Original Articles

A shifting paradigm in metabolic syndrome; time for a new definition

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Abstract

Metabolic syndrome (MetS) is a complex multisystem disorder, including visceral obesity, hypertension, raised fasting glucose and dyslipidaemia, which increases the risk of cardiovascular disease (CVD) and type 2 diabetes (T2DM). MetS has been defined by various organisations with the latest iteration in 2006 and has a varying worldwide prevalence (<10% to 84%). There is increasing data confirming that obstructive sleep apnoea (OSA) and non-alcoholic fatty liver disease (NAFLD) share common underlying pathological features which no doubt add complexity to this syndrome. They are also both independently associated with increased CVD. This editorial discusses recent advances in MetS with an aim to update the current definition and present the importance of a new multi-specialty integrated approach in order to improve patient care.

Keywords

Metabolic syndrome, Cardiovascular disease, Diabetes, Obstructive sleep apnoea, Non-alcoholic fatty liver disease

Introduction

Metabolic syndrome (MetS) is a complex multisystem disorder, defined by several interconnected factors, which increases the risk of both atherosclerotic and non-atherosclerotic cardiovascular disease (CVD) and type 2 diabetes (T2DM). While many international groups have proposed criteria to define MetS, they all have similar underlying principles of visceral obesity, hypertension, raised fasting glucose and dyslipidaemia.[1,2] MetS prevalence worldwide is set to increase given rising rates of obesity and T2DM and a better patient focused approach is necessary. Additionally, recent data has confirmed that obstructive sleep apnoea (OSA) and non-alcoholic fatty liver disease (NAFLD) share common underlying pathological features adding complexity to this syndrome. Whilst medicine is currently practiced with a single organ, specialist approach, it is time to rethink this. Patients do not come pre-packaged in specialties but rather present with a constellation of symptoms and signs which likely represent a myriad of underlying pathologies. MetS is a prime example of this, whereby; the underlying pathogenesis likely represents a continuum with patients accumulating further risk and morbidity if certain aspects of the disease are left untreated. This calls for a multi-system and multidisciplinary approach whereby specialists work together to integrate patient care to improve outcomes. This review discusses MetS with a hope to find a new, practical definition, taking into account recent evidence, and presents a new way of clinically managing an ever-increasing health burden.

Definition and Prevalence of metabolic syndrome

MetS, currently also called 'insulin resistance syndrome', 'syndrome X' and 'the deadly quartet' has been defined by various organisations with the latest iteration in 2006 by the International Diabetes Federation (IDF)[3]. The other commonly used definitions for surveys include the WHO 1999 classification[4] and the national cholesterol education program adult treatment panel three (NCEP ATP3) guidance of 2005[5]. Table 1 shows the distinction between these commonly used definitions.

There is increasing data on further characterising obese patients into those that are metabolically healthy and those that are not. A recent large study published in the Journal of American Medical Association (JAMA) classified patients as metabolically obese and healthy if they had a systolic BP <130mmHg, no BP-lowering medication, waist-to-hip ratio less than 0.95 for women and less than 1.03 for men, and no self-reported diabetes.[6] They concluded that this population group was not associated with increased CVD risk. However, we feel that while this may be the case, obesity itself should be classified as a disease, echoing the call from

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Table 1. Definitions of Metabolic Syndrome

Clinical Measure	WHO 1999 Criteria[4]	NCEP ATP3 2005 Criteria[5]	IDF criteria 2006[3]
Criteria	Insulin Resistance / Diabetes / impaired glucose tolerance + 2 of the following measures	Any 3 of 5	Central Obesity (WC – ethnicity specific values* or BMI >30kg/m^2 + 2 of the following
HDL	< 0.9mmol/L	<1.0 mmol/L (men) <1.3mmol/L (women) Or on treatment	< 1.03mmol/L (men) < 1.29mmol/L (women) Or on treatment
Triglycerides	≥ 1.7mmol/L	> 1.7mmol/L Or on treatment	> 1.7mmol/L Or on treatment
Waist/hip ratio	> 0.9 (Males); > 0.85 (Females)	-	-
Waist	-	> 102cm (men) >88cm (women)	-
BMI	> 30kg/m^2	-	-
Blood pressure	≥ 140/90	> 130/85	Systolic ≥ 130 or diastolic ≥ 85 Or on treatment
Fasting Plasma glucose	(required as above) ≥ 6.1mmol/L	> 5.6mmol/L or on anti-hyperglycaemic treatment	≥ 5.6mmol/L Or diagnosed with diabetes
Microalbuminuria	Urinary ACR ≥ 30mg/g	-	-

*The IDF uses ethnic specific values for waist circumference: Europids (Men ≥ 94cm, women ≥ 80cm); and for South Asians, Chinese and Japanese (Men ≥ 90cm, women ≥ 80cm). For ethnic South and Central Americans, Sub-Saharan Africans and East Mediterranean and Middle East (Arab) populations to use Europid data.

the Royal College of Physicians in the UK.[7] Classifying obese patients as 'healthy' gives people validation and less resolve to lose weight. Obesity is also linked with a huge number of health conditions, not just cardiovascular which is outside the scope of this review. We have therefore not included this new proposal in our proposed definition of MetS. Furthermore, classifying people early in their disease trajectory, prior to end-organ damage is the key to successfully preventing cardiovascular events and diabetes. Our proposed definition of MetS will capture people at an early stage and therefore empower individuals to change to make real differences in their morbidity and mortality.

The prevalence of MetS varies around the world (from <10% to as high as 84%). Higher socioeconomic countries, sedentary lifestyles and populations with higher BMI averages are significantly associated with an increased prevalence of MetS.[8] The IDF estimates that up to 25% of the world's adult population has MetS. This is likely to increase even further as the prevalence of obesity is predicted to rise. A global survey of obesity in 195 countries concluded that in 2015, 604 million adults were obese with the disease no longer mainly affecting affluent populations.[9,10] The highest increase in prevalence of obesity occurred in young men from low socio-economic index countries. More recently the Royal College of Physicians has called for obesity to be recognised as a disease,[7] in a hope to focus attention on a clearly escalating problem.

According to the IDF, global prevalence of diabetes was 8.8% in 2015, expected to increase to 10.4% in 2040. While the highest prevalence was in North American regions, over half of all people with diabetes were in Southeast Asia. Prevalence was low in Africa but this is expected to change.[10]

Therefore, MetS prevalence is set to rise rapidly in line with increasing rates of obesity and diabetes. This will lead to significant multi-morbidity, global health burden and significant cost implications.

Pathophysiology of metabolic syndrome

While there are several hypothesised mechanisms, the most widely accepted is the interplay between visceral adiposity and insulin resistance leading to a pro-inflammatory state through neuro-humoral activation (Figure 1). Visceral adiposity is thought to be biologically active endocrine tissue, with adipocytes undergoing hypertrophy, outgrowing their blood supply, resulting in a hypoxic state and subsequent necrosis. This in turns leads to the release of many pro-inflammatory cytokines including leptin, tumour necrosis factor alpha, interleukin 6 and resistin.[11,12] There is also a reduction of adiponectin, an anti-inflammatory and anti-atherogenic adipokine. All these factors combined lead to insulin resistance.[13] Moreover, there is an increased production of non-esterified fatty acids (free fatty acids, FFAs) which have different roles in skeletal muscle and the liver. In skeletal muscle the FFAs inhibit insulin-dependent glucose uptake, leading to a hyperglycaemic state, whilst in the liver they promote increased production of glucose, triglycerides and apo-B containing triglyceride-rich very-low density lipoproteins. These are highly atherogenic. FFAs are

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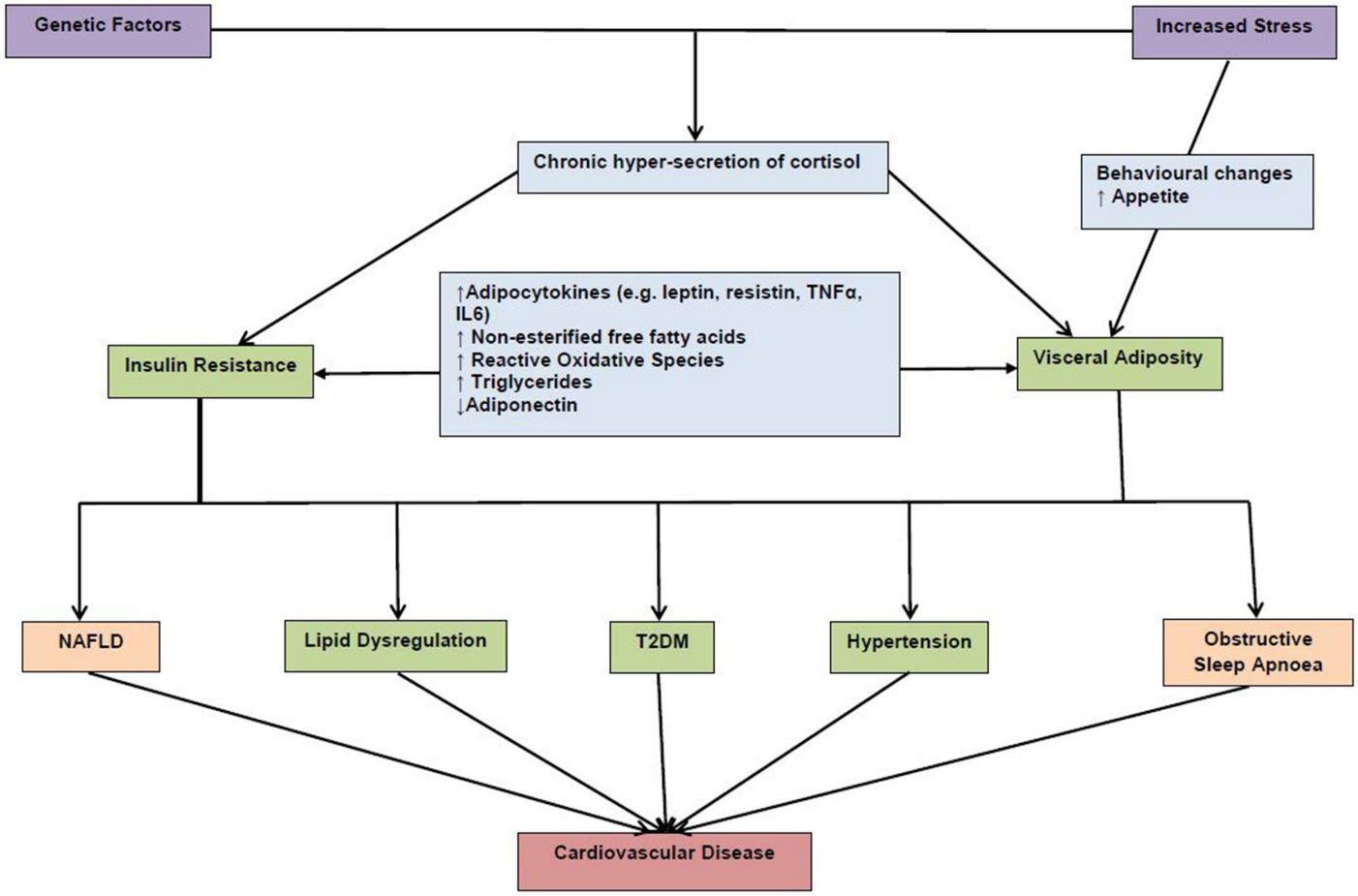


Figure 1. Metabolic syndrome – a chronic pro-inflammatory state

usually derived from triglyceride stores in adipose tissues via lipolysis, a process inhibited postprandially by insulin. In a state of insulin resistance, there is an increased rate of lipolysis, resulting in increasing levels of FFA which in-turn inhibit insulin-dependent glucose uptake, creating a vicious cycle. [11-13]

Other contributory factors include a state of chronic hypersecretion of stress mediators including cortisol which may occur in genetically predisposed individuals. People with insulin resistance can also exhibit low growth hormone and hypogonadism, all of which contribute to increased visceral fat accumulation and insulin resistance. In addition, increased stress can lead to behavioural changes, increased appetite and contribute to visceral fat formation.[2]

Historical definitions of MetS do not include obstructive sleep apnoea (OSA) or non-alcoholic fatty liver disease (NAFLD), however recent evidence suggests both conditions have similar contributory factors and can also lead to cardiovascular complications (Figure 1). Prior studies have shown that fasting glucose and insulin levels are significantly higher in obese patients with OSA compared to weight matched individuals. There is a complex interplay between insulin resistance and OSA, and they have been shown to be associated independently of obesity.[14,15]

OSA is associated with sleep fragmentation and nocturnal hypoxia, which leads to the activation of the sympathetic nervous system and an increased pro-inflammatory state. Furthermore, intermittent hypoxia has also been shown to affect beta cell function, leading to insulin resistance.[16] Visceral fat is also linked with OSA with data demonstrating increased visceral adipose tissue in those with OSA. The underlying pathogenesis of NAFLD seems to be secondary to lipid dysregulation and FAAs secondary to insulin resistance and visceral adiposity.[17] Given the common underlying pathophysiology, an updated definition of MetS including both OSA and NAFLD should be considered such that patients can be managed holistically with multi-specialist multidisciplinary team input.

Metabolic syndrome and cardiovascular disease

MetS increases both atherosclerotic and non-atherosclerotic cardiovascular disease. A large systematic review and meta-analysis including 87 studies and 951,083 patients concluded that metabolic syndrome is associated with an increased risk of CVD (RR 2.35, 95% CI 2.02-2.73), cardiovascular mortality (RR 2.40, 95%CI 1.87-3018) and myocardial infarction (RR 1.99, 95%CI 1.61-2.46). This increased risk was maintained even in patients with metabolic syndrome without diabetes. Interestingly this

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analysis also concluded (as supported by prior meta-analysis) that the risk was higher in women. There have been some postulations as to the reasons underlying this. Central adiposity is more pronounced in post-menopausal women and the lipid profile is different, with lower HDL and denser LDL particles.[18] Furthermore, another meta-analysis showed that an increase in triglycerides of 1.0mmol/L was associated with a 75% increased cardiovascular risk in women compared with 30% in men.[19] Whilst there is no doubt that MetS increases cardiovascular risk, the prognostic importance of MetS remains to be elucidated. Whether MetS has a synergistic effect remains to be seen in large scale prospective studies. Previous studies have reported a similar relative risk for isolated impaired fasting glucose and hypertension. Furthermore, a previous systematic review in over 3400 people suggested that MetS was not an independent predictor of atherosclerotic plaque progression after adjustment of individual parameters.[20] Clearly further work in this field is necessary to elicit whether MetS is of prognostic importance, independent of its defining factors.

Metabolic syndrome and diabetes

Several large-scale studies and meta-analyses have concluded that the presence of MetS, regardless of definition, is predictive of new-onset type 2 diabetes mellitus (T2DM). A large meta-analysis (16 cohorts and 42,419 participants) concluded the average estimated RR for diabetes was 3.5-5.2 (definition dependent). Moreover, several of the included studies found that the risk increased in patients with more abnormalities.[21,22] As an example, in the British Heart Regional Study, the estimated RR for developing diabetes for patients with three abnormalities was 4.56 (95%CI 2.48-8.78) vs. 10.88 (5.77-20.50) for those with four or more abnormalities.[21] Impaired fasting glucose (IFG) unsurprisingly is the strongest predictor for T2DM development and patients with MetS, which included IFG, have a significantly higher RR for diabetes (11.0, 95%CI 8.1-14.9) compared to those without IFG (RR 5, 95%CI 3.7-6.8). It is clear from previous data that MetS is a strong predictor of diabetes especially when patients have IFG.[21] This is not a surprise given that insulin resistance underpins both conditions.

Prior debates have discussed that T2DM should be included within the definition of MetS. However, the value of MetS as a predictive tool for diabetes allows patients to modify risk factors potentially preventing cardiovascular disease and diabetes in the future.[21,23] Patients with IFG and those with an increasing number of components of MetS seem to have increased risk of developing diabetes suggesting that this group of patients need more intensive intervention. This potentially calls for a change in the paradigm of MetS and the need to incorporate a severity score, thereby classifying patients in further detail to help target intervention appropriately.

Finally, the role of diagnosing MetS in those who already have diabetes is also important. A study in the USA concluded that in patients with diabetes over 50 years, 86% had MetS.[23] Cardiovascular disease is a leading cause of death in T2DM and given the high number of patients who also have MetS, a holistic view in treating all modifiable risk factors aggressively is important for improving patient outcomes.

Metabolic syndrome and OSA

OSA, defined as the presence of an apnoea-hyponoea index (AHI) ≥ 5events/hour has an estimated worldwide prevalence of 936 million people.[24] The relationship between MetS and OSA is known as 'syndrome Z' and both conditions share visceral adiposity and insulin resistance as mechanistic factors. A recent large systematic review and meta-analysis (15 cross-sectional studies, 2456 patients with OSA) demonstrated a pooled OR of MetS of 2.87 (95%CI 2.41-3.42). Furthermore, the pooled OR of MetS in patients with mild and moderate-severe OSA was 2.39 (95%CI 1.65-3.46) and 3.45 (95%CI 2.33-5.12) respectively.[25] This clearly shows a significant relationship between OSA and MetS. Insulin resistance may be part of the pathogenic process in OSA or likely a result of OSA. Patients with OSA have been shown to have a lower insulin sensitivity and higher fasting insulin level. Furthermore, patients with OSA have increased systemic inflammatory markers (IL-6 and TNF-α) independent of obesity which contribute to insulin resistance. Intermittent hypoxia has also been shown to affect beta cell function, leading to insulin resistance.[16] Moreover, there is increasing evidence linking T2DM and OSA. Some population studies estimate that up to 40% of patients with OSA have diabetes and in those with diabetes the combined prevalence of sleep disordered breathing may be has high as 58%.[26] Whether OSA causes T2DM or vice versa remains to be elucidated. However, a strong relationship between the two with similar underlying risk factors is clear. Furthermore, there is some evidence to suggest that treatment of OSA with CPAP can decrease inflammatory markers (such as IL-6) and reduce vascular complications of diabetes. Conversely there has also been a study that shows treatment of OSA with continuous positive airway pressure (CPAP) therapy did not substantially lead to a reduction in HbA1c. However, it is important to note that this study was small in number and the compliance of CPAP was poor.[27] The role of CPAP therapy and it's overall effect on T2DM remains to be fully elucidated.

It is well documented that OSA significantly increases cardiovascular risk independently of obesity, diabetes, dyslipidaemia and hypertension.[28] Whether OSA poses synergistic cardiovascular risk in patients with currently defined MetS remains to be seen. However, given the extent of cross-over between conditions, common risk factors and outcomes, it is likely that altering an individual's metabolic profile will improve their OSA, overall health and decrease their overall cardiovascular risk. Given the wealth of evidence linking OSA with MetS, obesity, insulin resistance, diabetes, and cardiovascular disease, thought should be given to including OSA in a new definition of MetS. This will enable clinicians to focus on modifying risk in this multimorbid group of patients, encouraging patients to modify lifestyle behaviours and engage with care, prior to onset of cardiovascular disease.

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Table 2. A new definition of Metabolic Syndrome

Clinical Measure	New Proposed Definition	IDF criteria
Criteria	**Mild (1-3/7 criteria) **Moderate (4-5/7 criteria) or isolated OSA / liver fibrosis **Severe (6-7/7 criteria)	Central Obesity (WC – ethnicity specific values* or BMI >30kg/m^2 + 2 of the following
HDL	< 1.03mmol/L (men) < 1.29mmol/L (women) Or on treatment	< 1.03mmol/L (men) < 1.29mmol/L (women) Or on treatment
Triglycerides	> 1.7mmol/L Or on treatment	> 1.7mmol/L Or on treatment
Waist/hip ratio*	> 0.9 (Males); > 0.85 (Females)	-
Waist (cm)*	Men ≥ 90cm, women ≥ 80cm	-
BMI*	> 30kg/m^2	-
Blood pressure	Systolic ≥ 130 or diastolic ≥ 85 Or on treatment	Systolic ≥ 130 or diastolic ≥ 85 Or on treatment
Fasting Plasma glucose	≥ 5.6mmol/L Or diagnosed with diabetes	≥ 5.6mmol/L Or diagnosed with diabetes
Obstructive Sleep Apnoea	AHI ≥ 5 events/hour	-
Evidence of Fatty Liver Disease	Fibroscan >8KPa[35] Liver biopsy showing significant fibrosis	

* Only one of these counts as 1 point in the new definition (take the measurement with the highest reading).
** We have chosen 3 or fewer clinical measures to represent mild disease as studies have previously shown patients with 3 abnormalities vs. 4 or more have an increased risk of diabetes (RR 4.56, 95%CI 2.48-8.78 vs. 10.88, 95%CI 5.77-20.5). The differentiation between moderate and severe is arbitrary at this stage, and based on expert opinion.It therefore needs validation and clarification. The presence of OSA and/or liver fibrosis already indicates end-organ damage and therefore we feel this should classify patients in the moderate category.

Metabolic syndrome and NAFLD

NAFLD is characterised by increased liver fat content in the absence of alcohol misuse or other secondary causes of steatosis, with a global prevalence of around 25%.[29] The pathogenesis of NAFLD is closely associated with co-morbid occurrence of multiple conditions characterising metabolic syndrome. Moreover, the progression of NAFLD to steatosis (NASH) and cirrhosis is strongly dependent on T2DM and obesity. There is a dose-dependent relationship between increased BMI and risk of developing NAFLD. However, there is also a cohort of patient's increasingly being recognised called 'lean-NAFLD' where obesity is not present. A recent systematic review which compared lean NAFLD patients to lean controls, found that there was a significant increment in parameters associated with MetS including: fasting plasma glucose, triglycerides, blood pressure and waist circumference. When lean-NAFLD patients were compared with obese-NAFLD patients there was further significant increase in the same parameters (i.e. higher in the obese NAFLD population). This review suggests that lean patients with NAFLD, while classified as non-obese, have metabolic derangements that need addressing to prevent future complications.[30] Given the recent developments, a panel of 22 international experts have recently proposed that nomenclature and definition of NAFLD changes to that of metabolically associated fatty liver disease (MAFLD). The proposed criteria for the diagnosis of MAFLD are based on histological, imaging or blood biomarker evidence of hepatic steatosis with one of either obesity and/or T2DM and/or evidence of metabolic dysregulation. Metabolic dysregulation includes waist circumference, hypertension, lipid dysregulation and impaired fasting glucose.[31]

NAFLD has also been shown to be associated with cardiovascular disease independent of BMI, smoking, hypertension, and dyslipidaemia. A meta-analysis with 34,043 patients showed that patients with NAFLD had a 64% higher risk of developing fatal or non-fatal cardiovascular events compared to patients without NAFLD (OR 1.64, 95%CI 1.26-2.13).[32] However, it remains to be seen whether NAFLD itself causes increased CVD or whether the underlying metabolic comorbidities that prevail in NAFLD result in CVD. Either way, the pathogenic mechanisms leading to NAFLD are shared with T2DM and OSA and this further emphasises the need for a new definition and paradigm shift in MetS.

Metabolic syndrome: time for a new definition?

As our understanding of the underlying pathophysiology of MetS grows, the clinical importance of MetS remains to be optimised in multi-disciplinary, cross-specialty pathways that benefit patients. While visceral adiposity, insulin resistance, dyslipidaemia and a chronic inflammatory state underpins

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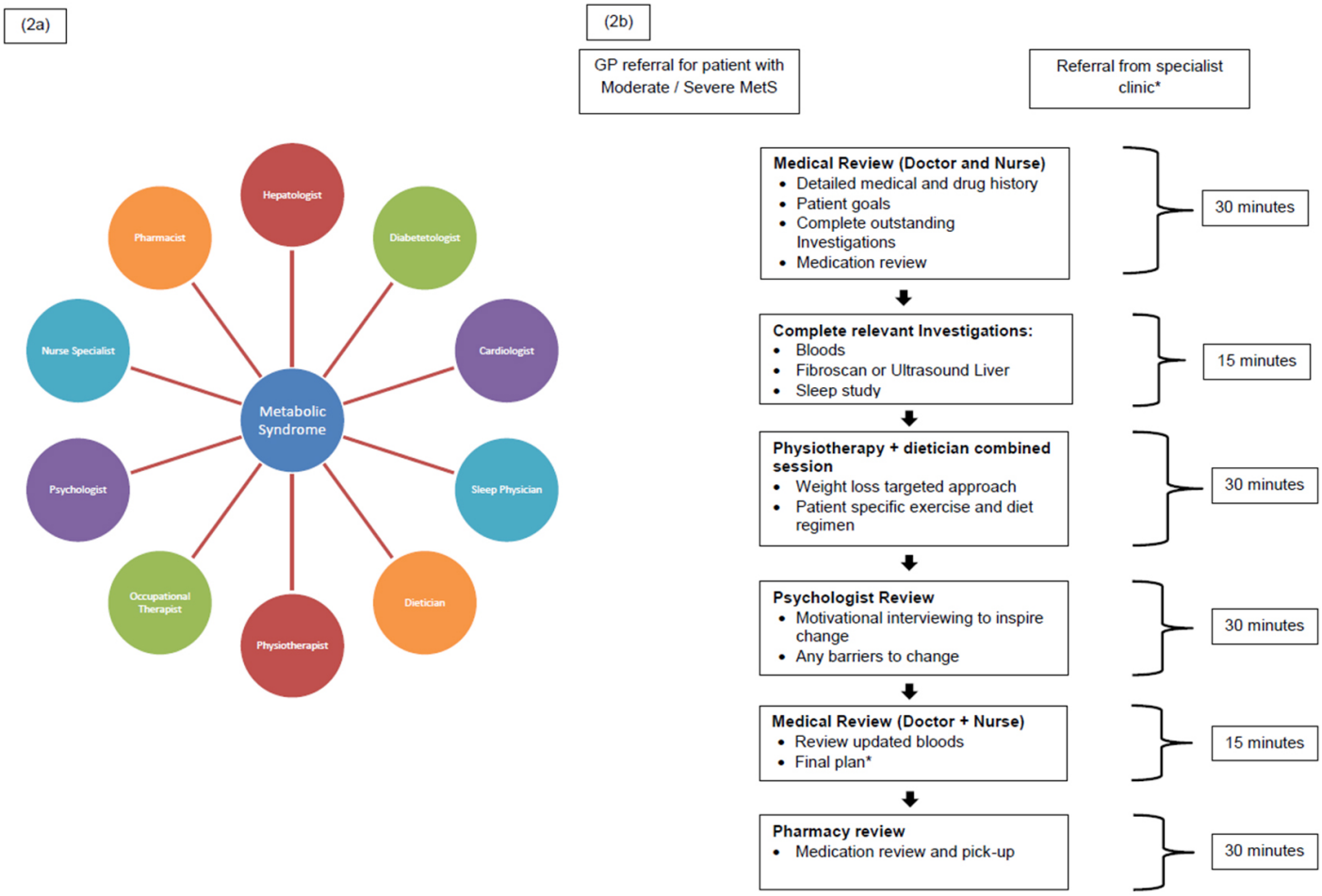


Figure 2. Metabolic syndrome and a proposed future treatment pathway. (a) The range of specialties involved in managing someone with metabolic syndrome. (b) A proposed new one-stop-shop pathway for metabolic syndrome patients with moderate-severe disease, with a suggested time frame.

this syndrome, the consequences are more than simply cardiovascular. Moreover, whether the effects are synergistic is still unknown. According to the National Health Service in the UK, around one in three adults over 50 have MetS.[33] This is roughly 8 million people,[34] living with a ticking time bomb.

The current definitions of MetS have not been reviewed since 2006 and do not include increasingly prevalent conditions such as OSA and NAFLD which have the same underlying pathophysiology and are independent risk factors for developing cardiovascular disease. Given that previous guidance has not included increasingly prevalent conditions and a risk stratification system, would a new more inclusive definition of MetS with a severity scale, improve patient outcomes? We propose a model such as Table 2, which may have better utility so that future patient optimisation, resources and research, can be prioritised between primary and secondary care.

This new definition would require validation in prospective randomised trials but provides a valuable starting point to modernise this entity in a patient centred approach. It also allows treatment templates to be built for both primary and secondary care. The current definition excludes key criteria with similar underlying pathophysiology and prevents potentially modifiable risk factor modification in a time-critical manner.

Metabolic syndrome: future treatment pathway

Metabolic syndrome is a multi-system condition that needs specialist input from a wide multi-disciplinary team as highlighted in Figure 2a. Mild MetS likely encompasses a large number of patients and can be managed in primary care. However, this means home sleep studies and tests for liver fibrosis such as a fibroscan need to be readily available for primary care practitioners to request. Moderate / severe MetS should be managed in secondary care with dedicated multidisciplinary specialist clinics in a one-stop pathway (Figure 2b). Whilst the onus is largely on the general practitioner to refer into this service, patients should also be actively screened and referred from diabetes, cardiovascular, hepatology and sleep outpatient services if patients meet the criteria for moderate / severe disease. The idea for this clinical pathway or 'one-stop shop' comes from well-established cancer pathways e.g. breast cancer

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services. Furthermore, the development of a new role, the metabolic nurse specialist, would be akin to a cancer specialist nurse and would act as the main point of contact for patients and their journey. The pathway will streamline services for patients and aid modification of all risk factors (both conservative and medical) in a co-ordinated way. This will enable patients to be treated effectively, in a holistic and multi-disciplinary way. Of course, patients who have OSA, NAFLD, complex diabetes or cardiovascular complications will need to be referred back to the specialist pathway services. The idea of this service is to only see the patient once with primary care physicians having a detailed plan in place for medications, risk modifications and re-referral as necessary. While patient's will spend a considerable time in hospital on the one day, this holistic approach puts them at the centre of care, encourages active lifestyle changes and ensures an understanding of the severity of the condition.

Conclusion

In an ever-changing landscape of increasing obesity, insulin resistance and cardiovascular disease, as healthcare specialists, prevention should be our primary goal. The current definitions of MetS have not evolved with increasing evidence of common underlying pathological processes leading to equally prevalent conditions. We propose a new, up-to-date definition of MetS which incorporates OSA and NAFLD and adds a severity / graded system. This ensures patients with more severe disease receive early targeted care in specialist secondary care services. This concept remains to be validated and tested in clinical practice but provides a framework for future care that is both cross-speciality and multi-disciplinary.

Declarations of completing interests

Nothing to declare

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