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Development of the Multiple Metabolic Syndrome: An Epidemiologic Perspective

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INTRODUCTION

It has been observed repeatedly that risk factors for cardiovascular diseases tend to co-occur within individuals (1, 2). Typically, disturbances of glucose metabolism, dyslipidemias, central obesity, and elevated blood pressure are among the metabolic and hemodynamic components considered. These observations have been made both on the individual level and at the population level as associations between these risk factors. Since each of these conditions is highly prevalent in adulthood, it is reasonable to expect clusters due to chance alone. However, it has been speculated for some time that co-occurrence of these conditions is due to a common underlying process. Several terms have been proposed to describe the clustering of metabolic disorders, among them syndrome X, the insulin resistance syndrome, and the multiple metabolic syndrome (table 1) (3–13). For the purposes of this review, the latter terminology, the multiple metabolic syndrome, will be adopted since it does not rely on assumptions about underlying etiologic mechanisms and retains a certain neutrality. The term "multiple metabolic" implies primarily more than one metabolic abnormality, but does not preclude the interpretation that several syndromes may, in fact, be subsumed under this heading. This review will focus on the multiple metabolic syndrome largely from an epidemiologic perspective. There are several excellent review papers that have concentrated on the physiologic or clinical perspectives (3, 12, 14).

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Abbreviations: ARIC, Atherosclerosis Risk in Communities; HDL, high density lipoprotein; IRAS, Insulin Resistance Atherosclerosis Study; LDL, low density lipoprotein; VLDL, very low density lipoprotein.

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DEFINING THE MULTIPLE METABOLIC SYNDROME

A syndrome is defined as "The aggregate of signs and symptoms associated with any morbid process, and constituting together the picture of the disease" (15, p. 1522). With respect to the multiple metabolic syndrome, there is still substantial debate over what components constitute this syndrome (table 2). Some investigators have focused on one or more continuous traits (16–20), others have defined the multiple metabolic syndrome as a multivariable phenotype of several discrete traits (6, 21, 22). Common to most studies using an a priori definition of the multiple metabolic syndrome (6, 22–26) is that they have included at least one measure of glucose metabolism or insulin resistance, blood pressure, triglycerides, and at least one measure of lipoprotein cholesterol. Obesity or central adiposity are frequently included. Other syndrome components that have been more sporadically suggested include uric acid (25), plasminogen activating inhibitor factor 1 (27), lipolytic enzymes (28), free fatty acids (29), and factor VII (30).

A somewhat different approach was taken by Edwards et al. (31) who employed principal components and factor analysis, two relatively data-driven statistical methods, to reduce a large number of prespecified clinical characteristics to a small subset of uncorrelated factors. Finding the factors associated with body mass and fat distribution, measures of glucose and insulin, and lipids to be three distinct components of the multiple metabolic syndrome is consistent with many a priori definitions of this syndrome.

The difficulty in defining this syndrome reflects the diversity in terms associated with it. It is in part the result of the incongruence between a taxonomy based largely on disease manifestations or phenotypes and the etiologic conceptualization that cuts across current classifications.

While the following major sections (clustering characteristics, role of insulin resistance and obesity, genetic epidemiology, natural history of the multiple metabolic syndrome) each focus on one broad theme,

TABLE 1. Terms associated with the multiple metabolic syndrome

Study (reference no.)	Syndrome name
Hanefeld and Leonhardt (7)	Metabolic syndrome
Reaven (12)	Syndrome X
Kaplan (9)	Deadly quartet
Kesäniemi et al. (10)	Multiple metabolic syndrome
Hjermann (8); Os and Nordby (11)	Metabolic cardiovascular syndrome
DeFronzo and Ferrannini (3); Haffner et al. (6)	Insulin resistance syndrome
Després (4)	Insulin resistance-dyslipidemia syndrome
Zimmet et al. (13)	Chronic cardiovascular risk factor clustering syndrome

tables 3 and 4 divide the reviewed literature by their primary aim into more descriptive studies exploring the characteristics of the multiple metabolic syndrome (table 3) and analytic epidemiologic studies (table 4).

CLUSTERING CHARACTERISTICS

The term "clustering" is frequently associated with the multiple metabolic syndrome but rarely explicitly defined (table 3). While "clustering" can imply the co-occurrence of similar events over time or space in a defined population, in the context of the multiple metabolic syndrome this term has been used to describe the co-occurrence of multiple abnormalities (discrete traits) in one individual.

Earlier investigations into the clustering characteristics of the multiple metabolic syndrome utilized correlation coefficients to express the association between various cardiovascular disease risk factors (continuous traits) (32). These investigations were more concerned with the description of overall risk factor patterns for cardiovascular disease in populations and, therefore, included a broad spectrum of metabolic, anthropometric, behavioral, and demographic characteristics. Only more recently has the assessment of clustering shifted toward the description of a disease entity and focused on metabolic components.

Comparison of the observed frequency of disorders and their combinations to the occurrence expected under the assumption of independence of their components (i.e., due to chance) is an approach used repeatedly to assess aggregation in cross-sectional population-based studies. The statistical assumptions of this method have been discussed (33). Investigators of the the San Antonio Heart Study (6, 23), the Atherosclerosis Risk in Communities (ARIC) Study (25, 34), and others (13, 32, 35–38) explored directly the clustering characteristics of obesity, non-insulin-dependent diabetes mellitus, impaired glucose tolerance, hypertension, high triglycerides, and high cholesterol. While the overall prevalence of metabolic abnormalities varies across populations, evaluations of clustering in the middle-aged Mexican-American and non-Hispanic white population of the San Antonio Heart Study (6, 23) and the slightly older African-American and European-American ARIC cohort (34) and other populations (13) have shown striking similarities. The ratio of observed-to-expected frequencies indicated an excess of individuals free of disorders, a deficit of individuals exhibiting one or two disorders, and a significant excess of individuals exhibiting three or more disorders simultaneously. The prevalence of abnormalities occurring in isolation—while clearly a function of the total number of disorders considered—was nonetheless low.

Few prospective epidemiologic studies have focused on the clustering characteristics of the multiple metabolic syndrome. Raitakari et al. (39) employed cluster-tracking (the probability of remaining in a defined quantile of the population distribution over time) in a prospective study of cholesterol and blood pressure in children. Using the same methodology, Bao et al. (40) found that the multiple risk index, a composite of various component disorders of the multiple metabolic syndrome, tracked substantially in the Bogalusa Heart Study population. A total of 61 percent of individuals initially in the highest quintile of the index remained there over the course of 8 years. Haffner et al. (6) reported that individuals who developed incident components of the multiple metabolic syndrome had higher mean insulin levels at baseline than those individuals whose component status did not change.

Instead of focusing on the *type* of disorder clusters, additional insight into the clustering characteristics of the multiple metabolic syndrome may be gained by differentiating incident components by the *number* of disorders, i.e., the size of the multiple metabolic syndrome clusters (6, 22, 26, 41). The hypothesized exposure-outcome association may then be reassessed in each of the outcome strata. Factors that are more integral to the clustering process should be more strongly associated. We have recently shown in the ARIC cohort that insulin, body mass index, and waist-to-hip ratio were indeed more strongly associated with incident clusters of syndrome components than with incident components occurring in isolation (22).

ROLE OF INSULIN RESISTANCE AND OBESITY

Several hypotheses regarding the etiology of the multiple metabolic syndrome have been postulated in the literature. The insulin resistance/hyperinsulinemia hypothesis attributes the co-occurrence of disorders to primary insulin resistance (3, 12). It builds on results

TABLE 2. Definitions of the multiple metabolic syndrome

Study (reference no.)	Components of the multiple metabolic syndrome							
	Insulin*	Glucose†	Triglycerides	HDL‡ cholesterol	LDL‡,§	Blood pressure	Body mass index WHR‡	Uric acid
Haffner et al. (6)	X	X	X	X		X		
Selby et al. (26)	X		X	X	X	X	X	
Ferrannini et al. (23)	X	X	X	X		X	X	
Zimmet et al. (13)	X	X	X	X		X	X	X
Schmidt et al. (25)	X	X	X	X		X	X	X
Carmelli et al. (21)		X				X	X	
Liese et al. (22)	X	X	X	X		X	X	
Mitchell et al. (19)	X	X	X	X		X	X	
Hong et al. (20)	X	X	X	X		X	X	

* Fasting or post-load insulin.
† Fasting or post-load glucose or diagnosis of non-insulin-dependent diabetes mellitus.
‡ HDL, high density lipoprotein; LDL, low density lipoprotein; WHR, waist-to-hip ratio.
§ LDL subclass phenotype B.

of clinical and metabolic studies that explain the physiologic link between insulin resistance/hyperinsulinemia to elevations in triglyceride levels, systolic and diastolic blood pressure, and reduced high density lipoprotein (HDL) cholesterol levels. Insulin resistance is therefore viewed as the underlying cause for clusters of subsequently occurring disorders. Insulin resistance is furthermore conceived of as being primarily the result of obesity (acquired either genetically or nongenetically) or as an inherited genetic defect. A substantial number of analytic epidemiologic studies have focused on the role of insulin and insulin resistance (table 4).

Starting with the well established observation that obesity is not one homogenous condition (42), a different concept posits that central adiposity or upper body obesity is responsible for the development of multiple metabolic and hemodynamic disturbances, part of which are mediated by the level of insulin (9, 43, 44). The associations between multiple risk factors have also been hypothesized to be due to an underlying abnormality of the lipid metabolism which is reflected in low density lipoprotein (LDL) peak particle diameter. LDL subclass phenotype B, based on a dichotomization of LDL peak particle diameter, has been proposed as an integral part of the multiple metabolic syndrome (26, 45).

The next section of this review focuses on the relation of insulin and obesity and provides the framework for the two main hypotheses outlined above. The following four sections will then each focus on one component disorder of the multiple metabolic syndrome (diabetes, hypertension, and dyslipidemias) and cardiovascular disease (as an extension of the multiple metabolic syndrome) and evaluate evidence regarding the involvement of insulin resistance and obesity in their development.

Particularly from a public health perspective, prevalence differences, such as the high prevalence of obesity and non-insulin-dependent diabetes mellitus among the Pima Indians (46) or among African-Americans compared with European-Americans (47), are noteworthy. Whenever race/ethnic differences are pointed out, one should keep in mind that in most epidemiologic studies race/ethnic groups are defined according to skin-color and/or self-reported identification with a cultural grouping. However, race should not be understood to subsume genetic differences, but is a primarily social category (48, 49). In this context race/ethnicity may reflect any combination of genetic and environmental (cultural, life-style, socioeconomic) influences both separately and jointly. While "race/ethnicity" has been preferred by some authors, the term "ethnicity" will be used here to keep the focus on the cultural component.

Insulin, insulin resistance, and obesity

Insulin resistance is defined as resistance to insulin-stimulated glucose uptake. The relations between insulin levels, insulin resistance, and obesity have been described in detail in the clinical literature. As a person gains weight and becomes obese, the sensitivity of muscle tissue to the action of insulin declines (3). To counterbalance this insulin resistant state and maintain normal glucose levels, augmented levels of insulin are secreted resulting in hyperinsulinemia. Thus, higher fasting insulin levels may indicate a greater degree of insulin resistance (50). Increased insulin resistance and higher insulin levels may in turn be associated with a decreased rate of weight gain in middle-aged adults (51–53), but not in young adults or children (53, 54). It is important to keep in mind, however, that

TABLE 3. Epidemiologic studies on the characteristics of the multiple metabolic syndrome

Study (reference no.)	Study focus	Analytic technique	Design	Study	Population size	Race/ethnic group	Gender*	Age (years)
Wingard et al. (37)	Clustering in diabetics versus non-diabetics	Ratio of frequency of clusters	Cross-sectional	LaJolla Lipid Research Clinic	2,632	White	M/F	35–79
Ferrannini et al. (23)	Clustering, characteristics of isolated disorders versus normal	Frequencies, Obs/Exp*, difference in means	Cross-sectional	San Antonio Heart Study	2,930	Mexican-American non-Hispanic white	M/F	25–64
Selby et al. (45)	Concordance for dyslipidemic hypertension	Concordance analysis	Twin study	NHLBI* twin study	514 pairs	White	M	42–56
Eriksson et al. (36)	Metabolic characteristics of hypertensives versus normotensives	Difference in means, frequencies	Cross-sectional	'Men born in 1913' living in Göteborg, Sweden	644	Swedish	M	67
Zimmet et al. (13)	Clustering, characteristics of isolated disorders versus clusters	Obs/Exp, difference in means	Cross-sectional	Mauritius	5,080	Indian, Creole, Chinese Mauritians	M/F	25–74
Carmelli et al. (21)	Clustering	Concordance analysis	Twin study	NAS NRC* twin survey	2,508 pairs	White	M	56–68
Edwards et al. (31)	Clustering	Factor analysis	Twin study	Kaiser Permanente Women Twins Study	281 pairs	White	F	50 (mean)
Schmidt et al. (25, 34)	Clustering	Frequency of clusters, Obs/Exp	Cross-sectional	ARIC* Study	14,481	White, African-American	M/F	45–64
Chan et al. (18)	Interrelationships between components	Structural equation modeling	Cross-sectional	Hong Kong Chinese working population	1,513	Hong Kong Chinese	M/F	30–65

* M, male; F, female; Obs/Exp, observed-to-expected ratio; NHLBI, National Heart, Lung, and Blood Institute; NAS NRC, National Academy of Sciences, National Research Council; ARIC, Atherosclerosis Risk in Communities.

insulin concentrations are only one component of an intricate system that maintains glucose tolerance, which includes factors such as insulin secretion, hepatic and peripheral insulin action, insulin clearance, and the effect of counterregulatory hormones (55).

Insulin-related parameters can be measured by a variety of more or less invasive and time-consuming techniques (56). While some techniques allow more direct measurement of insulin sensitivity or resistance, fasting insulin is frequently used as a surrogate measure of insulin resistance. In normoglycemic individuals, insulin has been shown to correlate very well with whole-body glucose uptake ($r = -0.68$) as measured by an euglycemic clamp, which is considered the gold standard. In individuals with impaired glucose tolerance or with non-insulin-dependent diabetes mellitus the correlation is moderate ($r = -0.47$) (50).

A variety of measures of body mass and body fat exist, each measuring and expressing a slightly different aspect of general obesity, fat distribution, patterning, or fat percentage (57–59). Body mass index (weight/height^2) is considered a good surrogate measure of percent body fat (60) or total adipose tissue as measured by magnetic resonance imaging ($r_{women} = 0.92$, $r_{men} = 0.85$) (61). The ratio of waist and hip circumference is highly correlated with visceral adipose tissue as measured by computed tomography ($r_{women} = 0.83$, $r_{men} = 0.77$) (62). Body mass index and waist-to-hip ratio are among the most routinely used anthropometric indices in large-scale epidemiologic studies since they are easy to ascertain and have a high reliability ($R = 0.96–1.00$) (63, 64). A strong correlation exists between fasting insulin concentrations and body mass index (correlation coefficients ranging from 0.36 to 0.60) that usually exceed pairwise correlations with other physiologic parameters (16, 24, 65).

Both similarities (66, 67) and differences (68, 69) among ethnic and gender groups have been documented with respect to insulin levels, the degree of insulin resistance, or the relation between insulin sensitivity and obesity. In the Insulin Resistance and Atherosclerosis Study (IRAS), African-Americans and Hispanics seem to be more insulin resistant (as measured by frequently sampled intravenous glucose test with minimal model analyses) when compared with non-Hispanic whites (70). Higher insulin levels have been reported in European-American men, compared with women, that are only in part explained by body mass index or waist-to-hip ratio (71, 72). Karter et al. (66) found insulin sensitivity to be inversely associated with waist-to-hip ratio independent of body mass index in both gender and all ethnic groups in IRAS.

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l. Analytic epidemiologic studies on the multiple metabolic syndrome

Study ference no.)	Study association	Multiple metabolic syndrome definition			Design	Study	Popula-tion size	Demo charact
		Components†	Type	Approach				
ır et al. (6)	Insulin—MMS* components	NIDDM, TG, LDL, HDL, HTN	Discrete	Individual components plus multivariable	Cohort (8 years)	San Antonio Heart Study	1,125	Non-Hispa Mexic Americ 25–64
ıll et al. (17)	Insulin—change in lipids, lipoproteins, blood pressure	G, 2-h-G, TG, TC, HDL, LDL, SBP, DBP	Continuous	Individual components	Cohort (8 years)	San Antonio Heart Study	1,383	Non-Hispa Mexic Americ 25–64
et al. (22)	Insulin/BMI*/WHR*—MMS	NIDDM, TG, HDL, HTN	Discrete	Multivariable	Cohort (3 years)	ARIC* Study	6,113	African-An white, 45–65
ılli et al. (21)	(Common) genetic and environmental influence on MMS components	NIDDM, HTN, obesity	Discrete	Multivariable	Twin study	NAS NRC* twin survey	2,508 pairs	White, M,
ıll et al. (19)	Genetic influences on insulin and MMS components	I, 2-h-I, TG, HDL, SBP, DBP, BMI, WHR, ST	Continuous	Individual components	Family study	San Antonio Family Heart Study	921	Mexican-A M/F, 1
ıt al. (20)	(Common) genetic and environmental influence on MMS components	I, G, TG, HDL, SBP, BMI	Continuous	Multivariable	Twin study	Swedish Adoption/ Twin Study of Aging	289 pairs	White, M/F
ıt al. (196)	Parental history of diabetes/ hypertension—MMS	NIDDM, TG, HDL, HTN	Discrete	Multivariable	Cross-sectional	ARIC Study	14,406	African-An white, 45–65
ıt al. (195)	Maternal versus paternal history of diabetes—MMS components	I, 2-h-I, G, 2-h-G, TG, TC, LDL, HDL, SBP, DBP, BMI, WHR, S, UA	Continuous	Individual components	Cross-sectional	Algonquin Indian communities	352	Algonquin M/F, 3 (mean
dt et al. (25, 34)	Insulin/BMI/WHR—pairs of MMS components	NIDDM, TG, HDL, HTN, UA	Discrete	Multivariable	Cross-sectional	ARIC Study	14,481	African-An white, 45–64
et al. (16)	Insulin—MMS components (genetic plus environmental contributions)	TG, HDL, SBP, DBP, BMI, WHR	Continuous	Individual components plus multivariable	Twin study	Kaiser Permanente Women Twins Study	278 pairs	White, F, 5 (media
ıt al. (30)	Insulin—MMS components	G, TG, TC, HDL, LDL, SBP, DBP, F VII, Fib, BMI, Lp(a)	Continuous	Individual components	Cross-sectional	Jichi Medical School Cohort, Japan	2,606	Japanese, 30–90
et al. (26)	LDL* subclass phenotype B—MMS components	I, TG, HDL, HTN, WHR	Continuous	Individual components plus multivariable	Twin study	Kaiser Permanente Women Twins Study	341 pairs	White, F, 5 (media
r et al. (106)	LDL size and subclass phenotype B—MMS	G, TG, HDL, HTN	Discrete	Individual components plus multivariable	Cross-sectional	San Antonio Heart Study	488	Non-Hispa Mexic Americ 50 yea

S, multiple metabolic syndrome; BMI, body mass index; WHR, waist-to-hip ratio; LDL, low density lipoprotein; ARIC, Atherosclerosis Risk in Communities; NAS NRC, National Academy of
esearch Council.
components: I, insulin; 2-h-I, 2-hour-insulin; G, glucose; 2-h-G, 2-hour-glucose; NIDDM, non-insulin-dependent diabetes mellitus; TG, triglycerides; TC, total cholesterol; LDL (low density l
l; HDL (high density lipoprotein) cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; BMI, body mass index; WHR, waist-to-hip ratio; S, subscapul
ST, subscapular/triceps ratio; UA, uric acid; F VII, factor VII; Fib, fibrinogen; Lp(a), lipoprotein (a).
ographic characteristics: M, male; F, female; race/ethnic group; age range in years (unless otherwise specified).

Insulin resistance and obesity in the pathogenesis of non-insulin-dependent diabetes mellitus

The interrelation between insulin and obesity is exemplified in the development of non-insulin-dependent diabetes mellitus. A large number of primarily clinical studies indicate that insulin resistance is a feature of both non-insulin-dependent diabetes mellitus and obesity (3, 12). Insulin resistance causes elevations in blood glucose that are compensated, at least temporarily, by increased insulin secretion. This intermediate step may be classified as impaired glucose tolerance. When insulin secretion begins to fail, however, hyperglycemia appears and non-insulin-dependent diabetes mellitus becomes manifest (73–75).

The predictive role of body mass index, body fat distribution, and weight gain on the development of non-insulin-dependent diabetes mellitus has been reported consistently in prospective population-based studies (76–82). Insulin has also been shown to predict impaired glucose tolerance (83) and non-insulin-dependent diabetes mellitus independent of body mass index and glucose in the Mexican-American and non-Hispanic white population of the San Antonio Heart Study (6, 79). Findings in the Pima Indians (73, 84) and the male population enrolled in the Paris Prospective Study (85) similarly indicated that fasting insulin levels (and other measures of insulin secretion and insulin resistance) predict the development of non-insulin-dependent diabetes mellitus independent of obesity. It is unclear to what extent differences in body fat distribution, the level of obesity, and insulin resistance can explain the marked differences in prevalence of non-insulin-dependent diabetes mellitus in populations (67, 76, 86–89).

Insulin resistance and obesity in the pathogenesis of dyslipidemias

The association of insulin and insulin resistance with very low density lipoprotein (VLDL) cholesterol and triglyceride levels is well documented epidemiologically (90–93). In the male participants of the San Antonio Heart Study, insulin was the primary correlate of triglycerides, but insulin, body mass index, and waist-to-hip ratio were independently associated with HDL cholesterol, a finding similar to that of the cross-sectional analyses of the Paris Prospective Study (91). Somewhat different results were reported in the European Fat Distribution Study, where all three variables were associated with triglycerides in men, but only body mass index was independently associated with HDL cholesterol (94). In European premenopausal women, both insulin and waist circumference were independently associated with triglycerides, HDL cholesterol, and total cholesterol (95), while body mass index was not an independent correlate. In an American study population of premenopausal women (96), insulin and body mass index were both associated with HDL cholesterol and triglycerides, but waist-to-hip ratio was not included in the analyses. In Mexican-American and non-Hispanic white women, all three variables were associated with HDL cholesterol and, with the exception of waist-to-hip ratio, with triglycerides (97). In contrast, a Finnish study including postmenopausal women reported that only measures of fasting insulin or insulin sensitivity were associated with various lipid levels (98). These cross-sectional associations between insulin and dyslipidemias have additionally been demonstrated at varying degrees of glucose tolerance (99).

Addressing temporal relations, Haffner et al. (6) reported that baseline insulin significantly predicted the development of elevated triglycerides, low HDL cholesterol, but not elevated LDL cholesterol in a population of middle-aged adults independent of age, gender, ethnicity, body mass index, and centrality. A Finnish prospective study of elderly people (100) focused on the association of insulin with various lipids and lipoproteins and reported that hypertriglyceridemia, high apolipoprotein B, and low apoprotein A1 at follow-up were significantly associated with baseline insulin. With the exception of the latter association, this relation was not independent of baseline lipid levels. The authors interpreted this observation as indicating that compositional changes in lipoproteins, rather than adverse changes in absolute concentrations, are associated with increased insulin levels.

The biologic mechanisms linking insulin resistance and lipid levels are still being explored (3, 101, 102). Central obesity, which is clearly associated with insulin resistance, is also associated with mobilization of free fatty acids which, in turn, are metabolized into triglycerides (103, 104). While the inverse relation between triglyceride and HDL cholesterol levels is well established, the possible independent mechanisms linking insulin to HDL cholesterol are less well understood. Hepatic lipase, cholesterylester transfer protein, and lecithin cholesterol acyltransferase have been proposed as instrumental (90, 105).

LDL particle size is associated with both specific insulin and proinsulin (106). LDL subclass phenotype B, which is characterized by small, dense LDL particles, is associated with increased levels of triglycerides, VLDL, intermediate density lipoprotein, and decreased levels of HDL cholesterol independent of age, gender, and body mass index. The similarities between

the atherogenic lipoprotein profile (107) of LDL phenotype B and that of the multiple metabolic syndrome (26, 108), plus the observation that LDL phenotype B is prevalent among families with familial combined hyperlipidemias (109), led to the suggestion that LDL subclass phenotype B may well be an integral part of the multiple metabolic syndrome (26, 45).

In a study of women twins (26), the prevalence of LDL subclass phenotype B increased steadily with the number of co-occurring metabolic disorders. Furthermore, waist-to-hip ratio, body mass index, systolic blood pressure, triglycerides, HDL cholesterol, and fasting insulin were all independently associated with LDL subclass phenotype B. With the exception of systolic blood pressure, the same variables were associated with LDL particle size. These results have been corroborated in part in other populations that have included both men and women of different ethnic backgrounds (106, 110, 111). LDL size has been demonstrated to be smaller in diabetics than in nondiabetics cross-sectionally (112), and the prevalence of LDL subclass phenotype B higher. Interestingly, the association of diabetes with LDL size was stronger in women. A case-control study has also demonstrated that LDL subclass phenotype B is associated with a significantly increased risk of myocardial infarction, independent of body mass (107). A recent study by Austin et al. (113) reported that LDL phenotype B preceded the onset of non-insulin-dependent diabetes mellitus in an elderly population and was a risk factor for the development of non-insulin-dependent diabetes mellitus independent of waist-to-hip ratio, family history of diabetes, and hypertensive medication. However, the association was reduced to nonsignificance after the inclusion of fasting insulin at baseline, which emphasizes the tight association of insulin resistance with the lipid metabolism.

Insulin resistance and obesity in the pathogenesis of hypertension

While the predictive role of obesity and central adiposity for the development of hypertension is well established (114–116), the role of insulin is still under debate (23, 91, 96, 117–121). The mechanisms postulated to be responsible include increased sympathetic nervous activity, altered cation transport, increased sodium reabsorption, decreased peripheral blood flow, and proliferation of smooth muscle cells (3, 122). A family study of offspring of hypertensive Mexican-Americans reported a significant correlation between insulin sensitivity and salt sensitivity that was not explained by body mass index (123). Two recent reviews have focused on the role of insulin in hypertension (14, 124).

Cross-sectional findings on the relation of insulin with blood pressure (125) have been particularly inconsistent. The San Antonio Heart Study (97) and the Beaver County Study (92) demonstrated a significant association between insulin and both systolic and diastolic blood pressure in men that was independent of body mass index and waist-to-hip ratio. In contrast, in European men only body mass index and waist-to-hip ratio, but not insulin, were significantly associated with either blood pressure measurement (91, 94). Both insulin and body mass index were significantly and independently associated with both systolic and diastolic blood pressure in premenopausal European-American women (96), but only body mass index was associated with either blood pressure in European women (95) and in the female population of the San Antonio Heart Study (97). In the Beaver County Study women, insulin and body mass index were independently associated with systolic blood pressure, while for diastolic blood pressure only body mass index remained informative (92). Saad et al. (126) reported a significant association between blood pressure and fasting insulin and insulin resistance independent of body mass and fat distribution in European-Americans, but not in Pima Indians or African-Americans.

Findings from prospective studies are still scarce. Only few studies have shown insulin as a predictor of incident hypertension independent of body mass index, waist-to-hip ratio, weight change (127), and baseline blood pressure (128). Studies reporting a significant association that was either removed once body mass index was controlled (120, 129) or limited to lean individuals (6, 130) raise the issue whether obesity may be an intermediary factor and statistical control, in fact, an overadjustment. Findings by Liese et al. (131) on the predictive association of elevated insulin with incident hypertension occurring in combination with diabetes or dyslipidemias independent of body mass index and waist-to-hip ratio, but not with hypertension occurring in isolation, support the concept of an etiologic heterogeneity of hypertension.

Insulin resistance and obesity in cardiovascular disease development

Reaching beyond the associations between insulin and various metabolic disorders, prospective cardiovascular disease morbidity and mortality studies have pointed toward an atherogenic potential of insulin. Most publications on this issue have been summarized by Ferrara et al. (132) and McKeigue and Davey (133) and are, therefore, not included in table 4. Results of the Helsinki Policemen Study (121) indicated that 1-hour postload insulin at baseline was associated with an increased risk of coronary heart disease indepen-

dent of body mass. After 15 years of follow-up in the Paris Prospective Study, 2-hour postload insulin was predictive of coronary heart disease mortality in men independent of body mass (134). Interestingly, body mass index was not a significant predictor for coronary heart disease mortality after age, blood pressure, smoking, total cholesterol, and insulin were taken into account. A different publication on the same study population confirmed previous results and additionally found iliac-to-thigh ratio to be a significant predictor of coronary heart disease mortality (135). Additional findings in men (136, 137) have since supported the predictive role of serum insulin, but also have been contradicted (132, 138, 139). Findings in women have similarly been conflicting (139, 140). Additional support for the potential independent effect of insulin resistance on atherogenesis comes from IRAS (141). Insulin sensitivity was inversely associated with intimal-medial thickness of the carotid artery in Hispanics and non-Hispanic whites.

Several studies have shown general obesity and central adiposity to be a significant risk factor for cardiovascular disease, oftentimes independent of such traditional risk factors as smoking and cholesterol (142–145). In the Charleston Heart Study, body mass index was associated with coronary heart disease mortality in European-American but not in African-American women (146). Conversely, body mass index was not associated with coronary heart disease mortality in European-American men but was in African-American men (147).

The association of insulin with cardiovascular disease mortality may be due to direct atherogenic effects of insulin or, as the critics point out, mediated through its association with confirmed cardiovascular disease risk factors (148–151). Further questions arise from the observation that Pima Indians, an ethnic group with high prevalence of central obesity and diabetes and high fasting insulin levels, have a low incidence of cardiovascular disease (152).

GENETIC EPIDEMIOLOGY

Research on the genetic epidemiology of the multiple metabolic syndrome has started to address many of the questions outlined in the preceding sections. Simultaneously it cuts across previously circumscribed areas of research and adds a new dimension of complexity. Population-based epidemiologic studies typically have evaluated the independent contribution of specific physiologic characteristics. The application of this paradigm becomes increasingly more complex as the knowledge of genetic influences increases.

The concept of heritability, the proportion of phenotypic variance attributable to genetic differences, is frequently employed in genetic epidemiology. Important for the interpretation of these estimates is that heritability is a highly population-specific parameter, which assumes that the underlying biologic mechanisms are strictly mendelian, including a lack of gene-environment interaction. Furthermore, twin studies probably provide what can be considered an upper estimate of heritability (153).

Genetic determinants of insulin resistance and obesity

The heritability of insulin concentrations has been estimated as 0.50 in a large study of women twins (16). Family studies of the genetic determinants of insulin resistance have focused on families with diabetic members. The strong similarity of insulin levels among sibling pairs points toward the influence of several additive genes (154). While the majority of families demonstrated a moderate amount of within-family variability, a group of families with the lowest values for insulin sensitivity demonstrated the largest within-family variability. This latter observation would be consistent with the presence of an autosomal dominant trait in a subset of families (154). Commingling analyses (155) and segregation analysis support the role of a major genetic locus in the determination of fasting insulin levels and sensitivity (156).

Strong genetic components in the etiology of obesity have been demonstrated repeatedly (157–159). Heritability analyses indicate that 70 percent of the variation in body mass index levels may be explained by genetic components. Després et al. (158) found a low heritability of subcutaneous fat, but a higher heritability for deep or visceral fat. Change in body mass index may also be highly heritable (160). Despite the strong influence of genes on obesity, the non-genetic determinants of obesity and weight change in adulthood, such as dietary behavior, life style, and physical activity, seem important for the influence of obesity on other cardiovascular disease risk factors, as demonstrated by Newman et al. (161).

Population studies have shown that fasting insulin levels in middle-aged non-diabetics increase in a stepwise fashion with the number of diabetic parents (162–164). A similar relation was shown with body mass index but this was nonetheless significant and independent of insulin levels. Non-diabetic first degree relatives of patients with non-insulin-dependent diabetes mellitus have been shown to be more insulin resistant (165–167). In contrast, the association of waist-to-hip ratio or centrality index with family histories has been less consistent (168). A positive family history of hypertension was also associated with higher insulin levels and waist-to-hip ratio even after adjust-

ment for body mass index and exclusion of individuals with a family history of diabetes (164). This same study reported that in multiple regression analyses, body mass index was the strongest predictor for fasting insulin levels, followed by weight change and parental history of hypertension and diabetes.

Environmental influences on insulin levels and obesity have similarly been demonstrated. Insulin levels seem to be associated positively with fat intake (169) and inversely with habitual physical exercise (170, 171) and moderate alcohol consumption (172). A combination diet and exercise program resulted in weight loss and substantially decreased levels of insulin in diabetics, insulin resistant non-diabetics, and normal individuals (173). Habitual cigarette smokers tend to be more insulin resistant and have higher fasting insulin levels than matched nonsmokers (174, 175).

Given that insulin and obesity seem to be both genetically and environmentally influenced, the question arises how their mutual relation can be described, whether their strong correlations are more under genetic or environmental control. A study of monozygous twins on the association between insulin, body mass index, and waist-to-hip ratio, by Mayer et al. (16), was able to provide some insight into this question by contrasting results of an unmatched analysis (in which twins are included as individuals and genetic differences are "permitted") with a matched analysis (in which all genetic influences are removed by focusing on twin intrapair differences). While insulin levels were associated independently with body mass index, waist-to-hip ratio, and glucose intolerance in the unmatched analyses, after removal of all genetic influences insulin levels were only associated with body mass index. These results indicate that aside from the genetic influences on insulin levels, especially nongenetic variation in obesity is an important determinant of insulin levels.

Genetic determinants of non-insulin-dependent diabetes mellitus, dyslipidemias, and hypertension

Intensive research on the genetic basis of non-insulin-dependent diabetes mellitus led to the concept that this disease is not a monogenic but, rather, a complex disorder (176). Recently, Hanis et al. (177) reported the first evidence for a major susceptibility locus for non-insulin-dependent diabetes mellitus on chromosome 2 in a Mexican-American study population. Their results may provide the basis for future genetic analyses. An indication that genes may play a more predominant role has come from twin (178, 179) and migration studies (180). Substantial evidence for environmental influences on non-insulin-dependent diabetes mellitus development exists (179, 181).

Familial influences (genetic and environmental) have been implicated in the development of non-insulin-dependent diabetes mellitus by a variety of studies assessing the contribution of a positive family history (46, 76, 81, 182). Metabolic studies of first-degree relatives of non-insulin-dependent diabetes mellitus patients have helped elucidate the metabolic impairments and the role of insulin concentrations and insulin resistance therein (163, 165, 167).

High heritabilities of various lipids have been reported in female twins (157) and moderate heritabilities in male twins (183). Morrison et al. (184) have shown that with increasing severity of a probands' hypercholesterolemia, the percent of affected siblings and offspring increases. About 50 percent of the variation in LDL peak particle diameter may be due to genes (185), leaving significant room for environmental influences: 63 percent of female twins were discordant for LDL subclass phenotype (26).

Familial aggregation of blood pressure has also been documented consistently (186–188). As would be expected, a parental history of hypertension is associated with increased levels of systolic and diastolic blood pressure (164). Family studies have included segregation, association, and linkage studies as reviewed by Williams et al. (189). While several loci seem to be implicated, their relevance to essential hypertension in the general population is yet to be assessed. Heritability estimates in women twins (157) were moderate for systolic blood pressure (0.34–0.42) and marginal for diastolic blood pressure (0.23–0.33) compared with male twins (approximately 0.60 for both systolic and diastolic blood pressure) (183).

Clustering in the framework of genetic epidemiology

The clustering of metabolic disorders has also been evaluated in the framework of genetic epidemiology (table 3). Research on metabolic disorders such as familial combined hyperlipidemia (109, 190, 191) and familial dyslipidemic hypertension (45, 192) has pointed toward the importance of familial components in the etiology of combination disorders reminiscent of the multiple metabolic syndrome.

A recently published twin study by Carmelli et al. (21) reported significantly higher concordance rates of clusters of diabetes, hypertension, and obesity in monozygotic versus dizygotic twins. These were reflected in very high, statistically significant relative risks (range 2 to 11) of being concordant associated with monozygotic twin status, which speaks to the genetic and shared environmental component of clus-

tering. Similar results have been reported by Selby et al. (45) for dyslipidemic hypertension. However, since a substantial proportion of monozygotic twins were discordant for the traits in both studies, the environmental or behavioral influences should not be overlooked.

Edwards et al. (193) estimated the heritability of the three uncorrelated factors, body mass/fat distribution, insulin/glucose, and lipids obtained from factor analysis and reported moderate to high heritabilities particularly of the former two factors. Their findings support the concept that genetic influences are relevant in the clustering of multiple metabolic syndrome components. Mitchell et al. (19) examined genetic and environmental influences on insulin levels and other components of the syndrome. They reported high genetic correlations between insulin and body mass index, triglycerides, and HDL, respectively. These and other studies (20, 21) have suggested that a common gene or set of genes may influence the clustering of components of the multiple metabolic syndrome.

Several epidemiologic, population-based studies have pointed toward the influence of familial components on the offspring's cardiovascular disease risk factor levels or disorder status (194–196). Burke et al. (194) reported that with an increasing number of disorders in the parental generation, metabolic and hemodynamic measures in the offspring tended toward less favorable risk factor levels. In young African-Americans, however, this association held only for blood pressure and body mass index. Liese et al. (196) have recently shown in the ARIC Study that a parental history of multiple metabolic syndrome components was associated with the clustering of multiple metabolic disorders in the offspring generation. Individuals with diabetes, hypertension, and dyslipidemia were significantly more likely to have had parents with diabetes or hypertension, or combinations thereof, than individuals with zero, one, or two metabolic disorders.

NATURAL HISTORY OF THE MULTIPLE METABOLIC SYNDROME

As the preceding sections have shown, each component of the multiple metabolic syndrome is influenced strongly by genes and the environment. The same might be said on the clustering of these conditions.

Few longitudinal studies document the natural history of the multiple metabolic syndrome, either in terms of the temporal relations between hyperinsulinemia, obesity, and other components of the multiple metabolic syndrome or the sequence in the development of clinical component disorders. A more comprehensive study on the prospective association of hyperinsulinemia with incident component disorders of the multiple metabolic syndrome was offered by Haffner et al. (6). In the San Antonio Heart Study population, hyperinsulinemia predicted non-insulin-dependent diabetes mellitus, low HDL cholesterol, high triglycerides, and hypertension independent of body mass index and index of centrality (with the exception of hypertension). Furthermore, baseline insulin levels were positively associated with an increasing number of component disorders of the multiple metabolic syndrome at follow-up, a finding that has since been replicated in other study populations (22, 197). Regarding the sequence of the development of disorders, however, most information on the natural history of the multiple metabolic syndrome must be assembled from publications focusing usually only on pairs of disorders (113, 198–203).

Given the involvement of obesity and insulin resistance in determining glucose tolerance, and the association of obesity with hypertension, one would expect that impairments of the glucose metabolism are associated with incident hypertension. Haffner et al. (198) reported that non-insulin-dependent diabetes mellitus was an independent risk factor for hypertension in women; in men, however, the association pointed in the same direction but did not reach statistical significance. Several studies (e.g., 199, 201) found that impaired glucose tolerance predicted incident hypertension in both men and women. Contrasting findings have also been reported (198, 203, 204). Vaccaro et al. (203) interpreted their finding of a nonsignificant protective association as consistent with the hypothesis that impaired glucose tolerance and hypertension share one or more antecedent factors which may first cause the development of hypertension and then the development of impaired glucose tolerance.

In the San Antonio Heart Study (200), baseline hypertension was associated with a twofold increase in risk of impaired glucose tolerance independent of body mass index, glucose, and insulin, and hypertensive medication, a finding similar to the San Luis Valley Diabetes Study (204). Hypertension was not, however, a risk factor for non-insulin-dependent diabetes mellitus (200). These findings seem highly plausible in the context of the two-step model of non-insulin-dependent diabetes mellitus development which posits that the transition from normal to impaired glucose tolerance is affected by insulin resistance, while the second step, the transition from impaired glucose tolerance to non-insulin-dependent diabetes mellitus, is not. Thus underlying insulin resistance associated with hypertension may be responsible for the association of impaired glucose tolerance

with hypertension. In the same study population, Stern et al. (202) found pulse pressure to be another significant predictor of incident non-insulin-dependent diabetes mellitus controlling for baseline fasting glucose, body mass index, and HDL cholesterol. Austin et al. (113) recently reported that LDL phenotype B was a significant predictor of non-insulin-dependent diabetes mellitus though not independent of baseline insulin. Baseline triglycerides were also associated with an increased risk of non-insulin-dependent diabetes mellitus independent of glucose and body mass index (76, 197).

To date, information is lacking on the sequences of disorders over time and the distribution of incident disorder combinations. Future studies will hopefully provide insight into temporal relations and offer information on the question of whether the multiple metabolic syndrome may actually describe several similar but etiologically distinct conditions or syndromes. Etiologic heterogeneity may be one possible explanation for some of the inconsistent findings reviewed and may be obscuring some of the relations.

OUTLOOK

As this review has shown, insulin resistance and obesity are integral in the development of the multiple metabolic syndrome. It has long been recognized that having multiple cardiovascular disease risk factors exerts a synergistic effect on the risk of developing cardiovascular disease (205). Yet recent studies have focused on the independent contribution of insulin resistance or hyperinsulinemia (table 4) and much less on the multiple metabolic syndrome as a metabolic risk factor constellation that includes many other, nonmetabolic correlates. This shift in perspective is also evident in the lack of studies on behavioral and environmental correlates of the multiple metabolic syndrome. One of the challenges of public health will be to identify effective preventive measures for insulin resistance, obesity, and the development of additional components of the multiple metabolic syndrome, particularly measures that will ultimately reduce the risk of cardiovascular disease. In the United States, approximately 42 percent of men and 52 percent of women in their fifties are overweight (206) and the co-occurrence of metabolic disorders is a common phenomenon (23, 34, 207). The fact that temporal trends of the prevalence of obesity have been increasing in many countries (206, 208, 209) therefore underscores the relevance of research on the etiology and on the prevention of the multiple metabolic syndrome.

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