Epidemiology of the Metabolic Syndrome

2

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2.1 Introduction

Insulin resistance—an essential component of the metabolic syndrome—has been known for nearly 70 years. Himsworth [1] suggested the existence of two different types of diabetes: one characterised by high levels of insulin sensitivity (what we now know as type 1 diabetes, characterised by beta-cell destruction) and another characterised by insulin insensitivity (what we now know as type 2 diabetes, characterised by insulin resistance). Detailed, explanatory studies in this field were impossible until the introduction of the radioimmunoassay for insulin in 1960 [2]. This technology opened the door for larger studies of the role of insulin resistance in relation to diabetes as well as to cardiovascular disease (CVD). Throughout the following 25 years the association between hypertension, dyslipidaemia, glucose intolerance and hyperinsulinaemia was established through first smaller case–control studies and subsequently through large, population-based studies [3–6].

In 1988 Reaven reviewed the existing knowledge around the association between insulin resistance and a variety of metabolic risk factors for diabetes and CVD in his paper "Role of insulin resistance in human disease" [7]. Reaven had a background in physiology, and he concludes his review by elegantly proposing a hypothesis offering the suggestion that insulin resistance could be the common denominator underlying a syndromic clustering of metabolic risk factors explaining the clustering of CVD risk factors in selected groups. By doing so, he offered a pathophysiological model that could be tested, confirmed or rejected. The scientific community rather uncritically accepted his suggestion of a new "syndrome", and rather than designing studies that could test his hypothesis, a plethora of studies confirming the basic associations or proposing new markers that were also

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associated with insulin resistance were published. Through this process, epidemiology contributed more to confusion than to clarity and understanding. The observational evidence of association was all too often taken as evidence of causality. The literature proliferation popularised the concept of the "metabolic syndrome", and from being hypothesised in 1988 it became fully established by the World Health Organization (WHO) in 1999 [8]. The underlying rationale was reviewed by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) in 2005 [9], and they concluded that: "the criteria are ambiguous and incomplete; the rationale for thresholds are ill defined; the value of including diabetes in the definition is questionable; the role of insulin resistance as the unifying aetiological factor is uncertain; there is no clear basis for including or excluding other CVD risk factors; the CVD risk value is variable and dependent on the specific risk factors present; the CVD risk associated with the "syndrome" appears to be no greater than the sum of its parts; the treatment of the syndrome as a whole is no different from that of each of its components and the medical value of diagnosing the syndrome is unclear".

Despite this rather harsh criticism, the "metabolic syndrome" demonstrated its capacity to survive even in a hostile scientific environment. Definitions of the syndrome were disputed (Chap. 1), but the name survived. Most importantly the rationale changed from being a hypothetical, explanatory physiological model into being that the metabolic syndrome represents an easy risk prediction model identifying individuals at risk of developing CVD (and diabetes) and as such we have learned to live with the term. Many clinicians have found the risk tool easy to use, despite the fact that other risk prediction programmes may be more sensitive and specific in separating those at high risk from those at low risk.

The first section of this chapter will be devoted to classical epidemiological characteristics of the syndrome including global variation in the prevalence of the metabolic syndrome and will focus on the impact of age, gender and ethnicity. The second section of the chapter will focus on the clinical, epidemiological aspects of the syndrome focusing on the ability of the syndrome to predict the risk of developing diabetes and CVD. The concluding section of the chapter will be devoted to reflections on the future of the metabolic syndrome in relation to risk prediction and public health.

2.2 Epidemiology of the Metabolic Syndrome

The rapid changes in the definition over time make it very difficult to compare studies and therefore also to evaluate temporal trends and regional variations in the prevalence of the metabolic syndrome. The most recent definitions have introduced region-specific cut-points for the level of obesity (waist circumference) defining the metabolic syndrome. The introduction of region-specific cut-points is rational from the point of view that the association between obesity and glucose intolerance [10],

Table 2.1 Prevalence of the metabolic syndrome in population-based surveys

Country	Age (year)	Number	Prevalence (%)	Diagnostic criteria	Study
Saudi Arabia	10–18	1,231	10 (M) 8 (F)	NCEP	[15]
Oman	20+	1,419	20 (M) 23 (F)	NCEP	[16]
Turkey	49 ± 13	2,398	27 (M) 39 (F)	NCEP	[17]
Finland	42–60	1,005 males	14 21	NCEP WHO	[18]
India	20+	1,091	8 (M) 18 (F)	NCEP	[19]
United States	12–17	2,014	7 (M) 2 (F)	IDF	[20]
United States	30–79	Framingham offspring 3,224 San Antonio Heart S. 1,081 (white) 1,656 (Mexican Hispanic)	15 (M) 14 (F) 9 (M) 13 (F) 14 (M) 21 (F)	NCEP	[21]
China (urban)	15+	1,206	26 (M) 28 (F)	NCEP	[22]
China (rural)	18–74	13,505 females	22 17 23	IDF NCEP ATP-III modified	[23]

blood pressure [11] and dyslipidaemia [12] varies between ethnic groups. On the other hand, the use of the region-specific cut-points may also mask some of the true regional differences in the prevalence of the syndrome.

2.2.1 Regional Variation in the Metabolic Syndrome

Most epidemiological studies have used definitions that did not include region-specific cut-points for obesity like the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) [13], European Group for the Study of Insulin Resistance (EGIR) [14] or WHO [8]. Using these definitions, population-based studies have demonstrated marked regional differences in the prevalence of the metabolic syndrome. The highest prevalence is found in the Middle East region (Table 2.1), where more than every third person above the age of 20 fulfils the criteria for having the metabolic syndrome.

Within countries, the prevalence also varies by ethnicity. In the National Health and Nutrition Examination Survey III (NHANES III) [24], the age-adjusted prevalence was 30–40 % higher in people of Mexican–American origin than in persons of White and African–American origin.

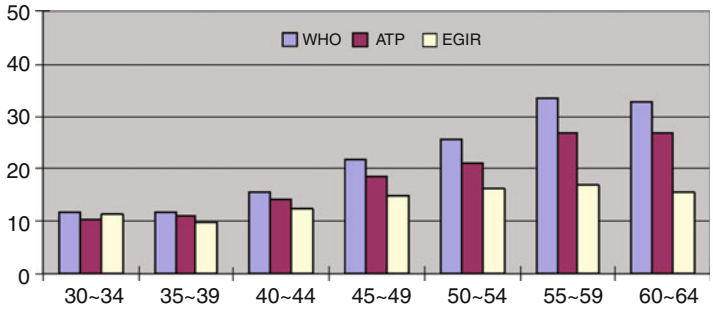

Fig. 2.1 Prevalence of the metabolic syndrome in a population-based sample of 6,667 non-diabetic Danes aged 30–60 years (Inter-99 study). The prevalence increases by age with the diagnostic criteria from the World Health Organization (WHO) [8], the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP-III) [13] and the European Group for the Study of Insulin Resistance (EGIR) [14] although the EGIR criteria are less age dependent

2.2.2 Ageing and the Metabolic Syndrome

The prevalence of obesity, hypertension, dyslipidaemia and hyperglycaemia all increase with age (Fig. 2.1), and thus it is not surprising that the prevalence of the metabolic syndrome also increases by age. In a large, collaborative European study [25–27] including 11 population-based cohorts, the prevalence increased markedly from the age of 30, and similar observations have been made in the United States and China [24, 28]. The prevalence peaks around the age of 60–75 years, whereafter it decreases. This decrease is likely to be explained by differential survival of those with and without the metabolic syndrome.

2.2.3 Gender and the Metabolic Syndrome

Data regarding gender effect are conflicting with the majority of the studies finding the highest prevalence in women compared to men [28, 29] while the collaborative European analysis found no gender difference [26, 27]. The conflicting results with respect to gender effect may partly be explained by the application of different definitions for the metabolic syndrome. When applying the NCEP ATP III and the International Diabetes Federation (IDF) criteria respectively to an Asian Indian population, the gender difference was higher using the NCEP-ATP III definition than when applying the IDF criteria [30].

2.3 Consequences of the Metabolic Syndrome

One important argument for maintaining the concept of the metabolic syndrome has been the assumption that presence or absence of the syndrome predicts the future risk of developing diabetes and CVD, respectively. This assumption is natural as the definition of the metabolic syndrome includes important risk factors for both

diabetes and CVD. Consequently, the rational question is not whether the presence of the metabolic syndrome predicts development of diabetes or CVD, but rather whether the presence of the syndrome predicts these diseases over and above the predictive value of the individual components of the syndrome.

2.3.1 Prediction of Diabetes by the Metabolic Syndrome

Several epidemiological studies have shown that presence of the metabolic syndrome increases the probability of developing type 2 diabetes three to fourfold, and that the risk increases with the number of elements of the syndrome present. This has been shown using several different definitions of the metabolic syndrome [51, 18, 52–54, 31]. Some very strong risk factors for development of type 2 diabetes are not included in the definition, the most important being age and family history. These factors are among the strongest predictors of diabetes in diabetes risk scores like the FINDRISK [32] and the Danish diabetes risk score [33].

In 2004 Stern et al. [34] published an analysis where they compared the NCEP ATP-III definition of the metabolic syndrome [13] with the San Antonio Heart Study risk score for diabetes [35] with respect to ability to predict future development of diabetes. Their analysis was based on two population-based cohorts: the San Antonio Heart Study [36], including 3,301 Mexican Americans and 1,857 non-Hispanic whites, aged 25–64 years at baseline and followed for a median of 7 years and the Mexico City Diabetes Study [55], including 2,282 persons aged 35–64 years followed for a median of 6.3 years. As shown in Table 2.2, both the metabolic syndrome and the diabetes risk score predicted incident diabetes (as expected), but if the effect of the metabolic syndrome was adjusted for the effect of the diabetes risk score, then the odds ratio was reduced from 6.3 to 1.9. In contrast, when the effect of the diabetes risk score was adjusted for the effect of the components of the metabolic syndrome, then this only markedly reduced the odds ratio from 6.5 to 5.2. Consequently, diabetes risk scores appear to be of greater value in identifying those at risk of developing diabetes and therefore at need of lifestyle intervention [38–40].

2.3.2 Prediction of CVD by the Metabolic Syndrome

Numerous studies have confirmed that presence of the metabolic syndrome increases the risk of subsequent development of CVD [18, 26, 27, 41–43]. Unfortunately, some of the definitions of the metabolic syndrome have included individuals with diabetes, and consequently some studies of the association of the syndrome with incident CVD may have been confounded by the strong association between diabetes and CVD.

As was the case for the prediction of diabetes, several important and very strong risk factors for CVD are not included in the metabolic syndrome. The two most

Table 2.2 Odds ratio (95 % confidence interval (CI)) for prediction of diabetes and cardiovascular disease using the metabolic syndrome (NCEP ATP-III), the San Antonio Diabetes Risk Score [35] and the Framingham Risk Score [37]

	Univariate	Multivariate
Prediction of diabetes in the San Antonio heart study		
Metabolic syndrome	6.32 (4.61–8.65)	1.94 (1.34–2.82)
Diabetes risk score	6.46 (4.97–8.40)	5.18 (3.89–6.91)
Prediction of diabetes in the Mexico City diabetes study		
Metabolic syndrome	2.63 (1.80–3.85)	1.15 (0.74–1.77)
Diabetes risk score	4.22 (3.11–5.72)	4.03 (2.87–5.65)
Prediction of CVD in the San Antonio heart study		
Metabolic syndrome	4.28 (3.08–5.94)	1.50 (1.03–2.18)
Framingham risk score	9.41 (6.53–13.6)	7.87 (5.29–11.7)

The multivariate model for prediction of diabetes combined the metabolic syndrome and the diabetes risk score in a stepwise model. The multivariate model for prediction of cardiovascular disease combined with the metabolic syndrome and the Framingham risk score (From [34])
NCEP ATP-III National Cholesterol Education Program Adult Treatment Panel III

important are not only age and smoking but also family history and physical activity are generally included in CVD risk scores.

The previously mentioned study by Stern et al. [34] based on the San Antonio Heart Study and the Mexico City Diabetes Study also analysed whether presence or absence of the metabolic syndrome improved the identification of individuals at risk of developing CVD when risk prediction was based on the Framingham Risk Score for incident CVD [37]. In the analysis of prediction of CVD, only data from the San Antonio Heart Study were included. As shown in Table 2.2, the odds ratio for CVD based on the univariate analysis using the Framingham Risk Score was 9.4 compared with 4.3 for the metabolic syndrome. In the multivariate analysis, where the effect of the metabolic syndrome was adjusted for the effect of the Framingham Risk Score and vice versa, the results were even clearer. In the multivariate analysis, the odds ratio using the metabolic syndrome decreased from 4.3 to 1.5, while for the Framingham Risk Score decreased from 9.4 to 7.9. Similar conclusions were drawn by Eddy et al. [44] and Sattar et al. [31] based on other CVD risk scores.

2.4 The Future of the Metabolic Syndrome in Epidemiology, Risk Prediction and Clinical Practice

While the definition of the syndrome has been disputed, and while its relevance as risk predictor for diabetes and CVD is still controversial, there is still no doubt that the term has been established and is likely to stay. Unless the definition of the syndrome continues to change, it may also be a simple tool for monitoring the

future societal risk diabetes and CVD based on risk factors that can easily be monitored. This type of monitoring at regional or country level may guide health authorities in prioritising and targeting their preventive efforts.

At the individual level, presence or absence of the metabolic syndrome appears to create a tool for guiding the clinician and the patient with respect to the risk of developing diabetes. For diabetes, other risk assessment tools are available. Most of these can be self-administered and most do not require blood sampling or measurements by health professionals [32, 33, 45–48]. The challenge when using risk scores, however, seems to be sure they are implemented rather than choosing the right test [49].

For prediction of CVD, the problem is even greater. Although the metabolic syndrome predicts the development of CVD, it is still by far outperformed by other, very well-validated CVD risk scores like the Framingham Risk Score and by the European correspondent, the Systematic Coronary Risk Evaluation (SCORE) [50].

The real importance of the syndrome may well be reverting to the hypothesis formulated by Reaven in [7]. Although nearly 25 years have passed since his Banting lecture, many of his questions regarding the role of insulin resistance in human disease remain unanswered. If these are answered, they may guide us in our efforts to prevent the development of diabetes and CVD.

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