

Key points

- The metabolic syndrome represents a link between abdominal obesity, a clustering of the major individual cardiovascular and metabolic risk factors and an increased risk of cardiovascular disease and type 2 diabetes.
- GPs should regularly screen the metabolic profile of all adult patients; patients who are older and at higher risk should be screened bi-yearly.
- The presence of one cardiovascular risk factor should lead to a careful assessment of the patient for the presence of the other cardiovascular and metabolic risk factors that characterise the metabolic syndrome.
- Patients with the metabolic syndrome should be carefully assessed for related comorbidities.
- Treatment should follow a multidisciplinary approach, addressing the common underlying cause (excess weight) and intensively targeting individual risk factors.
- Successful weight loss and regular physical activity can help reduce the risk of cardiovascular disease and type 2 diabetes in patients with the metabolic syndrome.

The practical value of the metabolic syndrome



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The presence of the metabolic syndrome can be a useful tool to help GPs identify patients at higher risk for cardiovascular disease and type 2 diabetes. To help reduce such risks, patients with the metabolic syndrome should be targeted with interventions following a multifaceted approach.

Vascular inflammation, hyperglycaemia, elevated blood pressure and dyslipidaemia are all known to be risk factors for cardiovascular disease and type 2 diabetes. That the same risk factors underlie both diseases suggests they share a common pathophysiological pathway – namely obesity. In obesity (especially abdominal obesity), increasing levels of free fatty acids drive resistance to insulin action on peripheral glucose utilisation, while inflammatory cytokines produced by abdominal adipocytes cause vascular endothelial dysfunction. This understanding has advanced from a concept of

shared pathophysiology to the recognition that the clinical clustering of cardiovascular and metabolic risk factors could be understood as a common clinical entity.¹⁻³ This clinical clustering has previously been referred to as the ‘insulin resistance syndrome’, the ‘deadly quartet’ and ‘Syndrome X’ (not to be confused with syndrome X whereby symptomatic angina pectoris develops despite normal coronary arteries) but is now widely known as the metabolic syndrome.

This article discusses recent updates to the definition of the metabolic syndrome, its associated risks and provides a clinical framework

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NCEP/ATP III AND IDF DEFINITIONS OF THE METABOLIC SYNDROME

The NCEP/ATP III criteria (2001, revised 2005) defines the metabolic syndrome as the presence of any three of the following traits:⁴

- abdominal obesity (waist circumference*): ≥ 102 cm in men; ≥ 88 cm in women
- elevated serum triglyceride levels: ≥ 1.7 mmol/L; or if the patient is taking medication for elevated triglyceride levels
- decreased serum HDL cholesterol level: < 1 mmol/L in men; < 1.3 mmol/L in women; or if the patient is taking lipid-modifying medications
- elevated blood pressure: $\geq 130/85$ mmHg; or if the patient is taking antihypertensive medications
- elevated fasting plasma glucose levels: ≥ 5.6 mmol/L; or if the patient is taking medication for hyperglycaemia.

The IDF definition of the metabolic syndrome includes as its central element ethnicity-specific abdominal obesity (waist circumference*):⁵

- European: ≥ 94 cm in men; ≥ 80 cm in women
- South East Asians, Chinese and Japanese: ≥ 90 cm in men; ≥ 80 cm in women.

Plus any two of the following:

- elevated serum triglyceride levels: ≥ 1.7 mmol/L; or if the patient is taking medication for elevated triglyceride levels
- decreased serum HDL cholesterol levels: ≤ 1.03 mmol/L in men; ≤ 1.29 mmol/L in women; or if the patient is taking lipid-modifying medication
- elevated blood pressure: systolic blood pressure of ≥ 130 mmHg; diastolic blood pressure of ≥ 85 mmHg; or if the patient is taking antihypertensive medication
- elevated fasting plasma glucose levels: ≥ 5.6 mmol/L; or a prior diagnosis of type 2 diabetes.

* Waist circumference is assessed by locating the top of the right iliac crest, placing a measuring tape horizontally around the waist at the level of the iliac crest, ensuring the tape is snug and parallel to the ground. Measurements are made at the end of expiration. The wearing of light clothing is acceptable.

ABBREVIATIONS: IDF = Inherited Diabetes Federation; NCEP/ATP III = National Cholesterol Education Program/Adult Treatment Panel III.

with which GPs can approach and manage patients with the metabolic syndrome.

DEFINING THE METABOLIC SYNDROME

The metabolic syndrome is made up of individual cardiovascular disease and metabolic risk factors, including:

- increased waist circumference
- abnormal fasting blood glucose levels
- abnormal LDL cholesterol, HDL cholesterol and triglyceride levels
- elevated blood pressure.

Various historical definitions of the metabolic syndrome have placed emphasis on different individual risk factors. The two most widely used and accepted

definitions of the metabolic syndrome in current research and clinical practice are those of the National Cholesterol Education Program/Adult Treatment Panel (NCEP/ATP) III and the International Diabetes Federation (IDF; see the box on this page).^{4,5} The definition preferred by the authors is that of the IDF because it uses central adiposity as the common factor, is practical to apply and offers ethnic-specific reference ranges.

EPIDEMIOLOGY AND ASSOCIATED RISKS

The staggeringly high rates of global overweight and obesity are mirrored in the high prevalence of the metabolic syndrome.⁶

In Australia, the prevalence of the metabolic syndrome ranges from 13 to 22% according to the 2007 AusDiab study of over 11,000 adults in Australia.⁷ In the USA, prevalence is even higher, with over one-third of adults shown to have the metabolic syndrome in the 2009 United States National Health and Nutrition Examination Survey.⁸

Studies have also confirmed an increased risk of cardiovascular disease and type 2 diabetes among patients with the metabolic syndrome compared with patients without the syndrome. The AusDiab study reported an odds ratio of 3.5 to 6.6 for 10-year cardiovascular disease risk, whereas a 2007 review of the Framingham Offspring cohort of 2800 patients showed a relative risk of 1.7 to 1.8 for cardiovascular disease and 2.1 to 3.5 for type 2 diabetes.^{7,9} This increased risk for cardiovascular disease and type 2 diabetes has been convincingly demonstrated in a large meta-analysis of 950,000 patients, which showed that the metabolic syndrome was associated with more than a twofold increase in risk for cardiovascular disease and more than one and a half-fold increase in all-cause mortality.¹⁰

CONTROVERSIES

Debate continues within parts of the cardiology and endocrine communities as to whether the metabolic syndrome represents anything beyond its constituent cardiovascular and metabolic risk factors and whether it is indeed a 'real' or useful clinical construct. The specific details of the controversy are beyond the scope of this article, but reference articles are available for further reading.¹¹⁻¹³ More useful than rehashing ontological arguments is to acknowledge that experts agree that the clustering of common metabolic risk factors for cardiovascular disease and type 2 diabetes is real, and that the presence of one component of the metabolic syndrome should lead to a clinical assessment of the patient for the other associated risk factors.

Overweight and obesity are common factors in the clinical cluster of the metabolic syndrome and may be a key underlying pathogenic cause of the condition (along with attendant abnormal lipid levels and glucose metabolism). However, although numerous studies and real world clinical experience have shown that most patients who are obese also have the metabolic syndrome, it should be noted that not all people who are overweight or obese necessarily have the condition.

Despite these controversies, the metabolic syndrome continues to be widely used as a research and clinical tool in the field of obesity, cardiovascular disease and type 2 diabetes.

CLINICAL IMPLICATIONS

Screening for the metabolic syndrome

For GPs, the metabolic syndrome can represent a useful framework to help identify patients in need of early, aggressive and targeted multifactorial interventions that reduce weight, increase physical activity and treat individual cardiovascular and metabolic risk factors. The goal of such interventions is to reduce a patient's long-term risk of developing cardiovascular disease and type 2 diabetes.

During routine patient consultations, GPs should consider whether patients have had their metabolic profile assessed. This should include assessments of weight, waist circumference, are blood pressure and measurements of fasting lipid and blood glucose levels.

Current expert guidelines offer a range of screening protocols. The RACGP Red Book recommends bi-yearly assessments of body mass index and waist circumference for all overweight adults, as well as comprehensive health checks for all patients aged 45 years or older every two to five years (including assessment of their metabolic profile).¹⁴ The Australian lipid management guidelines also advise annual assessment of fasting lipid profiles in all adults of Indigenous and Torres Strait

ONLINE CARDIOVASCULAR DISEASE RISK CALCULATORS

Framingham Heart Study

www.framinghamheartstudy.org/risk/index.html

HeartSCORE: cardiovascular risk assessment and management

www.heartscore.org/Pages/welcome.aspx

Australian Absolute Cardiovascular Disease Risk Calculator

www.cvdcheck.org.au

Island descent.¹⁵ The US Endocrine Society suggests metabolic screening of all adult patients every three years, with more frequent evaluations for individuals at higher risk (e.g. patients who are overweight or obese, smokers, of older age or members of at-risk population groups).¹⁶

At the authors' complex obesity clinic services, the metabolic profile of all obese patients is assessed annually. In the authors' opinion, it is reasonable to assess the full metabolic profile of all overweight and obese adult patients at least bi-yearly.

Screening for comorbidities

Patients identified with the metabolic syndrome may benefit from a five- to 10-year cardiovascular risk assessment using one of the validated online cardiovascular disease risk calculators, such as the Framingham Risk Score,¹⁷ the European HeartSCORE¹⁸ or the Australian Absolute Cardiovascular Disease Risk Calculator (see the box on this page).¹⁹

Physicians treating patients with a moderate-to-high risk of cardiovascular disease (estimated at greater than or equal to 15% risk for a cardiovascular event) should apply a reduced threshold for prescribing medical therapy when targeting the individual cardiovascular and metabolic risk factors.

As well as being an indicator of increased risk for cardiovascular disease

TABLE 1. LIFESTYLE MANAGEMENT GOALS AND RECOMMENDATIONS

Risk factor	Goals and recommendations
Waist circumference/ abdominal obesity	7 to 10% weight loss from baseline <ul style="list-style-type: none"> • Low-calorie diet (a reduction of 500 to 1000 kcal per day)
Physical inactivity	At least 150 minutes per week of moderate intensity exercise <ul style="list-style-type: none"> • 30 to 60 minutes per day of brisk walking, at least five days per week • Increase levels of incidental activities to over 10,000 steps per day (using a pedometer to measure steps) • Encourage higher levels of exercise
Diet	Reduce intake of saturated fats, trans fat, cholesterol and simple sugars <ul style="list-style-type: none"> • Reduce total fat intake to below 30% of daily energy intake • Reduce saturated fat intake to below 7% of daily energy intake • Reduce overall trans fat and cholesterol intake
Cigarette smoking	Cessation of smoking <ul style="list-style-type: none"> • Refer patient to the QUIT program • Refer patient for motivational counselling • Pharmacotherapy

and type 2 diabetes, the metabolic syndrome has been associated with a higher risk of developing other disorders, including nonalcoholic steatohepatitis,²⁰ obstructive sleep apnoea,²¹⁻²⁴ chronic kidney disease (CKD),²⁵⁻²⁸ hyperuricaemia, gout²⁹⁻³¹ and polycystic ovary syndrome.³²⁻³⁵ GPs should consider tailoring the clinical history, examination and investigations of patients with the metabolic syndrome to screen for these associated conditions.

TARGETED, MULTIFACTORIAL MANAGEMENT

As described in the 2005 US National Heart Lung Brain Institute guideline for the diagnosis and management of the metabolic syndrome, the two major clinical goals in the management of the metabolic syndrome are:⁴

- treating one of the underlying causes of the metabolic syndrome (abdominal obesity) by instituting weight management that includes dietary changes and increased physical activity

- managing other individual cardiovascular disease and metabolic risk factors.

Lifestyle management

Weight loss

Effective weight loss can improve cardiovascular and metabolic risk factors associated with the metabolic syndrome and reduce the risk of type 2 diabetes in patients with the syndrome.^{4,36} A combined lifestyle management approach of a low-calorie diet, increased physical activity and behavioural change is the cornerstone of successful treatment leading to sustained weight loss. Patients who adhere to lifestyle recommendations (Table 1) can generally expect to lose between 7% and 10% of their initial body weight over a period of six to 12 months.^{4,37}

Dietary changes

A reduction of the daily food intake by 500 to 1000 kcal can lead to a weight loss of about 0.5 to 1 kg per week. General dietary

principles include recommending lower intakes of saturated fats, trans fats, cholesterol and rapidly absorbed simple carbohydrates (sugars), in addition to increasing the intake of vegetables, fruit and whole grains. Both the Mediterranean diet³⁸ (e.g. a high intake of fruits, vegetables, nuts, whole grains and olive oils) and the Dietary Approaches to Stop Hypertension (DASH) diet³⁹ (e.g. a low salt intake, high consumption of fruits, vegetables, nuts and legumes, and low-fat dairy) can form the nutritional basis to moderate metabolic cardiovascular disease risk factors. Both diets have supportive clinical evidence to warrant specific recommendation as dietary management for patients with the metabolic syndrome.

Physical activity

Regular moderate intensity exercise can facilitate weight loss and improve the metabolic risk factors associated with the metabolic syndrome. Reaching and sustaining the exercise target of at least 150 minutes of moderate-intensity exercise per week (e.g. achieved by 30 to 60 minutes per day of brisk walking on most, if not every, day of the week) will aid weight loss and is the key to maintaining such loss. Increasing the physical intensity of exercising will also enhance its beneficial effects. A pedometer to measure incidental activity levels can be a useful tool to help patients achieve the recommended incidental activity target of 10,000 steps or more per day.

Smoking cessation

Given the clear link between cigarette smoking and cardiovascular disease, any lifestyle intervention for smokers must recommend smoking cessation. The RACGP have published practice guidelines to aid GPs in managing patients who smoke.⁴⁰

Treatment challenges

Overweight and obesity is a chronic and relapsing condition and many patients

TABLE 2. RECOMMENDATIONS FOR THE MANAGEMENT OF METABOLIC CARDIOVASCULAR RISK FACTORS

Metabolic cardiovascular risk factor	Therapeutic goals	Recommendations
Elevated blood pressure	<ul style="list-style-type: none"> Below 130/80 mmHg 	<ul style="list-style-type: none"> Modify blood pressure through lifestyle changes and/or antihypertensive medication
Elevated lipid levels	<p>Primary target:</p> <ul style="list-style-type: none"> LDL cholesterol levels below 2.0 mmol/L (or below 1.8 mmol/L if known cardiovascular disease) <p>Secondary targets:</p> <ul style="list-style-type: none"> Total cholesterol levels below 4.0 mmol/L Triglyceride levels below 1.5 mmol/L HDL cholesterol levels above 1.0 mmol/L 	<ul style="list-style-type: none"> Improve lipid profile through lifestyle changes and lipid-modifying medication
Elevated glucose levels	<ul style="list-style-type: none"> Fasting blood glucose levels of below 5.5 mmol/L If pre-diabetes is present, regularly monitor for progression to type 2 diabetes If type 2 diabetes is present, aim for a HbA_{1c} of below 7.0% 	<ul style="list-style-type: none"> Avoid type 2 diabetes through lifestyle changes to achieve target blood glucose levels Improve blood glucose levels through lifestyle changes and medications as required (e.g. metformin first-line)
Prothrombotic state	–	<ul style="list-style-type: none"> Consider low-dose aspirin as primary prevention after balancing the patient's risk of cardiovascular disease with the risk of major bleeding

find it challenging to achieve and maintain weight loss. Although recent evidence confirms that Australian GPs can assist their patients to lose weight through routine clinical care, the importance of a multidisciplinary approach for weight loss is well established, particularly in patients with the metabolic syndrome.^{36,41,42} GPs should therefore consider using the skills of:

- dietitians and exercise physiologists (to help patients refine diet and exercise programs)
- self-help groups and psychologists (to assist patients with behavioural modifications)
- specialist obesity services (for patients who fail to lose weight despite compliance with a lifestyle approach).

The long-term effects of bariatric surgery in patients with the metabolic syndrome are unresolved. Evidence demonstrates that the significant weight loss associated

with bariatric surgery is due to the high short-term rates of remission of the metabolic syndrome. However, rates of long-term remission following the surgery remain unknown.⁴³

MANAGEMENT OF SPECIFIC RISK FACTORS

Recommendations for the management of specific cardiovascular and metabolic risk factors include aggressive treatment of hypertension, dyslipidaemia and dysglycaemia (Table 2).

Blood pressure

Lifestyle modification and weight loss can often improve high-normal blood pressure (e.g. 120/80 to 139/89 mmHg), but in patients with hypertension of any grade (greater than or equal to 140/90 mmHg) then antihypertensive therapy is generally required. The current Australian guidelines for patients without end-organ

damage suggest a target level for blood pressure of 140/90 mmHg or lower. However, given the link between the metabolic syndrome and cardiovascular disease, it is the practice of these authors to aim for a lower blood pressure target of 130/80 mmHg or lower, which is the level recommended for patients with cardiovascular disease, CKD and type 2 diabetes.⁴⁴

There is evidence to support the use of ACE inhibitors or angiotensin II receptor blockers as first-line antihypertensive therapy in patients with type 2 diabetes and mild CKD; however, the superiority of these agents in patients with the metabolic syndrome who do not have cardiovascular disease or type 2 diabetes remains unclear. Furthermore, thiazide diuretics have been associated with an increased risk for new onset type 2 diabetes and should be used with caution in patients at risk of dysglycaemia.⁴⁵

Dyslipidaemia

Following current Australian practice guidelines, target lipid levels for patients with the metabolic syndrome include an LDL cholesterol level of less than 2.0 mmol/L. This can be achieved through a combination of lifestyle modification and, if required, lipid-modifying medical therapy.¹⁵ Secondary lipid treatment targets are a total cholesterol level of less than 4.0 mmol/L, a HDL cholesterol level of greater than 1.0 mmol/L and a triglyceride level of below 1.5 mmol/L.

Dysglycaemia

The Diabetes Prevention Program clearly demonstrated that intensive lifestyle changes that focused on weight loss and increased physical activity delayed or prevented type 2 diabetes in patients with dysglycaemia and the metabolic syndrome.⁴² The same study also demonstrated that lifestyle changes were superior to metformin in preventing type 2 diabetes and reducing rates of the metabolic syndrome.

In the authors' clinical practice, in selected patients with the metabolic syndrome who have dysglycaemia and/or polycystic ovary syndrome, metformin can be used as an adjuvant to lifestyle modification. However, metformin should not be the initial or sole therapy used to prevent type 2 diabetes. The cost-effectiveness of using metformin to prevent type 2 diabetes is currently unknown.

Although thiazolidinediones are known to improve insulin sensitivity and reduce progression to type 2 diabetes, their use is associated with weight gain and fluid retention and they can exacerbate cardiac failure. Rosiglitazone has been associated with an increased risk for cardiovascular events. Thiazolidinediones may also increase the risk of fracture and low bone density. These issues suggest it is prudent to avoid using thiazolidinediones in all patients without type 2 diabetes or only after careful consideration of the alternative treatment

options in patients with type 2 diabetes.

In patients with the metabolic syndrome, there is no firm evidence to indicate whether treatment of insulin resistance with medications that potentiate insulin action (i.e. metformin and thiazolidinediones) further lowers risk of cardiovascular events beyond the reduction associated with lifestyle changes and weight loss.

ASPIRIN FOR PRIMARY PREVENTION

Several American expert committees have recently reviewed the use of aspirin for the prevention of cardiovascular disease.^{46,47} In summarising their positions, they concluded that aspirin should be considered for primary prevention in patients with a high 10-year risk of cardiovascular disease (as calculated by cardiovascular disease risk tools) following an individualised clinical judgement made after balancing the risk of cardiovascular disease with the risk of major bleeding. This is also the position of the National Heart Foundation of Australia.⁴⁸ In patients with a previous cardiovascular event, aspirin should be used for secondary prevention unless there is a specific contraindication.

The 2009 United States Preventative Task Force reported on the magnitude of aspirin benefit compared with the risk of major bleeding.⁴⁷ The data suggest that aspirin doses ranging from 75 to 325 mg are equally effective for reducing the risk of cardiovascular disease in treated patients, however, both a 2006⁴⁹ and 2009⁵⁰ meta-analysis of 22 and six large studies, respectively, demonstrated that low-dose aspirin was as likely as high-dose aspirin to cause major bleeding.⁴⁷ Although, as indicated in the 2009 meta-analysis, the benefits of aspirin as primary prevention in low-risk patients (including those with uncomplicated type 2 diabetes) remain unclear with the results of several long-term studies pending.

SUMMARY

The controversy about whether the metabolic syndrome is a 'real' entity clouds

the consensus that as worldwide obesity increases, so too do the rates of hypertension, dyslipidaemia and dysglycaemia. The clustering of metabolic risk factors for cardiovascular disease and type 2 diabetes is established and the presence of one risk factor should lead to an evaluation for the presence of the other risk factors and comorbidities associated with the metabolic syndrome.


It is recommended that GPs regularly assess their patients' cardiovascular and metabolic risk profile. Patients identified with the metabolic syndrome are at an increased risk of developing cardiovascular disease and type 2 diabetes. However, this risk can be reduced by the introduction of a multifactorial clinical management plan, targeting patients' lifestyle and their individual cardiovascular and metabolic risk factors. MT

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A list of references is available on request to the editorial office.

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The practical value of the metabolic syndrome: has it stood the test of time?

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