Challenges in developing therapies for the metabolic syndrome

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Abstract

Metabolic syndrome refers to a clustering of cardiovascular (CV) risk factors within a single individual. The established risk factor such as obesity, type 2 diabetes, dyslipidaemia, hypertension, and other emerging risk factors are closely related to intra-abdominal adiposity. Insulin resistance is also considered to be an important factor in the aetiology of this syndrome. The emerging risk factors include dysfunction of inflammation, coagulation, platelets, fibrinolysis, lipoproteins, endothelium, and other biological processes. Despite the potential utility of having all the CV risk factors under one umbrella term, debate continues about the very existence of the metabolic syndrome and its diagnostic criteria. Nevertheless, the component risk factors include some of the most common and serious public health challenges facing the developed and developing world today. By treating component risk factors, many existing therapies and new drugs in development target several aspects of metabolic syndrome. However, no drug is currently approved specifically for treatment of the metabolic syndrome.

The essential features of the metabolic syndrome, and some of the challenges in developing treatment options are discussed herein.

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Introduction

Metabolic syndrome refers to a clustering of established ('traditional') and emerging ('nontraditional') CV risk factors within a single individual.[1,2] Both the established risk factors, such as obesity, type 2 diabetes, dyslipidaemia, hypertension, and other, 'nontraditional' risk factors are closely related to abdominal or central obesity (especially intra-abdominal adiposity, which is also known as visceral obesity).[1,3] Insulin resistance is also considered an important factor in the aetiology of this syndrome.[1,3,4] The 'nontraditional' risk factors include dysfunction of inflammation, coagulation, platelets, fibrinolysis, lipoproteins, endothelium, and miscellaneous biological processes. Individuals may develop these factors in different sequences, at different severities, and at different ages.

However, despite the potential utility of having all the CV risk factors under an umbrella diagnosis of the metabolic syndrome, debate continues about the very existence of the metabolic syndrome.[5,6] This debate is (in part) related to lack of a universally accepted definition of this state, but also to doubts regarding the need for these disparate CV risk factors to be 'lumped' together under one 'artificial' diagnostic heading. Is the utility of the metabolic syndrome simply related to its value as an aide-mémoire for physicians to remember to consider other CV risk factors when confronted with a patient with one or more of these factors? Other experts prefer to use the term global cardiometabolic risk, which refers to the overall risk of developing type 2 diabetes and/or CV disease.

Despite the controversies regarding the metabolic syndrome, the component risk factors include some of the most common and serious public health challenges facing both the developed and developing world today.[7] According to recent worldwide estimates, 1.7 billion people are classified as either

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Abbreviations

ACE	angiotensin-converting enzyme
ARB	angiotensin receptor II blocker/antagonist
BP	blood pressure
CV	cardiovascular
HDL	high density lipoprotein
HIV	human immunodeficiency virus
hsCRP	high-sensitivity C-reactive protein
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
OGTT	oral glucose tolerance test
LDL	low density lipoprotein
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
PAI-1	plasminogen activator inhibitor type 1
PCOS	polycystic ovarian syndrome
TZD	thiazolidinedione

Acronyms

AACE	American Association of Clinical Endocrinologists
ATP III	Adult Treatment Panel III
EGIR	European Study Group for Insulin Resistance
FDA	Food and Drug Administration
HOMA-IR	Homeostatic model assessment–insulin resistance
IDF	International Diabetes Federation
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organisation

overweight or obese, more than one billion have hypertension, and more than 500 million have either type 2 diabetes or IGT.[7] As a consequence of these alarming figures, the prevalence of the metabolic syndrome is also (not surprisingly) very common, with almost 50 million individuals affected in the USA alone.

In view of the incredible numbers of people affected by these chronic conditions and associated complications, pharmaceutical companies are exploring the role of existing therapies and are developing new drugs targeting the metabolic syndrome.[8] Indeed, one recent review on new therapies for the metabolic syndrome listed the number of potential 'drug targets' at nearly 10,000.[8] However, no drugs are currently approved for the indication of metabolic syndrome.[9]

This review discusses the essential features of the metabolic syndrome, and also some of the challenges in developing future treatment options.

Definition of metabolic syndrome

The concept of the metabolic syndrome has been around for more than 80 years.[1,6] Recently, increased attention has led to a number of different names being attached to this syndrome (e.g. syndrome X, Insulin Resistance Syndrome, etc), and a number of different definitions have also been proposed. The two most commonly used clinical and research definitions of the metabolic syndrome, the National Cholesterol Education Program: ATP III and IDF, are defined in table 1.[10,11]

Table 1. Comparison of the two most commonly used definitions for the metabolic syndrome

Clinical diagnosis of metabolic syndrome : ATP III	**Clinical diagnosis of metabolic syndrome : IDF**
The diagnosis of the metabolic syndrome is made if three or more of the following are present:	The diagnosis of the metabolic syndrome is made if the following are present:
Waist circumference: Men > 102 cm* Women > 88 cm*	Central obesity (Waist circumference): Men > 94 cm (Europid)* Women > 80 cm (Europid)*
	Plus any 2 of the following four factors:
Triglycerides: ≥1.70 mmol/L (≥ 150 mg/dL)	Triglycerides: ≥ 1.70 mmol/L (≥ 150 mg/dL) or specific treatment for this lipid abnormality
HDL Cholesterol: Men < 1.00 mmol/L (< 40 mg/dL) Women < 1.30 mmol/L (< 50 mg/dL)	HDL Cholesterol: Men < 1.0 mmol/L (< 40 mg/dL) Women < 1.3 mmol/L (< 50 mg/dL) or specific treatment for this lipid abnormality
Blood pressure: ≥ 130/85 mmHg	Blood pressure : ≥ 130/85 mmHg or treatment for previously diagnosed BP abnormality
Fasting glucose#: ≥ 5.6 mmol/L (≥ 100 mg/dL)	Fasting glucose#: ≥ 5.6 mmol/L (≥ 100 mg/dL) or treatment for previously diagnosed type 2 diabetes

Key: *= Ethnic variations for waist circumference: IDF definition - Asians, Chinese and Japanese (recommendations for other ethnic groups being developed). ATP III definition – Asians only (as per IDF). # = No OGTT requirements – IGT not part of definition

The underlying pathophysiology of the metabolic syndrome is considered to be related to central obesity (especially intra-abdominal adiposity) and insulin resistance.[1,4] Although the exact cause of the metabolic syndrome is not known, the association with obesity is very compelling. Adipocytes are the source of a number of important adipokines involved in a wide range of processes related to the features of the metabolic syndrome, including glucose and lipid metabolism, inflammation, and thrombosis (e.g. adiponectin, leptin, visfatin, PAI-1, etc).[12] For example, adiponectin expression is greater in subcutaneous than visceral adipose tissue, and appears to have anti-diabetic, anti-inflammatory, and anti-atherogenic effects.[13] In contrast, visfatin expression is much greater in visceral fat (hence name) than subcutaneous adipose tissue, and appears to have insulin-mimetic effects (binding to the insulin receptor at a site distinct from where insulin

binds).[14] The other important aetiological factor related to the metabolic syndrome is insulin resistance. Insulin resistance can be defined in several ways, but is essentially an impaired biological response to insulin actions in the insulin-responsive tissues (i.e. liver, fat and skeletal muscle).[1,3,4] Such impairment can result in reductions in the rate of glucose uptake into fat and skeletal muscle, and increases in the release of glucose from the liver and of free fatty acids from fat. Insulin levels may rise in a physiological response to compensate for the insulin resistance, resulting in hyperinsulinaemia. Insulin resistance is also one of the two core defects in type 2 diabetes (the other being β-cell dysfunction).

Some of the controversy surrounding the metabolic syndrome relates to a lack of a universally accepted definition. The ATP III and IDF definitions are focused on obesity, specifically waist circumference which is a surrogate measure of central obesity. The IDF definition has the advantage of having specific ethnic-group-related definitions of waist circumference (i.e. Europids, Asian, etc), although the latest reiteration for the ATP III definitions accepts a similar cut-off for Asians (see table 1).[10,11] In comparison, the AACE, WHO and the EGIR, definitions are all largely focused on insulin resistance.[1,6] Despite the added complexity of deciding an optimal measurement or definition of insulin resistance, these various definitions should ideally be standardised for a number of reasons. Such standardisation will aid comparison of results from clinical practice, clinical trials, drug development programmes, and enable proper estimation of prevalence, etc. For example, in one recent study the prevalence of the metabolic syndrome in the USA using the IDF definition was 39%, as compared with 34.5% using the ATP III definition.[15] Similar discrepancies have been observed in other populations, including Europeans.[16] Other concerns about a proper definition of metabolic syndrome relate to the choice of the parameters, and also the thresholds for these parameters within the different definitions. In addition, a dichotomous recording of the different parameters (i.e. 'Yes' or 'No'), as in the final scoring of the ATP III and IDF definitions, does not allow any quantitative weighting (e.g. very high BP is presumably worse than slightly high BP levels).

Different weighting of risk factors can impact ability to predict specific outcomes i.e. CV (closely correlated with decreased HDL, increased BP, and type 2 diabetes, but not really correlated with IFG) versus type 2 diabetes (closely correlated with obesity and IFG). As both the ATP III and IDF definitions use a measure of fasting glucose, clearly no knowledge about post-challenge glucose will be captured in the risk assessment (i.e. IGT, or cases of type 2 diabetes diagnosed only on OGTT). This fasting-glucose-based definition persists despite the fact that IGT has been demonstrated to be a stronger marker of future CV risk (and some other complications) than IFG.[17] It is also clear that (by definition) the current metabolic syndrome definitions are more focused on CV risk, as opposed to developing type 2 diabetes risk.[16,18] Recognition of this CV emphasis has caused some experts to prefer the term cardiometabolic risk, which represents the overall risk of developing type 2 diabetes and/or CV disease.

Table 2. Original (as described by Reaven[4]) and expanded features of the metabolic syndrome

Metabolic Syndrome – 2007
Features defining the Metabolic Syndrome
(also known as Syndrome X, Insulin Resistance Syndrome, etc)

Original features (as described by Reaven)	**Expanded features**
Insulin resistance	Obesity
Hyperinsulinaemia	Abdominal (or Central) obesity, especially intra-abdominal (or Visceral) obesity
Hyperglycaemia	Prothrombotic tendency (e.g. high plasminogen activator inhibitor 1, PAI-1)
Hypertriglyceridaemia	Small, dense low density lipoprotein (sdLDL)
Decreased high density lipoprotein (HDL)	Increased apolipoprotein B
Hypertension	Increased Leptin
	Decreased adiponectin
	Proinflammatory tendency (e.g. increased hsCRP)
	Endothelial dysfunction
	Renin-angiotensin system activation
	Hyperuricaemia
	Polycystic ovarian syndrome (PCOS)
	Sleep apnoea syndrome
	Microalbuminuria
	Autonomic dysfunction
	Non Alcoholic Fatty Liver Disease (NAFLD) / Non Alcoholic Steatohepatitis (NASH)
	Erectile dysfunction
	Hypogonadism
	Cancer

Although it has been demonstrated that the presence of the metabolic syndrome as defined by the various definitions (e.g. ATP III), can predict CV risk, it is clear that the current set of parameters included in the definitions are not measuring all the risk.[3,10,18] Indeed, as much as 50% of the risk may not be captured by the current definitions. The so-called residual risk may be related to other factors such as gender, age, smoking, and also other factors associated with the metabolic syndrome (table 2), but not included in the current definitions i.e. LDL, endothelial dysfunction, liver transaminases, inflammation, plaque instability, visceral fat, prothrombotic tendency (e.g. PAI-1), small dense LDL, apolipoprotein B, measures of insulin resistance (e.g. HOMA-IR, serum insulin levels) etc. For example, we know that measurement of the inflammatory marker hsCRP provides incremental risk information at all levels of the metabolic syndrome.[19] Based on this type of evidence, should the clinical criteria for the metabolic syndrome be expanded? This issue is being actively explored, but to-date no additional markers have been added to the diagnostic criteria. However, it is clear that new treatments for the metabolic syndrome (or cardiometabolic risk) should also address the residual risk, and not just the traditional risk factors.[3,10,18]

Challenges in drug development for the metabolic syndrome

Although potentially helpful for clinical practice, current definitions of the metabolic syndrome are largely inadequate for

Table 3. Futility of ATP III metabolic syndrome definition for drug development using 'Yes' or 'No' response. In example shown, both β-blockers and fibrates appear to reverse metabolic syndrome diagnosis in individual cases after treatment

	Are β-blockers or fibrates drugs for the metabolic syndrome?			
ATP III Parameter	**Case 1 pre-treatment β-blocker**	**Case 1 post-treatment β-blocker**	**Case 2 pre-treatment fibrate**	**Case 2 post-treatment fibrate**
Abdominal circumference	√	√	√	√
High density lipoprotein	√	√	√	x
Triglyceride	x	x	√	x
Blood pressure	√	x	√	√
Glucose	x	x	x	x
Metabolic syndrome?	Yes	No	Yes	No
Parameters present out of total (5)	3/5	2/5	4/5	2/5

Key: √= ATP III parameter present. x = ATP III parameter absent

effective drug discovery and development. Diagnosis of the metabolic syndrome needs to be commonly accepted by clinicians, investigators, sponsors of clinical trials (e.g. pharmaceutical companies, academic institutes, etc), regulators, and payers of healthcare. With no adequately validated or universal definition of this diagnosis, the problem of inclusion in clinical trials and interpretation of outcome results will be problematic. It is forseeable that varying definitions will be implemented as varying inclusion criteria for different studies, and also heterogeneity within a given study i.e. some subjects meeting three criteria (e.g. increased waist circumference, hypertension, and low HDL), while other subjects meeting all five criteria (current ATP III and IDF definitions) are enrolled. Several drugs on the market that are currently used in cardiac and metabolic conditions (e.g. statins, ACE inhibitors, ARBs, TZDs, etc) could potentially confound results of a new agent under investigation for the metabolic syndrome. These agents can have pleiotropic effects on several different pathways associated with the metabolic syndrome. It would be unethical to stop or exclude patients on these drugs in clinical trials (as many as 60% of type 2 diabetes patients in clinical trials can be on an ACE inhibitor for example), but the effects on the study interpretation should be negated by appropriate randomisation (including consideration of stratified randomisation). One potential benefit of having a simple definition of metabolic syndrome for drug development would be in assessing how an investigational drug (e.g. erectile dysfunction or antihypertensive drug) behaves in clinical trial subjects with or without the metabolic syndrome as per ATP III or IDF definitions.

Targets and end points

Many features of the metabolic syndrome could be potential targets for new treatments: e.g. prevention of type 2 diabetes and its complications, artherogenic dyslipidaemia, NAFLD or NASH, PCOS-related abnormalities, HIV-related dysmetabolic problems, prevention of CV disease, or even prevention of cancer (see table 2). The ultimate proposed drug indications will clearly impact the appropriate study design and choice of end points (i.e. is the treatment targeting prevention of type 2 diabetes, or CV morbidity and mortality, etc). End points chosen must be able to be proven as medically valuable (i.e. based on pharmacoeconomic or other considerations) as well as scientifically valid. In lieu of proper outcome studies (hard end points could take many years, and studies would be large and costly), appropriate biomarkers and surrogate end points should be monitored. Framingham Risk Score or other global CV risk engines (e.g. UKPDS risk score) could also be utilised.[18] The simple use of counting of metabolic syndrome parameters should not be acceptable as an end point (e.g. three parameters out of the five at baseline, decreasing to two parameters at study end, does not necessarily mean 'reversal' or improvement in metabolic syndrome resulting from the therapy under investigation). Such dichotomous ('Yes' or 'No') scoring is too simplistic for many purposes (table 3). Despite this consideration, one recent study using rimonabant (a novel cannabinoid receptor antagonist indicated for the management of obesity) reported reversal of the diagnosis of metabolic syndrome in a proportion of subjects (64.8% reduction) who had metabolic syndrome as defined by ATP III at baseline, using such a simple counting system.[20]

Is metabolic syndrome a novel entity?

One of the most important considerations in drug development for the metabolic syndrome is the question: Is the metabolic syndrome a new entity or simply a new name for existing risk factors? We already have a growing arsenal of treatments for hypertension, dyslipidaemia, type 2 diabetes, and obesity. Are these conditions distinct in their genesis and more importantly, do they differ in their response to available drugs as part of the metabolic syndrome as opposed to their response in the absence of the metabolic syndrome? Does reversing metabolic syndrome, *per se*, alter risk? These and many other important questions are the subject of intense debate and investigation.

Key messages

- Metabolic syndrome refers to a clustering of established and emerging CV risk factors within a single individual
- Current definitions of the metabolic syndrome remain controversial
- The pathophysiology of the metabolic syndrome is unclear, but is closely related to intra-abdominal adiposity and insulin resistance
- Many challenges have so far thwarted the development of new treatment options for the metabolic syndrome

From a regulatory standpoint, the lack of a universal definition, the lack of a single aetiological factor or central pathophysiological abnormality identified as mediating the constellation of features, uncertainty regarding study end points, heterogeneous study populations, existing treatments and regulatory precedent for established risk factors, etc. all suggest that some challenges will have to be solved before there will be approval of any new or existing drug for the indication of metabolic syndrome. In February 2007, the US FDA stated that "it does not necessarily consider the metabolic syndrome to represent a distinct disease entity".[9] However, the FDA concluded that "a therapeutic product intended to treat metabolic syndrome should normalise or improve all components of the syndrome, independent of weight loss, and ultimately be shown to prevent the development of type 2 diabetes and reduce CV morbidity and mortality".[9] This is a very high aspiration for any one drug, hence, increased interest in formulations that contain several drugs addressing various components of the metabolic syndrome simultaneously (i.e. 'poly pill' and fixed-combination therapies).

'Poly Pill' for the metabolic syndrome?

The concept of a 'poly pill' which contains more than one agent and would simultaneously address more than one cardiometabolic risk factor appears attractive. One proposal by Wald and Law is combining aspirin, a β-blocker, an ACE inhibitor, a statin, a diuretic, and folic acid, all in one tablet.[21] This example and other proposed 'poly pills' may result in improved compliance (due to reduction in the poly-pharmacy pattern which is the norm for these complex patients), decreased costs for the patient and society (due to the use of generic drugs), and greater impact on complications (decreasing human and societal costs). Arguments against the use of such a 'poly pill' relate to the difficulties in initiating and titrating treatment (especially when some agents are given once-daily and others several times a day), size of the tablet, and critically, the exposure of patients to drugs they may not need. If a patient should experience an adverse event, it could prove difficult to determine which component (if any) had caused this adverse event. Nonetheless, several 'poly pills' are currently in development (for example, combining aspirin, β-blocker, ACE inhibitor, and statin), and may have specific value in the developing world.[22] Many pharmaceutical companies are also developing or have launched fixed-dose combination tablets addressing various components of the metabolic syndrome (e.g. anti-hypertensive agent combined with a statin). These fixed-dose combinations could contain generic and/or non-generic drugs.

Summary

This review has highlighted the controversies surrounding the background, including definitions, epidemiology, pathophysiology and clinical features of the metabolic syndrome. The variable nature of each of these aspects of the syndrome has presented a difficult challenge for the future development of treatment options for the metabolic syndrome.

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