AA, Folsom AR, Heiss G, et al: Fasting hyperinsulinemia and cardiovascular disease risk factors in nondiabetic adults: Stronger associations in lean versus obese subjects. Metabolism 44:914-922, 1995

34. ARIC Investigators: The Atherosclerosis Risk in Communities (ARIC) Study: Design and objectives. Am J Epidemiol 129:687-702, 1989

35. Haeckel R: The use of aldehyde dehydrogenase to determine H_2O_2-producing reactions. I. The determination of uric acid concentrations. J Clin Chem Clin Biochem 14:101-107, 1976

36. Nagele U, Hagele EO, Sauer G, et al: Reagent for the enzymatic determination of serum total triglycerides with improved lipolytic efficiency. J Clin Chem Biochem 22:165-174, 1984

37. Warnick GR, Benderson JM, Albers JJ: Quantitation of high-density-lipoprotein subclasses after separation by dextran sulfate and Mg^{2+} precipitation. Clin Chem 28:1574, 1982 (abstr)

38. The National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28:1039-1057, 1979

39. The Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure: The 1984 Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. Arch Intern Med 144:1045-1057, 1984

40. NCEP Adult Treatment Panel II: Summary of the Second Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. JAMA 269:3015-3023, 1993

41. Woodley M, Whelan A (eds): Manual of Medical Therapeutics. Department of Medicine, Washington University School of Medicine (ed 27). Boston, MA, Little, Brown, 1992, p. 518

42. Hosmer DW, Lemeshow S: Applied Logistic Regression. New York, NY, Wiley, 1989, pp 1-133

43. Kleinbaum DG, Kupper LL, Muller KE: Applied Regression Analysis and Other Multivariable Methods. Boston, MA, PWS-Kent, 1988, pp 206-219

44. Facchini F, Chen YDI, Hollenbeck CB, et al: Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA 266:3008-3011, 1991

45. Bonora E, Zavaroin J, Alpi O, et al: Relationship between blood pressure and plasma insulin in non-obese and obese non-diabetic subjects. Diabetologia 30:719-723, 1987

46. Ferrannini E: Insulin and blood pressure: Possible role of hemodynamics. Clin Exp Hypertens Theory Pract A14:271-284, 1992

47. Baron AD, Brechtel-Hook G, Johnson A, et al: Skeletal muscle blood flow. A possible link between insulin resistance and blood pressure. Hypertension 21:129-135, 1993

48. Baron AD: Cardiovascular actions of insulin in humans. Implications for insulin sensitivity and vascular tone. Baillière's Clin Endocrinol Metab 7:961-987, 1993

49. Lind L, Lithell H: Decreased peripheral blood flow in the pathogenesis of the metabolic syndrome comprising hypertension, hyperlipidemia and hyperinsulinemia. Am Heart J 125:1494-1497, 1993

50. Vuorinen-Markkola H, Yki-Jarvinen H: Hyperuricemia and insulin resistance. J Clin Endocrinol Metab 78:25-29, 1994

51. Laakso M: How good a marker is insulin level for insulin resistance? Am J Epidemiol 137:959-965, 1993

52. Arnesen H (ed): The Metabolic Cardiovascular Syndrome. J Cardiovasc Pharmacol 20:S1-S53, 1992 (suppl 8)

53. Tikkanen MS, Tuomilehto J: Multiple metabolic syndrome (syndrome X). Ann Med 24:461-489, 1992

54. Slattery ML, McDonald A, Bild DE, et al: Associations of body fat and its distribution with dietary intake, physical activity, alcohol, and smoking in blacks and whites. Am J Clin Nutr 55:943-949, 1992

55. Duncan BB, Chambless LE, Schmidt MI, et al: Correlates of body fat distribution—Variation across categories of race, sex and body mass in the Atherosclerosis Risk in Communities Study. Ann Epidemiol 5:192-200, 1995

56. Lissner L, Bengtsson C, Lapidus L, et al: Smoking initiation and cessation in relation to body fat distribution based on data

from a study of Swedish women. Am J Public Health 82:273-275, 1992

57. Duncan BB, Chambless LE, Schmidt MI, et al: Association of the waist-to-hip ratio is different with wine than with beer or hard liquor consumption. Am J Epidemiol 142:1034-1038, 1995

58. Feskens EJM, Loeber JG, Kromhout D: Diet and physical activity as determinants of hyperinsulinemia: The Zupten Elderly Study. Am J Epidemiol 140:350-360, 1994

59. Prichard BNC (ed): Insulin Sensitivity: Cardioprotection vs. Metabolic Disorders. J Cardiovasc Pharmacol 20:S1-S84, 1992 (suppl 11)

60. Scientific Seminar. Eur Heart J 13:1-108, 1992 (suppl G)

61. Johnston CI, Cooper ME, Nicholls GM: Meeting report of the International Society of Hypertension Conference on Hypertension and Diabetes. J Hypertens 10:393-397, 1992

62. Hall JE (ed): The Kidney, Obesity, and Essential Hypertension Symposium. Hypertension 19:I1-I129, 1992 (suppl)

63. Samuelsson O, Hedner T, Berglund G, et al: Diabetes mellitus in treated hypertension: Incidence, predictive factors and the impact of non-selective beta-blockers and thiazide diuretics during 15 years' treatment of middle-aged hypertensive men in the Primary Prevention Trial Göteborg, Sweden. J Hum Hypertens 8:257-263, 1994

64. Haffner SM, Mykkänen L, Valdez RA, et al: Disproportionately increased proinsulin levels are associated with the insulin resistance syndrome. J Clin Endocrinol Metab 79:1806-1810, 1994