Preventing cardiovascular–kidney–metabolic syndrome progression

A man with obesity, prediabetes and heart failure

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A 63-year-old man presents following a non-ST-segment elevation myocardial infarction and diagnosis of heart failure with reduced ejection fraction in the setting of obesity, prediabetes and other cardiovascular–kidney–metabolic (CKM) risk factors. Assessment and management of CKM syndrome in primary care are discussed, including prevention, lifestyle intervention and pharmacological treatment.

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KEY POINTS

- Cardiovascular–kidney–metabolic (CKM) syndrome describes the interconnected progression of obesity, prediabetes and type 2 diabetes mellitus, chronic kidney disease and cardiovascular disease, including heart failure.
- Primary care has a central role in identifying early CKM risk factors, including visceral obesity, hypertension, dyslipidaemia and prediabetes, before progression to advanced disease.
- Lifestyle intervention remains foundational across all CKM stages and includes healthy dietary patterns, physical activity, weight management, smoking cessation and engagement with community prevention programs.
- Contemporary CKM management includes therapies that target multiple metabolic pathways, including sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists and nonsteroidal mineralocorticoid receptor antagonists.
- Multidisciplinary care, structured chronic disease management and proactive follow up are essential to reduce the progression of CKM syndrome and improve long-term outcomes.

Case presentation

John is a 63-year-old accountant who has attended the practice for 10 years. He was recently discharged from a local tertiary hospital following a non-ST-segment elevation myocardial infarction and diagnosis of heart failure with reduced ejection fraction. During admission, an elevated glycated haemoglobin level of 6.3% (45 mmol/mol) was also identified.

Before John had been admitted to hospital, he had been treated for hypertension with telmisartan 80 mg daily. Over the preceding five years, he had experienced progressive weight gain of 10 kg, reaching a body mass index (BMI) of 33 kg/m^2 following separation from his wife.

His family history included ischaemic heart disease in his father at the age of 65 years and a haemorrhagic cerebrovascular accident in his mother at the age of 63 years. He stopped smoking five years ago and drinks two standard alcoholic drinks on weekend nights.

During his hospitalisation, John was commenced on aspirin daily, frusemide 40 mg every morning, rosuvastatin 20 mg daily, spironolactone 25 mg every morning, metoprolol succinate 23.75 mg daily and sacubitril/valsartan 48.6 mg/51.4 mg twice daily.

Results from investigations showed:

- fasting blood glucose level, 6.5 mmol/L, repeated two weeks later at 6.3 mmol/L
- glycated haemoglobin level, 6.3% (45 mmol/mol)
- total cholesterol level, 5.5 mmol/L
- HDL-cholesterol level, 1.1 mmol/L
- triglyceride level, 2.6 mmol/L

MedicineToday 2026; 27(6): 41-45

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TABLE 1. DEFINITIONS OF METABOLIC SYNDROME[4]

Criterion	Definition
Elevated waist circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternative indicator*)	≥1.7 mmol/L
Reduced HDL-cholesterol (drug treatment for reduced HDL-cholesterol is an alternative indicator*)	<1.0 mmol/L in men; <1.3 mmol/L in women
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternative indicator)	Systolic ≥130 mmHg and/or diastolic ≥85 mmHg
Elevated fasting glucose† (drug treatment of elevated glucose is an alternative indicator)	≥5.6 mmol/L

* Most patients receiving treatment for elevated triglycerides and reduced HDL-cholesterol levels will meet the criteria for metabolic syndrome.
† Threshold reflects the updated definition for impaired fasting glucose.

- LDL-cholesterol level, 2.5 mmol/L
- liver function tests (alanine aminotransferase and aspartate aminotransferase), about twice the upper limit of normal
- estimated glomerular filtration rate, 65 mL/min/1.73 m²
- haemoglobin level, 137 g/L (normal range = 135–175 g/L)
- platelet count, 225 × 10^9/L (normal range = 150–450 × 10^9/L)
- normal white cell count.

On examination at the clinic, his blood pressure was 130/75 mmHg, waist circumference 110 cm, jugular venous pressure was not elevated, and there was no peripheral oedema.

John has two questions:

- How could his health crisis potentially have been prevented, and what should his children know about their own future health risks?
- How can we help keep him healthy moving forward?

Commentary

Cardiovascular disease (CVD) and heart failure often represent the culmination of multiple intersecting risks present many years before a major clinical event, as occurred in John. These risks are now broadly classified under the term cardiovascular–kidney–metabolic (CKM) syndrome.[1]

The CKM concept was proposed to support a more focused paradigm highlighting the multidirectional impact of clinically identifiable risk factors, particularly visceral obesity, and opportunities for both early preventive and later interventional strategies.[1] The focus is on addressing the multiorgan dysfunction that may eventuate from prediabetes and type 2 diabetes mellitus through to CVD, chronic kidney disease (CKD) and metabolic dysfunction-associated fatty liver disease (MAFLD) as an interconnected clinical framework.

The pathophysiology of CKM syndrome includes progressive systemic inflammation related to visceral obesity, insulin resistance, oxidative stress and advancing inflammation from glycation end products, dysfunctional neurohormonal signalling (e.g. sympathetic overactivity and renin–angiotensin–aldosterone system activation) and abnormal haemodynamic effects.[2,3]

Modifiable clinical risk factors include visceral obesity, hypertension, smoking, physical inactivity, unhealthy dietary patterns, excess alcohol intake, sleep dysfunction (e.g. sleep apnoea) and serious mental illness.

Metabolic syndrome, defined in Table 1, has traditionally been used to cluster many of these modifiable risk factors.[4] However, it does not adequately incorporate risks associated with CKD and MAFLD. Historically, clinical guideline pathways have often focused on single diseases such as CVD, CKD, obesity and diabetes, potentially underemphasising the importance of a broader multisystem approach. Furthermore, metabolic measures such as the BMI may inadequately reflect risk in diverse populations, including non-Caucasian ethnic groups, First Nations peoples and those affected by social disadvantage.[5-7]

CKM stages

The stages of CKM syndrome are summarised as:[1]

- **stage 0:** normal weight, normal blood glucose levels, normal blood pressure and normal lipid levels
- **stage 1:** excess or dysfunctional adiposity (BMI >25 kg/m²), prediabetes
- **stage 2:** established risk factors, including hypertension, diabetes, dyslipidaemia, obesity and CKD
- **stage 3:** subclinical CVD with CKM risk factors; very high-risk CKD
- **stage 4:** clinical CVD (heart failure, coronary disease, peripheral artery disease, atrial fibrillation or cerebrovascular disease) and CKM risk factors.

Australian data demonstrate an increasing prevalence of CKM conditions in primary care since 2011. By 2020, 21.8% of patients attending primary care had at least one CKM condition, 8.3% had two CKM conditions and 1.9% had all three CKM risk conditions.[8]

Contemporary CKM frameworks therefore emphasise early identification and prevention, while supporting individualised therapy for progressively increasing multiorgan dysfunction. They also highlight the importance of multidisciplinary care and multisystem interventions rather than single disease-focused approaches.

On reflection, John's progression through the CKM stages may have been identified earlier, potentially creating opportunities for prevention before the development of stage 4 disease, particularly in relation to cardiovascular risk and weight gain.

Primary care plays a crucial role in early CKM identification and prevention strategies in stages 1 to 3, before the emergence of advanced disease such as that seen in John, with the aim of reducing morbidity and mortality through improved standards of care.

Clinical tools for CKM prevention and intervention

Addressing John's questions about prevention and support for his children, if risks are identified, includes facilitating access to evidence-based community programs focused on risk reduction.

Use of a broad range of CKM tools and biomarker assessments (lipids, proteinuria and glycaemia) can help translate current clinical risks into supportive pathways aimed at reducing future complications – so-called 'productive clinical care' (Box 1).[9] Chronic condition management programs supported through Medicare item numbers may also assist by aligning SMART (specific, measurable, achievable, relevant and timely) goals with appropriate individualised support services such as accredited practicing dietitians, exercise physiologists and psychologists.[10]

Healthy lifestyle: diet, activity and weight management across the CKM spectrum

Although John has stopped smoking, relapse prevention remains important and cessation support should be available across multiple domains of the healthcare system from community pharmacy to primary care.

Visceral adiposity remains a core driver of CKM risk.[1] Healthy dietary management is fundamental in reducing childhood weight gain and preventing adolescent- and adult-emergent CKM risk. Community programs and resources supporting healthy lifestyle engagement are outlined in Box 2 and Box 3.

There is no universally agreed ideal diet for adults with CKM risk; however, important principles include improved fibre intake, reduced kilojoule consumption, moderation of carbohydrate quantity and quality, and reduced salt and alcohol intake. Dietary approaches consistent with these principles include the Mediterranean diet, PREDIMED and the Dietary Approaches to Stop Hypertension (DASH) diet.[11,12] However, dietary support should remain individualised,

1. ASSESSMENT AND MONITORING IN CARDIOVASCULAR–KIDNEY–METABOLIC SYNDROME

Cardiovascular disease

- The Australian cardiovascular risk assessment tool provides a patient-focused resource incorporating social determinants of health and advancing CKM stages, including chronic kidney disease and diabetes
- The tool supports translation of cardiovascular risk before cardiovascular events emerge
- RACGP guidelines recommend assessing CVD risk every five years in people aged 45 to 79 years, or more frequently if risk factors worsen

Dysglycaemia

- AUSDRISK uses a scoring system to stratify diabetes risk
- AUSDRISK scores >12 should prompt investigation for prediabetes or overt diabetes (e.g. oral glucose tolerance test or HbA_{1c} testing) and scores of 6 to 12 indicate an increased diabetes risk and the need for individualised prevention advice
- RACGP guidelines recommend assessment every three years from the age of 40 years, or more frequently if risk escalation occurs

Kidney health

- Assessment includes BP measurement, eGFR and urinary albumin/creatinine ratio. These investigations support kidney disease classification using nationally recognised risk matrices
- Annual assessment is recommended for First Nations people aged over 18 years of age, and for people with diabetes, hypertension or established CVD
- Assessment every two years is recommended in people with obesity, smoking history or family history of kidney disease
- Increasing albuminuria correlates with long-term CVD risk and may support earlier intervention, including RAAS inhibition, SGLT-2 inhibitors and steroidal or nonsteroidal mineralocorticoid receptor antagonists, where appropriate

Metabolic dysfunction-associated fatty liver disease

- Assessment should focus on liver steatosis and progression to fibrosis
- In people with obesity or type 2 diabetes, assessment should progress beyond liver function testing and liver ultrasound to fibrosis risk stratification using tools such as FIB-4 scoring
- A FIB-4 score <1.3 suggests lower fibrosis risk, with reassessment recommended every three years
- A FIB-4 score of 1.3 to 2.7 warrants reassessment every two to three years and consideration of further fibrosis assessment (e.g. elastography)
- FIB-4 scores >2.7 warrant specialist hepatology review

Abbreviations: AUSDRISK = Australian Type 2 Diabetes Risk Assessment Tool; BP = blood pressure; CKM = cardiovascular-kidney-metabolic; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; FIB-4 = fibrosis-4 index; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA_{1c} = glycated haemoglobin; RACGP = Royal Australian College of General Practitioners; RAAS = renin–angiotensin–aldosterone system; SGLT-2 = sodium-glucose cotransporter-2.

2. LIFESTYLE RESOURCES FOR SPECIFIC POPULATIONS

- **Youth**
  - PODSQUAD (https://hw.qld.gov.au/podsquad/)
- **Aboriginal and Torres Strait Islander people**
  - Get Up & Grow Aboriginal and Torres Strait Islander resource collection (https://www.health.gov.au/resources/collections/get-up-grow-aboriginal-and-torres-strait-islander-resource-collection?language=en)
  - Aboriginal and Torres Strait Islander guide to healthy eating (https://hw.qld.gov.au/blog/ch-resource/aboriginal-and-torres-strait-islander-guide-to-healthy-eating/)
- **Culturally diverse populations**
  - Wellbeing and Nutrition for Diverse Communities (https://wandcre.org.au/resource-hub/)
- **Diabetes prevention**
  - Diabetes Australia prevention programs (https://www.diabetesaustralia.com.au/prevention-programs/)

culturally sensitive and sustainable, ideally with input from an accredited practising dietitian.

Physical activity goals should be negotiated collaboratively rather than imposed in ways that conflict with individual abilities or preferences. Evidence supports combined aerobic and resistance training, including high-intensity exercise, in stages 1 and 2 CKM.[13]

In more advanced disease, such as in John's case, enrolment and adherence to cardiac rehabilitation, interval aerobic exercise, resistance training and home-based walking programs should be encouraged. Lifestyle intervention trials have demonstrated benefit in preventing progression from prediabetes to diabetes. Guidelines also support the benefit of similar programs in MAFLD.[14]

Specific interventions targeting multiple metabolic targets in CKM

Recent therapeutic developments have created opportunities for therapies that can address the spectrum of CKM organ dysfunction when risks emerge. However, the evidence of benefit may vary according to CKM stage and across different populations, including those with or without diabetes and obesity. PBS subsidisation also varies according to indication and should be reviewed before prescribing. Therapeutic approaches across CKM stages are summarised in Table 2.[15-32]

Returning to John: practical management priorities

Practical management priorities for John require an organised primary care approach to include the following:

- a focus on John's goals and values and vigilance for psychological care needs
- implementation of Australian evidence-based guidelines for heart failure management[33]
- titration of sacubitril/valsartan, beta blockers and mineralocorticoid receptor antagonist therapy, if required
- addition of an SGLT-2 inhibitor, consistent with guideline recommendations, and consideration of the use of semaglutide
- optimisation of lipid-lowering therapy to achieve an LDL-cholesterol target below 1.4 mmol/L
- further investigation of abnormal liver function tests. John has a fibrosis-4 (FIB-4) score of 2.1, which supports further assessment for liver fibrosis, including liver ultrasound and elastography
- assessment of iron studies in the setting of heart failure, with consideration of intravenous iron therapy where appropriate. In patients with ferritin below 100 mg/L, or transferrin saturation below 20% with ferritin between 100 and 299 mg/L, intravenous iron has demonstrated reductions in heart failure hospitalisation[34]
- consideration of obstructive sleep apnoea assessment

3. STATE AND TERRITORY PREVENTIVE HEALTH PROGRAMS

- **Get Healthy Service** – New South Wales (https://www.gethealthynsw.com.au)
- **My health for life** – Queensland (https://www.myhealthforlife.com.au)
- **The COACH Program** – Tasmania (https://www.thecoachprogram.com)
- **Life!** – Victoria (https://lifeprogram.org.au)
- **Better Health Coaching Service** – South Australia (https://betterhealth.sa.gov.au)
- **Better Health Coaching Service** – Western Australia (https://betterhealthcoaching.com.au/wa-home/)
- **Getting Started prediabetes program** – Healthy Living NT (https://www.ntcommunity.org.au/organisations/healthy-living-nt/)

- development of a chronic condition management plan to support access to multidisciplinary care, including practice nurses, dietitians, exercise physiologists and psychologists
- encouragement of cardiac rehabilitation and transition to ongoing tailored physical activity programs.

Clear communication with his cardiologist, heart failure nurses and rehabilitation team is essential.

John remains at heightened CKM risk. Structured recall and review systems may support timely reassessment for progression of dysglycaemia, MAFLD, fibrosis and CKD. He should also be encouraged to discuss shared familial risk factors with his children and access preventive support programs where appropriate.

Summary

CKM syndrome places general practice at the centre of co-ordinated, proactive and patient-directed care for individuals with interconnected cardiometabolic disease.

Integrating lifestyle intervention, physical activity and targeted multimodal therapies provide opportunities

TABLE 2. SUGGESTED INTERVENTIONS ACROSS CARDIOVASCULAR–KIDNEY–METABOLIC STAGES[15-32]

CKM stage	Clinical focus	Suggested intervention
Stage 0	• Prevention and maintenance of cardiometabolic health • Lifestyle support and health goal advice	• Individualised structured lifestyle programs and weight management • Community programs including social prescribing[17] • PBS-subsidised medications only if specific conditions exist (e.g. familial hypercholesterolaemia requiring statins, hypertension requiring antihypertensive therapy)
Stage 1 (early risk factors: obesity, prediabetes, dyslipidaemia)	• Intensive lifestyle intervention and early risk-factor modification. • Weight-loss targets of 5 to 10%, BP target <130/80 mmHg and LDL-cholesterol target <2.0 mmol/L[18,19]	• Standard hypertension management and statins for high-risk lipid profiles (PBS listed for these indications) • Consider very-low-energy diet replacement programs[20] • Consider GLP-1 RA or dual GIP/GLP-1 RA for obesity (not PBS listed for this indication)[21] • Consider bariatric surgery according to guidelines[20] • Optimise age-appropriate vaccination strategies[22-26]
Stage 2 (established cardiovascular–kidney–metabolic risk factors or subclinical organ damage)	• Lifestyle intervention remains foundational, together with tight BP management, statins and RAAS blockade (if albuminuria or CKD) • Progressive weight-loss targets of 5 to 15%[18]	• Consider metformin with lifestyle intervention in prediabetes[27] • Semaglutide 2.4 mg may be considered in obesity, including obesity with high CVD risk without T2DM and stage 2 to 3 of liver fibrosis with metabolic dysfunction-associated hepatic steatosis (not PBS listed for these indications)[28] • Consider bariatric surgery in severe obesity • Initiate SGLT-2 inhibitors in T2DM with high cardiovascular or kidney risk (PBS listed for these indications)[29] • Optimise age-appropriate vaccination strategies[22-26]
Stage 3 (overt CKD, ASCVD or HF without endstage disease)	• Disease-modifying therapy together with ongoing lifestyle intervention for symptom control, functional capacity and risk reduction • LDL-cholesterol target of ≥50% reduction or ≤1.4 mmol/L • Progressive weight-loss targets of 10 to 15% if achievable[18]	• RAAS blockade and statins (PBS listed for these indications) • SGLT-2 inhibitors in T2DM, CKD, HFrEF and HFpEF (PBS listed for these indications) • GLP-1 RA (semaglutide) in CKD with T2DM (not PBS listed for this indication) • GLP-1 RA in T2DM, particularly in patients with ASCVD and obesity (PBS listed for T2DM; semaglutide 2.4 mg is not PBS listed for obesity)[30] • Dual GIP/GLP-1 RA in T2DM with ASCVD and HF (not PBS listed)[31,32] • Nonsteroidal mineralocorticoid receptor antagonist (finerenone) in T2DM with proteinuric CKD (PBS listed for this indication) • Vaccination strategies should be optimised
Stage 4 (advanced CKD, HF or recurrent ASCVD events)	• Maximally tolerated disease-modifying therapy • Lifestyle intervention adapted to frailty and comorbidity, with emphasis on quality of life and prevention of further decompensation	• SGLT-2 inhibitors in HFrEF and HFpEF (PBS listed for these indications) • RAAS blockade, beta blockers and neprilysin inhibitors in HFrEF (PBS listed for this indication) • Statins, MRA and GLP-1 RA where feasible • Vascular supportive and surgical therapies as indicated • Vaccination strategies remain important

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CKD = chronic kidney disease; GLP-1 RA = glucagon-like peptide-1 receptor agonist; GIP = glucose-dependent insulinotropic polypeptide; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; MRA = mineralocorticoid receptor antagonist; RAAS = renin–angiotensin–aldosterone system; SGLT-2 = sodium-glucose cotransporter-2 inhibitors; T2DM = type 2 diabetes mellitus.

for earlier intervention and reduction in long-term disease burden. Heart failure should be recognised as a signifier of broader CKM risk requiring comprehensive assessment.

The burden of CKM disease may be reduced through proactive primary care, structured chronic disease management and optimisation of clinical systems. Central to this approach is connecting a person's values and knowledge with clear communication of risk, co-ordinated multidisciplinary care and agreed clinical goals. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: Dr Deed provides education and advisory board advice to Abbott, AstraZeneca, Boehringer Ingelheim, Dexcom, Eli Lilly, MSD, Novartis, Novo Nordisk and Sanofi; has received payment for expert testimony and support for attending meetings and/or travel from the Royal Australian College of General Practitioners (RACGP); has participated in a Flash Glucose Monitoring (FlashGM) trial advisory board; and is a member of the RACGP Diabetes Specific Interest Group and the Australian Diabetes Society (ADS) Clinical Standards/Guideline Committee.

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