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General Characteristics of the Insulin Resistance Syndrome

Prevalence and Heritability

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Abstract

It has recently been recommended by a WHO expert committee that the insulin resistance syndrome, a cluster of cardiovascular risk factors linked to insulin resistance, should be termed 'the metabolic syndrome'. Characterisation with data from 2 large databases [the European Group for the study of Insulin Resistance (EGIR) and the Danish Twin Register] has shown that insulin resistance correlates closely with the various components of the metabolic syndrome, and that the prevalence of the syndrome is approximately 16% among Caucasians. Both genetically determined and environmentally induced insulin resistance may precipitate onset of the metabolic syndrome, and increased levels of abdominal fat may be of primary importance in its development.

Insulin resistance is known to be associated with cardiovascular risk factors, as initially demonstrated 10 years ago by Reaven and co-workers when they presented their description of 'syndrome X'.[1] Since then, the syndrome and its components have been discussed, and the cut-off levels for the individual contributing factors have also undergone investigation. However, lack of a definition of the syndrome has made it difficult not only to investigate its role in the development of cardiovascular disease and type 2 diabetes, but also to study the relationship between insulin resistance and the other components of the syndrome. A WHO expert committee has nevertheless recently proposed that the syndrome be referred to as 'The Metabolic Syndrome' and that its definition should focus mainly on its relationship to cardiovascular disease (table I).[2]

The expert committee decided to define insulin resistance as insulin sensitivity under hyperinsulinaemic euglycaemic clamp conditions below the lowest quartile for the population under investigation. This definition was chosen empirically, but the lowest quartile of insulin sensitivity in normal individuals matches the degree of insulin resistance in, for example, patients with type 2 diabetes. The committee proposed that metabolic syndrome should be diagnosed in patients who have glucose intolerance and/or insulin resistance together with 2 other components of the syndrome (table I). The

Table I. The metabolic syndrome (insulin resistance syndrome)

Insulin resistance: insulin sensitivity below lowest quartile for the population
Glucose intolerance: 2-hour OGTT plasma glucose level >7.8 mmol/L
Abdominal obesity: WHR female >0.85, male 0.95
Blood pressure >160/95mm Hg
Triglycerides >1.7 mmol/L
HDL-cholesterol: female <1.1 mmol/L, male ≤0.9 mmol/L

HDL = high density lipoprotein; **OGTT** = oral glucose tolerance test; **WHR** = waist **:** hip ratio.

Table II. Characteristics of individuals in the European Group for the study of Insulin Resistance (EGIR) database

	Mean ± SD (range)
Age (y)	42 ± 16 (18-85)
Height (cm)	172 ± 10 (140-200)
Weight (kg)	77 ± 15 (40-151)
BMI (kg/m^2)	25.7 ± 4.7 (15.4-55.1)
Fasting plasma glucose (mmol/L)	5.1 ± 0.5 (3.2-6.7)
Fasting plasma insulin (pmol/L)	62 ± 40 (10-343)
Steady-state plasma glucose (mmol/L)	5.0 ± 0.5 (3.4-7.1)
Steady-state plasma insulin (pmol/L)	492 ± 131 (146-1.198)
M-value (μmol/min/kg bodyweight)[a]	34.3 ± 13.1 (2.5-102.2)
M-value (μmol/min/kg FFM)	49.1 ± 17.7 (3.6-127.1)

a The M-value is the glucose disposal rate during the final 40 minutes of the euglycaemic insulin clamp normalised by the individual's bodyweight or FFM. There were 1146 participants in this study group (67% men and 33% women).

BMI = body mass index; **FFM** = fat free mass.

WHO definition of syndrome X (the insulin resistance syndrome or, as is now proposed, the metabolic syndrome) will be used in this paper, which deals with the characterisation of the syndrome according to results from the European Group for the study of Insulin Resistance (EGIR) database and the Danish Twin Register.

The EGIR database has been assembled during recent years with data from approximately 1500 hyperinsulinaemic, euglycaemic clamp studies in normal Caucasians from 21 clinical centres all over Europe.[3] The characteristics of the individuals in the database are given in table II, which shows the wide ranges of ages and bodyweights covered. Only individuals with fasting plasma glucose levels below 7.8 mmol/L and normal glucose tolerance during an oral glucose tolerance test (OGTT) were included. In addition, blood pressure was required to be lower than 160/95mm Hg, with no drug treatment being allowed. The exclusion of patients with diabetes or hypertension should be taken into account when viewing the data. With the WHO definition of the metabolic syndrome (i.e. insulin resistance + 2 other components), we found the prevalence of the metabolic syndrome in healthy Caucasians to be 15.6%. Less than 1% of the population presents with all the components of the syndrome.

We have in Denmark the most complete register of twins in the world, with a detection rate of more than 90%.[4] On the basis of a survey of all twins aged between 55 and 75 years (individuals known to have diabetes were excluded), we calculated the prevalence of the metabolic syndrome in Danish twins to be 12.5% (table III). This is close to the result obtained with the EGIR database, despite the fact that the Danish participants were older. It should be noted that these estimates are likely to be conservative because of the exclusion of individuals with overt diabetes.

When discussing the pathophysiology of the metabolic syndrome, it is important to consider whether insulin resistance underlies the other components (or vice versa) or precedes them chronologically. From a physiological viewpoint, insulin resistance is presumed to contribute to impaired glucose tolerance, increased blood pressure and dyslipidaemia.[5] However, the premise that insulin resistance is the primary defect needs to be tested before it can be accepted. The EGIR database, which represents the largest collection of clamp study and anthropometric data in Europe, offers a unique resource for this purpose.

We found that the degree of insulin resistance (M-value: glucose disposal rate during the final 40 minutes of the euglycaemic insulin clamp normalised

Table III. Overall prevalence of the components included in the metabolic syndrome among twins (n = 606)

	Prevalence (% of total)
Hyperinsulinaemia	20.6
Glucose intolerance	34.0
Abdominal obesity	30.7
Overall obesity	38.9
Hypertension	19.6
Triglycerides	23.9
HDL-cholesterol	9.9
Metabolic syndrome (hyperinsulinaemia + 2 other components)	12.5

HDL = high density lipoprotein.

by bodyweight or fat free mass) was statistically significantly correlated with all other components of the syndrome, including fasting plasma insulin levels ($r = –0.48$; $p < 0.01$), waist : hip ratio ($r = –0.14$; $p < 0.01$), fasting plasma triglyceride levels ($r = –0.26$; $p < 0.01$), high density lipoprotein (HDL)-cholesterol levels ($r = 0.14$; $p < 0.01$) and diastolic blood pressure ($r = –0.22$; $p < 0.01$). Multiple regression analysis indicated a specific correlation between M-values and fasting plasma insulin levels only, and only 50% of the variation in the M-value could be explained by the components of the syndrome. This indicates that other variables may play a role in the determination of the severity of insulin resistance. Physical fitness is an obvious candidate in this respect, as is intrauterine malnutrition. Notwithstanding this finding, the significant correlation between the M-value and the components of the metabolic syndrome is in agreement with the hypothesis that insulin resistance may be a common denominator underlying the other components of the syndrome. Since multiple regression analysis suggests that insulin resistance correlates only with fasting plasma insulin levels, however, the effect of insulin resistance on this latter component may be to some extent secondary to hyperinsulaemia itself. This conclusion makes sense, since it has been shown that hyperinsulinaemia may induce both dyslipidaemia and arterial hypertension.[5]

In addition to the question of whether insulin resistance precedes the other components of the metabolic syndrome, it is possible that insulin resistance itself could be secondary to, for example, abdominal obesity. In the Joslin Diabetes Center study, outcomes in the offspring of parents with type 2 diabetes indicated that insulin resistance may precede diabetes;[6] results of investigations in first-degree relatives of patients with type 2 diabetes were in agreement with this observation, since they appeared to show development of insulin resistance 2 to 3 decades before overt diabetes.[7] These findings in individual studies have been confirmed by data from the EGIR database, which show that non-oxidative glucose metabolism is reduced in individuals with a family history of type 2 diabetes. In conclusion, our results are in accordance with the hypothesis that early insulin resistance may provoke the development of the full metabolic syndrome; further studies are urgently needed to confirm this.

Table IV. Heritability of some of the components of the metabolic syndrome

Phenotype	Heritability: $2(r_{MZ}-r_{DZ})$
Weight	0.78
Body mass index	0.80
Fasting plasma insulin	0.26

MZ = monozygotic twin; **DZ** = dizygotic twin.

Genetic heritability of the insulin resistance trait would serve as a further indicator of insulin resistance as the primary defect in the metabolic syndrome. In our studies in twins, interclass correlations in monozygotic (MZ) and dizygotic (DZ) pairs were used to calculate heritability [i.e. the proportion of the total variance in a trait which is attributable to genetic variation under a polygenic model described by $h^2 = 2(r_{MZ}-r_{DZ})$]. Heritabilities of the components of the insulin resistance syndrome as estimated according to this equation are shown in table IV.[8] The most interesting finding was that the body mass index carries a high degree of genetic determinance ($h^2 = 0.80$), whereas the waist : hip ratio seems to be influenced mainly by environment (i.e. Western lifestyle with a high fat intake and low levels of physical activity). Insulin resistance was not measured in the twins population, and fasting plasma insulin levels were therefore used as a surrogate measurement. We have shown that this trait has an h^2 value of only 0.26, which is in agreement with several previous investigations.[8] Overall, the genetic contribution to insulin resistance (measured as fasting plasma insulin levels) is in the order of 40%, which indicates that environmental factors play a more important role than genetic factors. It may therefore be concluded that environmental factors predominate in the development of insulin resistance, and that increased levels of intra-abdominal fat play a specific role. In other words, in the majority of cases, the metabolic syndrome may be caused by a

Western lifestyle, but tends to develop in genetically susceptible individuals.

Our conclusions are therefore as follows:

- The prevalence of the metabolic syndrome in Caucasians is about 16%.
- Insulin resistance is closely correlated with the components of the metabolic syndrome.
- Both genetic insulin resistance and environmentally induced insulin resistance may lead to the development of the metabolic syndrome.
- Increased body fat may be a primary event in the development of the syndrome.

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