UNIT 1: PROTEINURIA & HYPERTENSION—WITH AND WITHOUT TYPE 2 DM (2026 UPDATE)

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ABSTRACT

INTRODUCTION. This Chronic Disease Management Skills Course is a yearly update on the management of six chronic medical conditions. Unit 1 covers the update of management of proteinuria and hypertension based on papers published in 2024, 2025, and 2026. **METHODOLOGY.** PubMed searches were conducted from 1–3 March 2026. **RESULTS.** Of 15 shortlisted papers, four are included in this 2026 update, which covers the following topics: Proteinuria without hypertension and proteinuria with hypertension; Differences in cutoffs in the hypertension classifications of 2018 and 2024; Hypertension mechanisms and factors; Aetiology of advanced CKD in Southeast Asia; and Kidney function outcomes in T2DM patients in Singapore circa 2024. **CONCLUSIONS.** Ten take-home messages are provided.

Keywords: Proteinuria, hypertension, chronic kidney disease, and type 2 diabetes mellitus

Acknowledgements. Grateful thanks are due to the authors of the papers cited in this paper for the tables and figures reproduced.

INTRODUCTION

This chronic disease management skills course was initiated in 2019 as a yearly update of management of six chronic medical conditions prevalent in Singapore. This Unit is the 2026 update on the management of proteinuria and hypertension, in patients with and without type 2 diabetes mellitus.

METHODOLOGY

PubMed searches were conducted from 1–3 March 2026 for recent papers published on the topic of proteinuria and hypertension, both with and without type 2 diabetes mellitus. Keywords used were: Proteinuria, hypertension, chronic kidney disease, without diabetes mellitus, and type 2 diabetes mellitus. Literature searches were limited to Singapore and Southeast Asia and for the years 2024, 2025, and 2026. Of the 15 papers shortlisted in the March 2026 literature search, four were added to the list of references in this 2026 update.

RESULTS

1. WHAT'S NEW

1.1. Additional Benefits of SGLT2 Inhibitors in Glomerular Diseases Beyond Glucose Elimination[1]

A paper published by Del Vecchio L et al[1] in Feb 2026 showed that SGLT2 inhibitors provide more than just the benefits of glucose elimination. Additional benefits in patients with glomerular diseases include:

- Have consistent nephroprotective effects across diverse populations, including those with glomerular disease without diabetes mellitus.
- Modulate inflammatory pathways through suppression of cytokines.
- May offer therapeutic advantages beyond non-specific kidney-cardiovascular protection.

1.2. Risk of Antihypertensive Drugs on Rapid Decline in eGFR in Japanese Patients with CKD[2]

Risk of antihypertensive drugs on rapid decline in eGFR in Japanese patients with CKD has been studied by Kenta Fujimoto et al,[2] and their findings include:

- Rapid decline in eGFR (defined as annual reduction >25 percent) is linked to increased mortality and morbidity in CKD.
- Data from 100,740 Japanese individuals aged 4–70 showed the incidence of 5.8 percent of participants being affected.
- Controlling BP to high normal or elevated levels in patients receiving antihypertensives reduced this risk.[2]

1.3. Contemporary Review of IgA Nephropathy

IgA nephropathy **(**IgAN) is the most common primary glomerulonrephritis worldwide with increased prevalence in Asia Pacific populations and relative rarity in those of African descent. Some 20–50 percent of IgAN patients progress to kidney failure. The pathogenesis is incompletely understood. Biomarkers predicting adverse outcomes are: proteinuria, reduced GFR, hypertension, and pathology.[3]

The mainstay of treatment is supportive, consisting of lifestyle modifications, renin-angiotensin inhibition (if hypertensive or proteinuric), and sodium-glucose transporter 2 inhibition (if GFR reduced or proteinuric). Corticosteroids are controversial and carry a high risk of serious side effects; they are observed to have the most positive results in ethnic Chinese. Similarly, mycophenolate may be effective in the Chinese.[3]

1.4. Treatment of IgAN

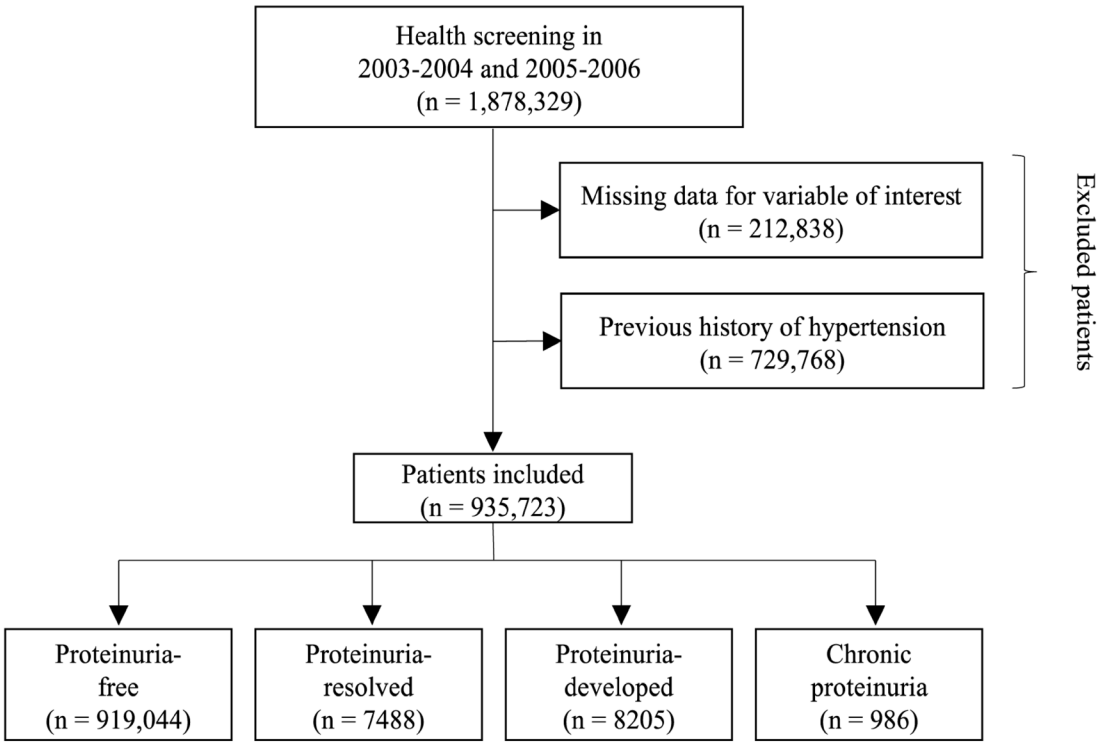
Dawn J Caster and Richard A Lafayette in a paper on treatment of igA nepropathy[4] noted that:

- SGLT2 inhibitors are likely to be effective;
- Endothelin blockade is effective; and
- Complement inhibition is effective.[4]

2. WHAT IS KNOWN

2.1. Proteinuria without Hypertension and Proteinuria with Hypertension

Figure 1. Proteinuria without hypertension



Source. Lee H, Park MS, Kang MK et al. 2023. PMID:37763181[5]

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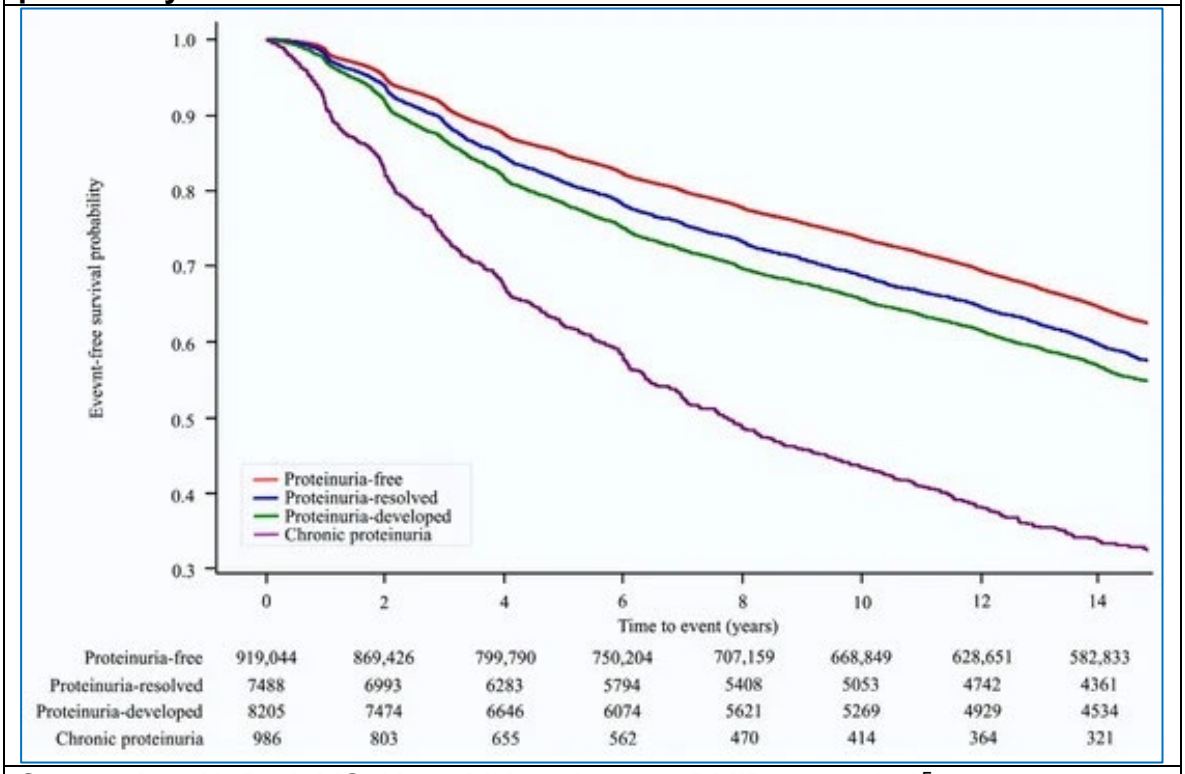
Figure 2. Proteinuria without hypertension and event-free survival probability



Source. Lee H, Park MS, Kang MK et al. 2023. PMID:37763181[5]

Table 1. Proteinuria without hypertension. Multivariable Cox Analysis for incident hypertension by changes in proteinuria status

Group	Total (n)	Hypertension (n)	Incidence Rate (per 1000 Person Years)	HR (95% Confidence Interval)		
				Model 1	Model 2	Model 3
Proteinuria-free	919,044	339,260	31.5	1 (ref)	1 (ref)	1 (ref)
Proteinuria-resolved	7488	3131	37.4	1.19 (1.15, 1.23)	1.17 (1.13, 1.21)	1.17 (1.13, 1.21)
Proteinuria-developed	8205	3638	41.3	1.31 (1.27, 1.35)	1.31 (1.27, 1.35)	1.31 (1.26, 1.35)
Chronic proteinuria	986	657	81.4	2.61 (2.41, 2.81)	2.11 (1.95, 2.27)	2.09 (1.94, 2.26)
		p for trend		<0.001	<0.001	<0.001

Footnotes:
Model 1 was adjusted for age and sex
Model 2 was adjusted for age, sex, body mass index, household income, smoking, alcohol consumption, physical activity, history of diabetes mellitus, dyslipidaemia, atrial fibrillation, cancer, and renal disease
Model 3 was adjusted for age, sex, body mass index, household income, smoking, alcohol consumption, physical activity, history of diabetes mellitus, dyslipidaemia, atrial fibrillation, cancer, renal disease, and Charlson Comorbidity Index
HR = hazard ratio
CI = confidence interval

Source. Lee H, Park MS, Kang MK et al. 2023. PMID:37763181[5]

Lee et al[5] in 2023 reported on the outcome of such patients as well as the risk of developing hypertension using the screening data from the Korean National Health Insurance Database. Data from participants without prior hypertension history who underwent their first health examination in 2003–2004 and a second examination in 2005–2006 were included in the study. Records with missing data for variable of interest, and patients with previous history of hypertension were excluded. A total of 935,723 patients were included in their study.

Based on their proteinuria status during these two examinations, participants were classified into four groups: the proteinuria-free; proteinuria-resolved; proteinuria-developed; and chronic proteinuria groups. See **Figure 1**.

The study outcome was the incidence of hypertension. During this period, 346,686 (37.1 percent) cases of hypertension were reported. The chronic proteinuria group had the highest hypertension risk, followed by the proteinuria-developed, proteinuria-resolved, and proteinuria-free groups ($p<0.001$). Those who recovered from proteinuria had a lower risk of developing hypertension than those with chronic proteinuria (hazard ratio: 0.58; 95% CI: 0.53–0.63, $p<0.001$). See **Figure 2** and **Table 1**. Conclusion: Effective management of proteinuria may potentially decrease the risk of developing hypertension and thus future mortality.

2.2. Hypertension Classifications 2018 and 2024 Compared: Differences

Unlike the 2018 ESC/ESH hypertension guideline, which had different BP targets for treatment depending on age group, the 2024 ESC hypertension has a BP treatment target of <140/90 mmHg for all age groups with the proviso of BP treatment target of less than 130/80 mmHg if tolerated based on the ALARA principle (which is BP target As Low as Reasonably Achievable for all age groups. **Table 2** compares the 2018 ESC/ESH and 2024 ESC hypertension guidelines in detail.

Table 2. Comparisons of Hypertension Classifications Between 2018 & 2024		
Reference	**2018 ESC/ESH**	**2024 ESC**
Hypertension Definition	≥140/90mmHg	**≥140/90 mmHg**
Normal BP Ranges (mmHg)	Optimal <120/<80 Normal 120–129 / 80–84 High–Normal: 130–139 / 85–89	**Non-elevated BP: <120/70** **Elevated BP: 120-129 / 70–89**
Hypertensive BP Ranges (mmHg)	Hypertension Grade1: 140–159 / 90–99 Hypertension Grade2: 160–179 / 100–109 Hypertension Grade3: ≥180 / ≥110 Isolated systolic hypertension ≥140/<90	**Hypertension: ≥140/90**
BP Treatment Targets		**120–129 / 70–79 and if not possible or not tolerated** **As Low As Reasonably Achievable (ALARA) principle (Page 3,961, 2024 ESC Guidelines)**
18–64 years (mmHg)	<130/80	
65–79 years (mmHg)	<130/80	
>80 years (mmHg)	<130/80	
Pharmacotherapy	Initial therapy with beta-blockers reserved for specific conditions including ischaemic heart disease or heart failure	**Beta blockers included as first-line therapy for hypertension**
Source: Whelton PK, Carey RM. Manda G, et al. 2022. PMID: 35965201.[6] McEvoy JW, McCarthy CP, Bruno BM, et al. 2024 ESC. PMID: 39210715[8]		

2.3. Hypertension Mechanisms and Hypertension Factors

Figure 3 reproduced from the 2024 ESC Figure 1 shows the current understanding of the hypertension mechanisms and factors. **Table 3** shows the effect of hypertension on organ damage in the eyes, brain, heart, large and medium arteries, kidneys, and microcirculation. Early and effective treatment of high blood pressure will hopefully attenuate such damage.

Figure 3. Hypertension Mechanisms and Factors

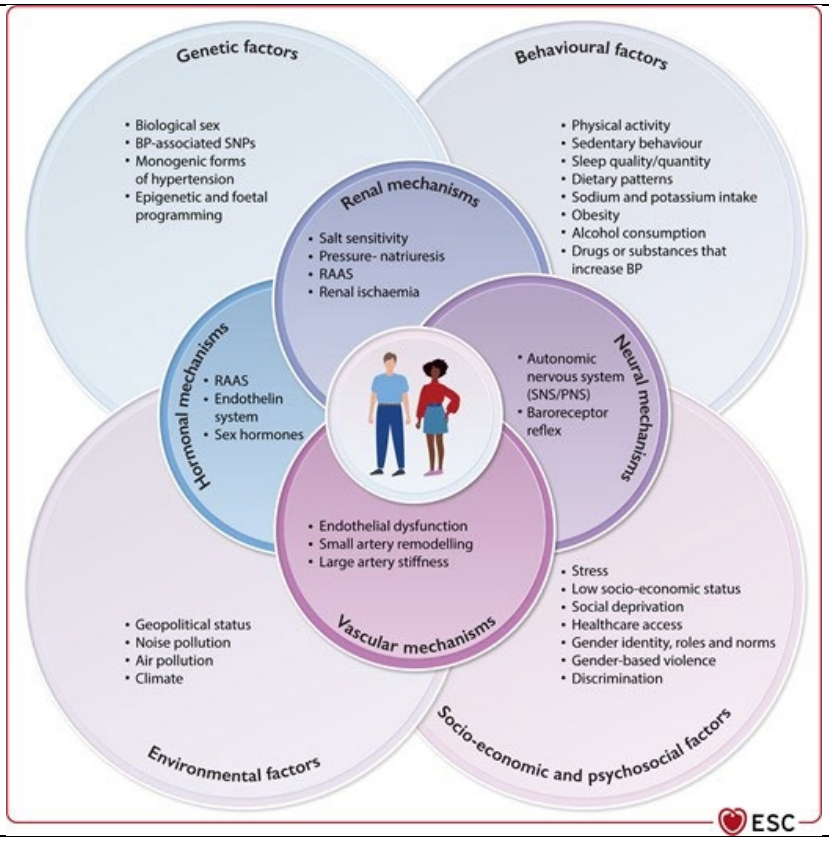
Hypertension mechanisms:

- ❖ Hormonal
- ❖ Renal
- ❖ Neural
- ❖ Vascular

Hypertension factors:

- ❖ Genetic factors
- ❖ Behavioural factors
- ❖ Socio-economic factors
- ❖ Environmental factors

2024 ESC Hypertension Guidelines



Source: Figure 1. McEvoy JW, McCarthy CP, Bruno BM et al. 2024 ESC. PMID: 39210715[8]

Table 3. 2024 ESC. Hypertension Mechanisms and Factors. Elevated BP, HT, and HMOD

No	Organ	Hypertension Mediated Organ Damage (HMOD)
1	Eye	Microvascular remodelling. Hypertensive retinopathy
2	Brain	White matter lesions, Silent microinfarcts, Microbleeds, Brain atrophy, Cognitive impairment, Vascular dementia, Ischaemic stroke, Cerebral haemorrhage
3	Heart	DM, LA and LV dilatation, AF, Obstructive and non-obstructive coronary artery disease, Myocardial infarction, Diastolic and/or systolic heart failure
4	Large & medium arteries	Atherosclerosis, Vascular calcification, Arterial stiffness
5	Kidney	Glomerular arteriolar hypertension, Glomerulosclarosis, Albuminuria/Proteinuria, Reduced GFR
6	Microcirculation	Endothelial dysfunction, Increased vasoreactivity, Vascular remodelling, Fibrosis and inflammation, Increased peripheral vascular resistance

Source: Figure 2. McEvoy JW, McCarthy CP, Bruno BM et al. 2024 ESC. PMID: 39210715[8]

3.2. Blood Pressure Measurement—Office, Home, and Ambulatory

Office blood pressure measurement needs to be checked against home blood pressure measurement or ambulatory blood pressure measurements. See details in **Tables 4–6**.

Table 4. Office blood pressure measurement	
1	Measure blood pressure after 5 minutes seated comfortably in a quiet environment
2	Use a validated device with an appropriate cuff size based on arm circumference
3	Place the BP cuff at the level of the heart with the patient's back and arm supported
4	Measure BP three times (1–2 min apart) and average the last 2 readings
5	Obtain further measurements if the readings differ by >10 mmHg
6	Measure BP in both arms at the first visit to detect between arm differences
7	Record heart rate and exclude arrhythmia by pulse palpation
Source: Figure 3. McEvoy JW, McCarthy CP, Bruno BM, et al. 2024 ESC. PMID: 39210715[8]	

Table 5. Home-Based Blood Pressure Measurement	
1	Measure blood pressure after 5 minutes of rest with arms and back supported
2	Use a validated BP device
3	Measure two readings on each occasion, 1–2 min apart
4	Obtain readings twice a day (morning and evenings) for at least 3 and usually 7 days
5	Measure BP in both arms at the first visit to detect between arm differences
6	Record and average all readings and present results to clinician Hypertension = average HPBM >135/85 mmHg
Source: Figure 4. McEvoy JW, McCarthy CP, Bruno BM, et al. 2024 ESC. PMID: 39210715[8]	

Table 6. Ambulatory Blood Pressure Measurement	
1	Use a validated BP device
2	Measure two readings on each occasion, 1–2 min apart
3	Obtain readings twice a day (morning and evenings) for at least 3 and usually 7 days
4	Measure BP in both arms at the first visit to detect between arm differences
Footnote: Hypertension: APBM ≥135/80 mmHg over 24 hours OR ≥135/85 mmHg for the daytime average OR ≥120/70 mmHg for the nighttime average	
Source: Figure 5. McEvoy JW, McCarthy CP, Bruno BM, et al. 2024 ESC. PMID: 39210715[8]	

Table 7 summarises the blood pressure readings for non-elevated blood pressure, elevated blood pressure, and hypertension for office BP, Home blood pressure measurement, and Ambulatory blood pressure measurements.

Table 7. Blood Pressure Classification 2024 ESC (Measurements in mmHg)

1	**Non-elevated blood pressure**	**Elevated blood pressure**	**Hypertension**
2	**Office BP** SBP<120 and DBP<70	**Office BP** SBP 120–139 or DBP 70–89	**Office BP** SBP≥140 and DBP≥90
3	**HBPM** SBP<120 and DBP<70	**HBPM** SBP 120–134 or DBP 70–84	**HBPM** SBP≥135 and DBP≥85
4	**ABPM** Daytime SBP<120 and Daytime DBP<70	**ABPM** Daytime SBP 120–134 or Daytime DBP 70–84	**ABPM** Daytime SBP≥135 or Daytime DBP≥85
5	Insufficient evidence confirming the efficacy and safety of BP pharmacological treatment	Risk-stratify to identify individuals with high cardiovascular risk for BP pharmacological treatment	Cardiovascular risk is sufficiently high to merit BP pharmacological treatment initiation
Footnote: The diagnosis of hypertension and elevated BP requires confirmation using out-of-office measurements (HBPM or ABPM) or at least one additional subsequent office measurement			
Source: Figure 6. McEvoy JW, McCarthy CP, Bruno BM, et al. 2024 ESC. PMID: 39210715[8]			

3.3. Risk Factors for Elevated BP Lowering

Table 8 shows the risk factors for elevated BP lowering to reduce adverse outcomes.

Table 8. Risk factors for elevated BP lowering to reduce adverse outcomes		
No	**Risk factor**	**Outcome being prevented**
1	Established clinical cardiovascular disease	Atherosclerotic cardiovascular disease Heart failure
2	Moderate or severe CKD	eGFR <60 mL/min/1.73m^2 OR Albuminuria >30 mg/g (≥3 mg/mmol)
3	Other forms of hypertension-mediated organ damage	Cardiac Vascular
4	Diabetes mellitus	Type 1 and type 2 diabetes mellitus
5	Familial hypercholesterolaemia	Probable or definite familial hypercholesterolemia
Source: Figure 7. McEvoy JW, McCarthy CP, Bruno BM, et al. 2024 ESC. PMID: 39210715.[8]		

3.4. Physical Activities and Lifestyle Changes That Can Reduce BP

Tables 9 and **10** show the physical activities and lifestyle changes that can reduce BP.

Table 9. Physical Activity and Lifestyle Changes to Reduce BP	
1	Aerobic exercise training of ≥150 min moderate intensity or 75 min vigorous intensity: brisk walking, jogging, cycling, swimming (Class I)

2	Increase daily physical activity (steps/day, take stairs, walk/cycle)
3	Avoid sedentary lifestyle
4	Isometric resistance training: Low-to-moderate-intensity (3 sets of 1–2 min contractions: hand-grip, plank, wall sit
5	Dynamic or isometric resistance training to complement aerobic exercise training 2–3 times/week (Class I)
6	Dynamic resistance exercise training: Large muscle groups, low-to-moderate-intensity (2–3 sets with 10–15 reps: squat, push-ups, sit-ups)
Source: Figure 16. McEvoy JW, McCarthy CP, Bruno BM, et al. 2024 ESC. PMID: 39210715.[8]	

Table 10. Physical Activity and Lifestyle to Reduce BP	
1	Increase potassium intake
2	Increase physical activity
3	Avoid sedentary lifestyle
4	Reduce salt (sodium chloride) intake
5	Reduce alcohol intake
6	No smoking
Source: Figure 17. McEvoy JW, McCarthy CP, Bruno BM, et al. 2024 ESC. PMID: 39210715.[8]	

3.5. Management of Hypertension in Frail Patients

Table 11 shows the management of BP in the nine categories of frail patients. The BP treatment targets are increasingly relaxed in frail patients as they enter into more frail categories and the number of hypertension medications is reduced.

Table 11. Management of BP in Frail Patients		
1	Very fit—People who are robust, active, energetic, and motivated. These people commonly exercise regularly. They are among the fittest for their age.	Follow BP-lowering treatment guidelines as per younger cohorts, ensuring treatment is tolerated.
2	Well—People who have no active disease symptoms but are less fit than Category 1. Often, they exercise or are very active occasionally, e.g., seasonally.	Evidence for benefits in reducing CVD events with more intensive treatment of BP.
3	Managing well—People whose medical problems are well controlled, but are not regularly active beyond routine walking.	Low-dose combination therapy to achieve BP control is reasonable.
4	Vulnerable—While not dependent on others for daily help, often symptoms limit activities. A common complaint is being slowed down, and/or being tired during the day.	ABPM if possible and regular review is important, particularly if change in frailty.
5	Mildly frail—These people often have more evident slowing, and	These people often have more evident slowing, and need help in high order

	need help in high order IADLs (finances, transportation, heavy housework, medications).	IADLs (finances, transportation, heavy homework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, and housework.
6	Moderately frail—Patients need help with all outside activities and keeping house. Inside, they often have problems with stairs, need help with bathing, and may need cueing (prompting) and standing by with dressing.	Evidence for benefit in CV event reduction not strong (poorly represented in clinical trials).
7	Severely frail—Completely dependent for personal care, from whatever cause (physical or cognitive). They seem stable and not at high risk of dying (within 6 months).	Exercise caution and clinical judgement in intensifying BP-lowering treatment, employing a shared decision approach
8	Very severely frail—Completely dependent, approaching the end of life. Typically, they are unable to recover from even a minor illness.	Single drug therapy may be reasonable in this cohort when initiating or maintaining BP-lowering treatment.
9	Terminally ill—Approaching the end of life. This category applies to people with life expectancy <6 months, who are not otherwise evidently frail.	Monitor for symptomatic orthostatic hypotension (OH), asymptomatic OH with falls, and poor treatment tolerance. Clinical judgement and APBM/HPBM to guide deprescribing or prescribing.
Source: Figure 17. McEvoy JW, McCarthy CP, Bruno BM, et al. 2024 ESC. PMID: 39210715.[8]		

3.6. Managing resistant hypertension

The resistant hypertension management steps are shown in **Table 12**.

Table 12. Resistant Hypertension Management Steps	
1	Office BP ≥140/90 mmHg despite 3 or more BP-lowering medications at maximally tolerated doses, including a diuretic
2	Referral to hypertension centre should be considered (Class IIa). Exclude secondary and pseudo-resident hypertension; Treatment optimisation of BP-lowering medications, ideally 3-drug single pill combination (SPC)
3	3-drug SPC not effective. True treatment-resistant hypertension diagnosed
4	Spironolactone. If spironolactone is not tolerated, use eplerenone (Class IIa)
5	Beta-blocker (if not already recommended for a compelling indication) (Class IIa)
6	Intensification of pharmacotherapy (alpha blockers, centrally acting BP-lowering drugs, K sparing diuretics, others (Class IIa)
7	Renal denervation (Class IIa)
Source: Figure 10. McEvoy JW, McCarthy CP, Bruno BM, et al. 2024 ESC. PMID: 39210715[8]	

4. PROTEINURIA AND HYPERTENSION IN DIABETIC AND NON-DIABETIC PATIENTS

Chronic kidney disease (CKD) aetiology varies greatly between developed and developing countries. The meta-analysis by Hustrini NM et al[9] aims to identify the aetiology of advanced CKD in Southeast Asian nations.

Methods. A systematic search in four electronic-databases and complementary search on national kidney registries and repository libraries was conducted until 20 July 2023. The risk of bias was assessed using Newcastle-Ottawa Scale for observational studies and Version-2 of Cochrane for intervention studies. A random-effects model was used to estimate pooled prevalence. The protocol is registered in the International Prospective Register of Systematic Reviews PROSPERO; Registration ID:CRD42022300786.

Results. A meta-analysis of advanced chronic kidney disease in Southeast Asia published in 2024 (PMID-38587764) provided useful current information. The authors analysed 81 studies involving 32,834 subjects. Pooled prevalence of advanced CKD aetiologies in Southeast Asia showed the following results:

- Diabetic kidney disease 29.2% (95% CI 23.88–34.78)
- Glomerulonephritis 20.0% (95% CI 16.84–23.38)
- Hypertensive 16.8% (95% CI 14.05–19.70)
- Other 8.6% (95% CI 6.97–10.47)
- Unknown 7.5% (95% CI 4.32–11.50)

Table 13 provides the details of the participating countries in Southeast Asia.

Table 13. Aetiology of advanced chronic kidney disease in Southeast Asia: A meta-analysis—2024. PMID: 38587764
Hustrini et al analysed 81 studies involving 32,834 subjects. Nine of the 11 Southeast Asian countries participated: (Brunei, Cambodia, Indonesia, Malaysia, Myanmar, Philippines, Singapore, Thailand, Vietnam). Two did not participate (Lao People's Republic, Timor Leste). Pooled prevalence of advanced CKD aetiologies in Southeast Asia showed the following results: ❖ Diabetic kidney disease 29.2% (95% CI 23.88–34.78) ❖ Glomerulonephritis 20.0% (95% CI 16.84–23.38) ❖ Hypertensive 16.8% (95% CI 14.05–19.70) ❖ Other 8.6% (95% CI 6.97–10.47) ❖ Unknown 7.5% (95% CI 4.32–11.50)
Hustrini NM, Susalit E, Widjaja FF, et al. The Aetiology of Advanced Chronic Kidney Disease in Southeast Asia: A Meta-analysis. J Epidemiol Glob Health. 2024 Sep;14(3):740–764. PMID:38587764[9]

Discussion. The leading cause of advanced CKD in Southeast Asia is Diabetic kidney disease (DKD), with a substantial proportion of glomerulonephritis. An efficient screening programme targeting high-risk populations (diabetes mellitus and glomerulonephritis) is needed, with the aim of delaying CKD progression.

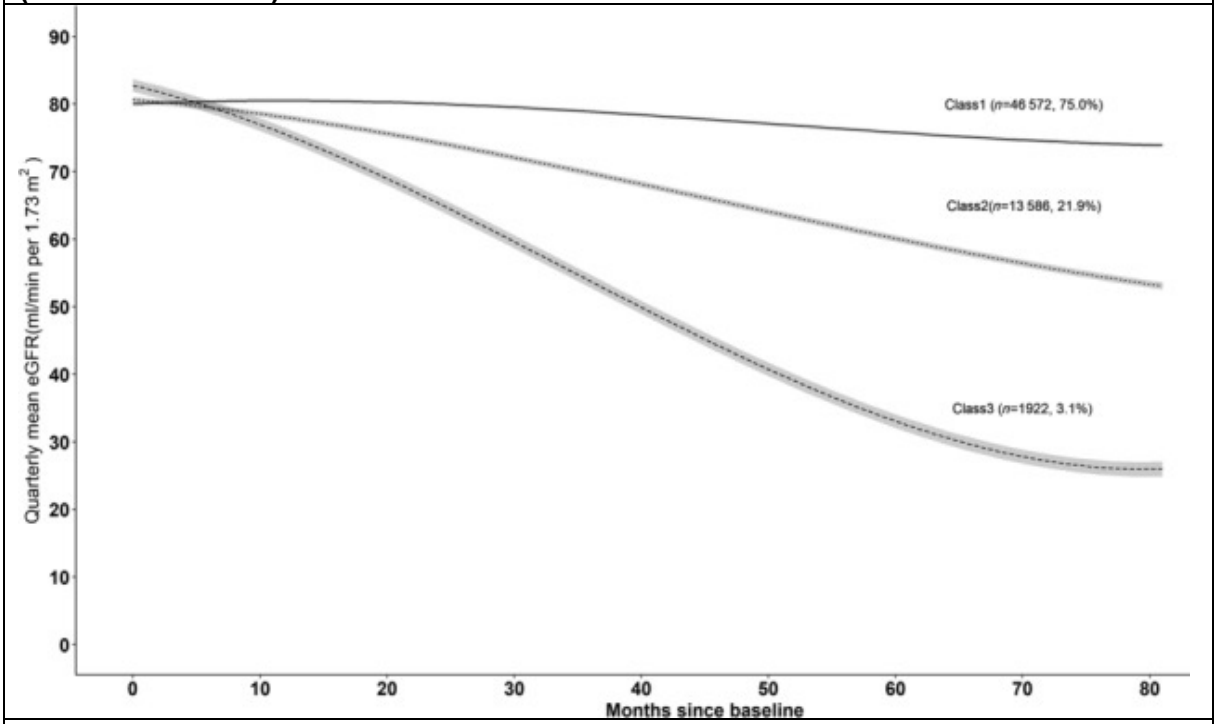
5. PROTEINURIA AND HYPERTENSION IN TYPE 2 DIABETIC PATIENTS IN SINGAPORE PATIENTS

The trajectory of estimated glomerular filtrate rate (eGFR), associated risk factors, and its relationship with end-stage kidney disease (ESKD) among a multiethnic patient population with type 2 diabetes in Singapore has been studied by Feng L et al[10] and published in 2024.

Methods: This study included 62,080 individuals with type 2 diabetes aged ≥18 years in a multi-institutional SingHealth Diabetes Registry between 2013 and 2019. eGFR trajectories were analysed using latent class linear mixed models. Factors associated with eGFR trajectories were evaluated using multinomial logistic regression. The association of eGFR trajectories with ESKD was assessed via competing risk models.

Results. Trajectory of kidney function, determined by eGFR, was nonlinear. The trajectory pattern was classified as stable initially then gradual decline (75 percent), progressive decline (21.9 percent), and rapid decline (3.1 percent). Younger age, female sex, Malay ethnicity, lower-income housing type, current smoking, higher glycated haemoglobin, lower low-density lipoprotein, higher triglyceride, uncontrolled blood pressure, albuminuria, cardiovascular disease, hypertension, and higher eGFR levels each were associated with progressive or rapid decline. Compared with the trajectory of stable initially then gradual eGFR decline, progressive decline increased the hazard of ESKD by 6.14-fold (95% confidence interval [CI]: 4.96–7.61)) and rapid decline by 82.55-fold (95% CI: 55.90-121.89). See **Figure 4**.

Figure 4. Kidney function trajectories, associated factors, and outcomes in multiethnic Asian patients with T2DM in SG (published in J Diabetes 2024 (PMID: 38169157)[10]



Younger age, female sex, Malay (vs Chinese) ethnicity, lower-cost housing type, current smoking, higher HbA1c, lower LDL-C, higher TG, higher albuminuria levels, uncontrolled BP, CVD, and hypertension were each associated with a progressive or rapid decline in kidney function

Discussion. Three nonlinear trajectory classes of kidney function were identified among multiethnic individuals with type 2 diabetes in Singapore. About one in four individuals had a progressive or rapid decline in eGFR. Results suggest that eGFR trajectories are correlated with multiple social and modifiable risk factors and inform the risk of ESKD.

CONCLUSION

The 2026 update on the topic of Proteinuria & Hypertension—With and Without Type 2 Diabetes Mellitus has added four new papers, one published in Feb 2026[1] on the benefits of SGLT2 inhibitors in glomerular diseases beyond glucose elimination in patients with diabetes, one published 2025[2] on avoiding the risk of rapid decline in eGFR by paying attention to controlling hypertension to near normal BP levels, and two papers on IgA nephropathy, both published in 2024.

This 2026 update also covered the following topics: Proteinuria without hypertension and proteinuria with hypertension; Differences in cutoffs in the hypertension classifications of 2018 and 2024; Hypertension mechanisms and factors; Aetiology of advanced CKD in Southeast Asia; and Kidney function outcomes in T2DM patients in Singapore circa 2024. Ten learning points were provided.

Learning Points

- SGLT2 inhibitors have additional benefits beyond glucose elimination in glomerular diseases.
- Controlling BP to high normal or elevated levels in patients receiving antihypertensive drugs reduced risk of rapid decline (defined as annual reduction >25%) in eGFR.
- The mainstay of therapy in IgA nephropathy is supportive, consisting of lifestyle modications, renin-angiotensin inhibition (if antihypertensive or proteinuric), SGLT2 inhibitors (if eGFR reduced or proteinuric), and endothelin-receptor antagonism (if proteinuric).
- The treatment of primary IgA nephropathy is likely to be effective with SGLT2 inhibitors, endothelin blockade, and complement inhibition.
- A nationwide population-based cohort study in South Korea demonstrated that proteinuria without hypertension needs to be treated to prevent persistent proteinuria and future mortality.
- Hypertension in older adults should be treated to prevent worse outcomes, but individualisation is important.
- The 2024 ESC retained the hypertension definition of ≥140/90 mmHg as defined by the 2018 ESC/ESH Additionally, 2024 ESC introduced two new BP reading cutoffs, namely, non-elevated BP of <120/70 mmHg and elevated BP 120–139 / 70–89 mmHg.
- In the 2024 ESC clinical practice guideline, the BP <140/90 mmHg, and less than 130/80 mmHg if tolerated, based on the ALARA (As Low as Reasonably Achieved) principle.
- A meta-analysis of advanced chronic kidney disease in Southeast Asia by Hustrini et al,[9] published in 2024 (PMID: 38587764), provided useful current information on advanced CKD aetiologies in Southeast Asia, namely: Diabetic kidney disease 29.2% (95% CI 23.88–34.78), Glomerulonephritis 20.0% (95% CI 16.84–23.38), Hypertensive 16.8% (95% CI 14.05–19.70), Other 8.6% (95% CI 6.97–10.47), and Unknown 7.5% (95% CI 4.32–11.50).

- Younger age, female sex, Malay (vs Chinese) ethnicity, lower cost housing type, current smoking, higher HbA1c, lower LDL-C, higher TG, higher albuminuria levels. Uncontrolled BP, CVD, and hypertension were associated with a progressive or rapid decline in kidney function.

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Unit No. 2

INSULIN THERAPY IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

Initiation of insulin therapy is challenging in the primary care setting without nursing support. Doctors have to prepare their practices to deal with these challenges in order not to delay insulin therapy when needed.

Keywords: insulin therapy, challenges, strategies

SFP2025; 51(2): 17-21

INTRODUCTION

Insulin therapy is initiated for patients early in their course of diabetes to relieve symptoms of severe hyperglycaemia or in the hope of achieving remission and during the course of diabetes to attain optimal control.[1,2] In the specialist outpatient setting, successful initiation of insulin therapy is very much dependent on having dedicated diabetes nurse educators (DNE) who would ensure the smooth transition of the therapy for the patient and the doctor. With the increasing prevalence of diabetes in Singapore, most patients with Type 2 Diabetes Mellitus (T2D) are now receiving their care in the community. The initiation of insulin in the polyclinics is facilitated by nurses trained in diabetes management who can assist with the initiation, optimisation and intensification of the therapy. For family practices that are not often supported by DNE, initiation of insulin therapy may be challenging. This article hopes to share some clinical pointers to help these doctors prepare their practices for their patients who require insulin therapy.

EMPOWERING PATIENTS DURING INSULIN INITIATION

A good resource that can be obtained easily online is the Royal College of Nursing booklet on "Starting injectable treatment in adults with Type 2 diabetes".[3] The chapter on a step-by-step guide to insulin therapy includes details on first appointment/first injection, choosing a delivery device, teaching injection technique, choosing injection site, rotating injection sites, timing of injection, insulin dosage, storage, and checklist. The following chapter on essential education elaborates on the subjects to be covered at three stages of insulin therapy: immediately upon starting the therapy; within the first few weeks of starting therapy; and once the patient is feeling more confident with the therapy. This is a very easy book to read and provides a simple, comprehensive, and practical overview for the initiation of insulin therapy.

In preparation for the conversation on insulin therapy with the patient, it is recommended that the practice gathers together the armamentarium or tool kit required for the education and support of insulin therapy. This could include:

1. Blood glucose monitoring (BGM) gadgets – glucometer, strips, lancets (include safety lancets that do not require a separate lancing device), lancing device, record book, swabs, and sharps disposal. If available, Flash (intermittent) continuous glucose monitoring demonstration kit or online video.[4,5]

2. Insulin therapy gadgets: vial, disposable prefilled pens, self-fill pens, syringes (30, 50, 100cc; 6 and 8mm), pen needles (gauge 31-33, length 4, 5 and 6mm), insulin wallets, sharps disposal, and swabs.[3,6]

3. Written information on instructions for insulin dose and time, delivery device, rotating sites, hypoglycaemia management, and sick day management.

4. Travel advice and letter for airport securities.

The doctor should be prepared to spend time to proactively engage and work with the patient to deal with the challenges faced with insulin therapy.[7,8] These anticipated barriers and challenges could be explored with the patient early on and during the course of diabetes to ensure timely initiation of insulin therapy when required. The doctor should be careful not to use insulin therapy as a threat for poor control but rather as an effective therapeutic option. The mnemonic PICK DMP is a useful reminder of the common barriers and challenges encountered. **Table 1** below elaborates on the use of this mnemonic.

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Table 1: Common barriers in insulin initiation and proposed strategies

Challenges/Barriers		Assess	Strategies
Pain	It is going to be painful.	If the fear is perceived or real; show range of needles currently available (smallest: 31-33 G x 4-5 mm) as compared to those used for drawing of blood (16-21 G x 12-40 mm).	Demonstrate how insulin is administered. Share experiences of others/self. Offer trial injection. Offer insulin port or pump for those on multiple dose injections.
Inconvenience Cost	It will disrupt my lifestyle. It is going to b expensive.	Current and desired lifestyle – daily activities at home, work (shift work) or school; meal times – regularity; driving; leisure, physical activity, travel, fasting needs; storage – fridge at home; insulin wallets. Cost of current oral therapy, financial status, eligibility for funding. Understanding of cost of complications.	Demonstrate the convenience of insulin pens. Offer to initiate regimen that will lead to least disruption. Offer cost-saving measure or funding application.
K(C)ompetence	I'm not sure I can handle so much.	Learning abilities (cognitive function), self-care skills (self-monitoring of blood glucose and interpretation of results), literacy, diabetes numeracy, dexterity, vision, support	Offer support for first jab and ongoing support until confident. Offer support from diabetes centre/specialist clinic if more assistance/training required. Goal setting to be decided with patient using SMART (specific, measurable, achievable, relevant/realistic, and time-based) and review and adjusted accordingly.
Denial	I'll try harder; I don't need this yet. I feel fine.	Understanding of diabetes as a "silent killer", concept of HbA1c as predictor of complication, progression of diabetes and failure of oral agents (not patient's failure).	Offer individual or group education, peer support. Stage approach to initiation of insulin – raise awareness and understanding of glycaemic levels and desired targets through SMBG training and interpretation. Offer trial of insulin with review date.
Myth	If I go on insulin, I'll lose a foot, my kidney or end up dying. If I start, I will need to continue for life.	Source of information; level of fears and misunderstanding. Understanding of hyperglycaemia as cause of complications and need to achieve glycaemic targets. Understanding of sick-day management and risk of hypoglycaemia. Understanding of need for insulin in Type 2 Diabetes – insulin deficiency and insulin resistance. Understanding of benefits of early initiation of insulin.	Offer evidence from trials with regards to safety and efficacy of insulin therapy; other patient's testimonies; peer support group. Reinforce sick day management and hypoglycaemia management.
Phobia	I can't possibly give myself an injection. I'll have low sugar reactions. I'll get fat.	If there's needle phobia. Understanding of action of insulin, why hypoglycaemia happens, how to avoid and manage if it happens. Ability to manage hypoglycaemia. Indication for insulin, fear of weight gain and understanding of reason for weight gain and measures to avoid excessive weight gain.	Offer to refer to a psychologist. Caregiver to perform jabs. Offer auto-injector, insulin port. Offer measures to reduce risk of hypoglycaemia – start with low dose and close monitoring of response and review during optimisation of therapy. Offer measures to reduce weight gain – lifestyle advice, concomitant use with SGLT-2 inhibitors, GLP-1RA, and metformin.

SELECTION OF INSULIN THERAPY AND REGIME

The prescription of insulin and therapy regime needs to be tailored to the patient. Insulin regimens such as basal only, basal-plus, basal-bolus, or pre-mixed insulin are reasonable options if the patient can adhere to it. The ideal dosing of insulin is to mimic normal pancreatic insulin physiology; therefore it is important to be familiar with the pharmacokinetic profiles of the insulin prescribed.

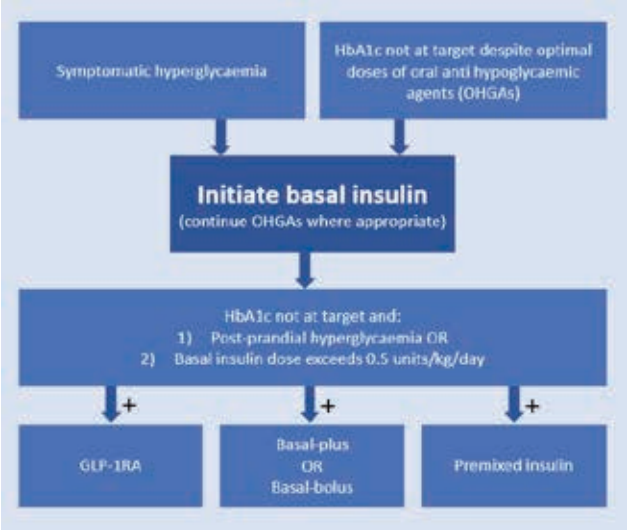
STEPS TO INSULIN INITIATION AND INTENSIFICATION OF THERAPY

The doctor should consider initiating insulin therapy when:

1. Glycaemic targets are not met on optimal treatment with oral glucose-lowering agents.
2. The patient has symptomatic hyperglycaemia.

There are various formulations of insulins that the doctor may choose. The Appropriate Care Guide (ACE) on Initiating Basal Insulin in Type 2 Diabetes Mellitus[10] is a useful resource to guide doctors in their choice of basal insulin and steps in titration. Basal insulin can be started at a dose of 0.1-0.2 units/kg/day depending on the patient's age, comorbidities, and blood glucose profile. The dose can be titrated by 2-4 units once or twice a week, until the target fasting blood glucose is achieved. Should the patient's HbA1c remain poorly controlled, and the patient has postprandial hyperglycaemia or a basal insulin dose that exceeds 0.5 units/kg/day, the doctor should consider adding on prandial insulin. This can be done in form of basal-plus, basal-bolus, or premixed (biphasic) insulin, depending on the patient profile. Injectable GLP-1 receptor agonists may also be considered.

Figure 1: Algorithm for insulin therapy



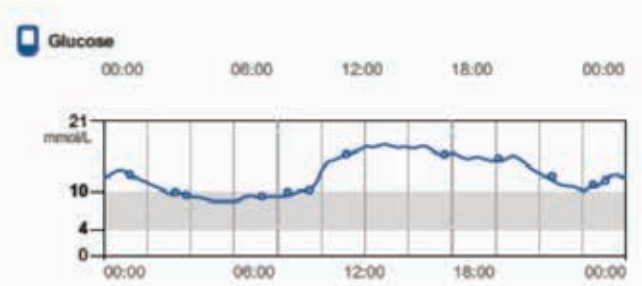
Insulin prescription is made easier if the doctor can figure out the glycaemic profile of the patient.[1,9] A prescription of BGM to be performed by the doctor, patient, or caregiver should first be given to evaluate the glycaemic profile of the patient. It can be done using the FITT model as illustrated in **Table 2** below:

Table 2: FITT model for Capillary Blood Glucose Monitoring

Frequency	Intensity	Time	Targets – to be individualised
Daily for 3 days	2 points	BT & FBG	FBG: 4-7mmol/L; BT: 7-10 mmol/L
Once a week	2 points	FBG & PD	FBG: 5-8mmol/L; PD: 5-8mmol/L
On off days or weekend	2 points, up to 7	Before and 2 hours after meals & BT	Pre-meal BG <7 mmol/L; post-meal BG <10 mmol/L

Legend: FBG: fasting blood glucose; PD: pre-dinner; BT: bedtime

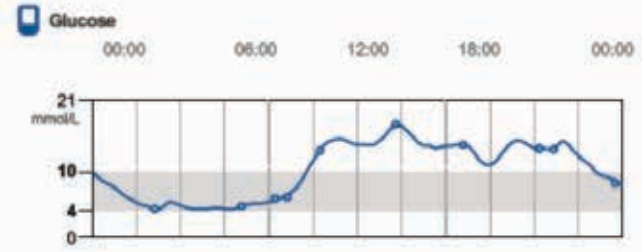
Figure 2 : Common patterns of glucose profiles and possible therapeutic interventions.



All day hyperglycaemia

BGM: BT & FBG

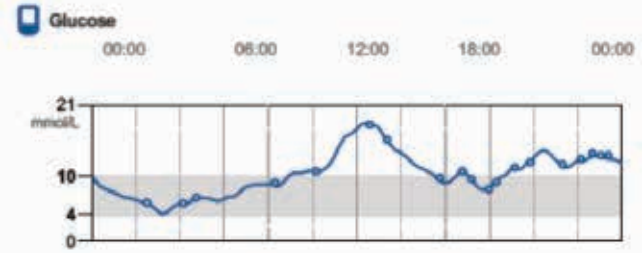
Insulin: Basal insulin – once a day either morning or bedtime



Daytime hyperglycaemia

BGM: FBG, Pre-lunch and Pre-dinner

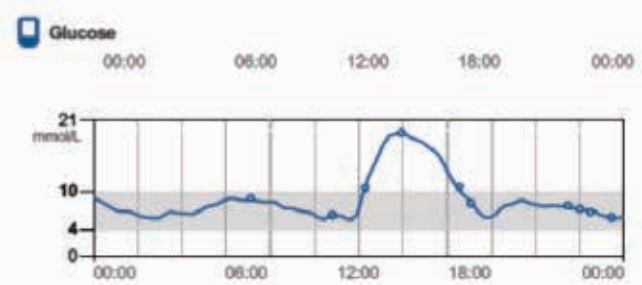
Insulin: Premixed (30/70) at breakfast



Predominant postprandial hyperglycaemia.

BGM: Pre-meal & mid-day

Insulin: Premixed (50/50) at culprit meal

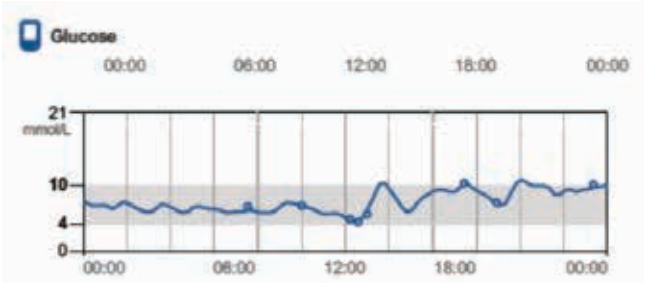


Predominant postprandial hyperglycaemia.

BGM: Pre and post-meal

Insulin: Prandial insulin

Desired blood glucose levels after initiation of insulin therapy:



Normoglycaemia.

BGM: FBG; when hungry

No evidence of hypoglycaemia.

BLOOD GLUCOSE MONITORING

In patients receiving insulin therapy, blood glucose monitoring is important to help our patients identify patterns in their blood glucose fluctuations. This can be done in the form of a capillary blood glucose or a flash continuous glucose monitoring system. The frequency of monitoring needs to be individualised in order to improve patient compliance and obtain sufficient information to have meaningful interpretation of the data. The target blood glucose levels also need to be individualised according to the patient's comorbids and risk of hypoglycaemia. **Table 2** provides some of the common used monitoring frequency and blood glucose targets, and **Figure 2** summarises the commonly encountered blood glucose profiles and their interventions.

BEWARE OF HYPOGLYCAEMIC UNAWARENESS

Hypoglycaemic unawareness occurs when the patient does not develop the early warning symptoms of hypoglycaemia when their blood glucose levels are low. These symptoms include tremors, palpitations, and diaphoresis. This may occur when the patients have repeated episodes of hypoglycaemia or concomitant autonomic neuropathy, and this results in a significant increase risk of developing severe hypoglycaemia. Patients with hypoglycaemic unawareness should be advised to increase their glycaemic targets for a few weeks to avoid hypoglycaemia.

CONCLUSION

In summary, insulin therapy is an important and effective therapeutic option in the management of Type 2 diabetes. Initiation, optimisation, and intensification will be challenging if doctors are not prepared to deal with the challenges. With careful preparation as proposed above, insulin therapy can be initiated safely and effectively even in primary care settings.

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RECOMMENDED READINGS:

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LEARNING POINTS

- **Insulin therapy should be introduced as an effective therapeutic option and not used as a threat for poor control.**
- **Challenges faced with insulin therapy should be managed with patients early in their course of diabetes.**
- **Clinicians have to be prepared to deal with the challenges faced with insulin therapy.**

CHRONIC DISEASE MANAGEMENT 2025
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Unit No. 3

OBESITY UPDATES: UNDERSTANDING OBESITY AS A DISEASE AND INTERMITTENT FASTING

Dr Benjamin Lam

ABSTRACT

Obesity is now recognised as a chronic disease that needs chronic treatment to treat or prevent obesity-related complications. This article discusses the biology of weight regulation as a basis to understanding obesity as a disease, and to appreciate the complex and multifactorial nature of the obesity problem. Finally, the article highlights the dietary approaches as part of the multi-pronged approach to treating obesity and gives a brief update on intermittent fasting.

Keywords: Obesity, Chronic Disease, Body Weight Regulation, Intermittent Fasting

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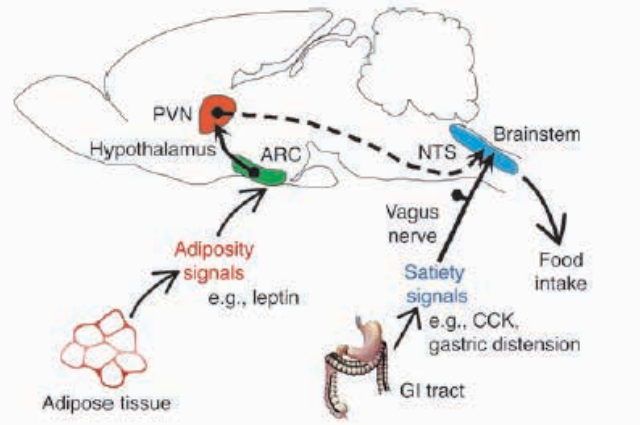
INTRODUCTION

Over the last 40 years, the prevalence of obesity has risen substantially in almost all regions of the world, such that there are now more than 600 million people with obesity worldwide.[1,2] This increasing burden of obesity affects all regions, including Singapore.[1] The National Health Survey (NHS 1992-2010) reports that 10.8 percent of adult Singaporeans were obese in 2010, more than double the prevalence in 1992.[3] Results from recent national health surveys, the National Population Health Survey (NPHS 2017-2022), suggest a continuing of this trend after a brief period of stabilisation from 2010 to 2017.[4]

BIOLOGY OF WEIGHT REGULATION

The body's adipose tissue represents energy stores to survive energy-scarce conditions. Hence, it would not be surprising that that body weight (or more accurately, adipose tissue in the body) is tightly regulated by an extremely complex neuroendocrine energy balance circuitry, which is composed of specific nuclei in various brain regions, most prominently the hypothalamic arcuate nucleus (ARC), the paraventricular nucleus, the lateral hypothalamic area, and the nucleus of solitary tract of the hindbrain[5,6] (refer to **Figure 1**). Under relatively constant environmental conditions, this regulatory system senses and processes various metabolic signals regarding the current energetic status and adjusts the metabolic responses to maintain a stable weight without conscious control.[5] This homeostatic regulation of body weight is similar to the regulation of other physiologic parameters, such as body temperature, blood pressure, or blood glucose, where a "set point" seems to exist and deviation from this "set point" elicits a compensatory response in an opposite direction to restore this body weight "set point". Therefore, weight regain after weight loss is physiological[7,8]{Sumithran, 2013, The defence of body weight: a physiological basis for weight regain after weight loss} and not necessarily due to a failure of conscious efforts (to lose weight).

Figure 1: Model for regulation of the hindbrain response to satiety signals by hormonal input from the ARC[6]



Additionally, there exists a different set of neuroendocrine signals that guides food intake based upon the reward value of the food, also known as the reward or "hedonic" system.[5,9] The brain regions responsible for this reward system are dispersed in the corticolimbic structures, and a primary characteristic of this system is its ability to override the signals from the homeostatic circuits as described.[5] Hence, the reward system is non-homeostatic with regard to energy balance. This system integrates basic midbrain and hindbrain functions with more complex cortical functions involving arousal at the sight of palatable food items and the procurement of food, mediating the "liking" (level of pleasure or reward) and "wanting" (the motivation or drive to consume food), which are subconscious processes.[5] In human studies, functional MRI (fMRI) studies have shown overactivation of reward-encoding brain regions and/or deficiency in cortical inhibitory networks in people with obesity.[5]

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OBESITY AS A DISEASE: PATHOPHYSIOLOGY AND HEALTH CONSEQUENCES

With the understanding of the biology of weight regulation, obesity (defined as a disproportionate body weight for height with an excessive accumulation of adipose tissue[10]) is now understood to signify an abnormal physiological state whereby there has been a surplus intake of energy and an elevated body weight set point is now defended.[5,11] The factors known to cause this are complex and multiple, and they range from genetic to environmental to emotional factors, which are well-known to be potent modulators of appetite.[9] Twin, family, and adoption studies show that the rate of heritability of BMI is high, ranging from 40 to 70 percent,[12] demonstrating a major genetic component.

In addition to syndromic and monogenic forms of obesity, genome-wide association studies (GWAS) have identified more than 700 independent loci associated with BMI and/or obesity.[13-15] Environmental and lifestyle factors favouring a positive energy balance and weight gain include increasing per capita food supplies and consumption, particularly of highly processed, energy-dense, and palatable foods that are often served in large portions; decreased amounts of time spent in occupational physical activities and displacement of leisure-time physical activities with sedentary activities such as television-watching and use of electronic devices; the growing use of medicines that have weight gain as a side effect; stress; and inadequate sleep.[12]

More recent studies have identified a potential role for the microbial content of the gut in determining a broad range of metabolic abnormalities, including obesity.[16,17] The evidence supporting causation includes animal studies that show that obesity, as a phenotype, is transmittable via the transfer of gut microbiota from the obese (mice/humans) to germ-free mice,[18,19] and mechanistic studies that demonstrate the possible mechanisms linking the gut microbiota with obesity.[16,20]

Obesity is not benign. The failure of adipose tissues to continually expand leads to pathological changes in the adipose tissue, which is characterised by macrophage invasion and/or increased release of pro-inflammatory adipokines and decreased release of anti-inflammatory adipokines such as adiponectin[10] (refer to **Figure 2**). In addition, this failure to further expand and act as a "metabolic sink" results in harmful ectopic fat deposition in lean tissues such as the heart, liver, pancreas, and kidneys.[10] These two phenomena contribute to a pro-inflammatory and insulin-resistant milieu, giving rise to metabolic complications such as type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), and cardiovascular disease (CVD).[10,21] Additionally, the physical forces as a result of excessive adipose tissue can give rise to biomechanical consequences (such as Obstructive Sleep Apnea (OSA) and low back pain), and obesity as a condition has been associated with various psychosocial issues, impacting on mental health.[22]

All these adverse consequences affect quality of life, increase healthcare costs, and finally, increase mortality.[23] Therefore, based on the current knowledge that the development of obesity results from established pathophysiology, with attending health consequences (complications, morbidities, and mortality), obesity fulfils the criteria for a disease state and is now determined to be a disease,[11] rather than just a lifestyle risk factor. Several associations and organisations, including the World Health Organisation (WHO), have now declared obesity as a disease (refer to **Figure 3**), and this is an important first step in tackling the problem of obesity, which has emerged as an epidemic that poses an unprecedented public health challenge.[11]

Figure 2: Pathological changes in adipose tissue[10]

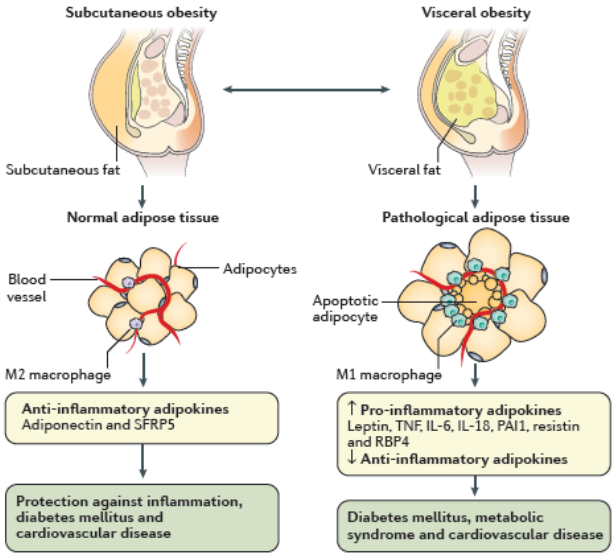

Figure 3: Associations or organisations that have declared obesity is a disease[11]

Box 1
Associations or organizations that have declared obesity is a disease

- National Institutes of Health
- US Food and Drug Administration
- Federal Trade Commission
- American Medical Association
- World Health Organization
- American College of Physicians
- American Association of Clinical Endocrinologists
- American College of Cardiology
- The Endocrine Society
- American Academy of Family Physicians
- Institute of Medicine
- The Obesity Society
- World Obesity Federation
- American Heart Association
- American Diabetes Association
- American Academy of Family Physicians
- American Society for Reproductive Medicine
- American Urologic Association
- American College of Surgeons

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SEVERITY OF OBESITY AND TREATMENT APPROACH TO OBESITY AND ITS COMPLICATIONS

As with any disease state, the management of it requires an understanding of how severe the disease is. For obesity, management guidelines have slowly moved from a BMI-centric approach, where the goal of therapy is to lose a given amount of weight (e.g., 5-10 percent), to a complications-centric approach, where weight is no longer the major determinant of appropriate treatment but now based on the risk, presence, and severity of obesity-related complications.[24] For example, at least 10 percent weight loss is needed to significantly improve NAFLD and OSA.[24] Hence, for a person with multiple complications, which include NAFLD and OSA, modest weight loss (defined as 5-10 percent weight loss) may be inadequate, and more aggressive treatment options, effecting more than modest weight loss, need to be considered. Although more aggressive treatment may involve higher risks, the benefits of treating the various obesity-related complications should outweigh these risks. Therefore, the main goal of therapy now is to treat or prevent obesity-related complications, rather than lose weight per se.

In line with this paradigm shift, the Working Group on Obesity, Diabetes, and the High-risk Patient from the European Society for Hypertension, and the European Association for the Study of Obesity published a consensus document that discusses the mechanisms of obesity-induced hypertension, diabetes, and dyslipidaemia, and highlights practice guidelines for the treatment of these conditions.[25] Essentially, this document calls for treatment of the underlying obesity in people with obesity-induced hypertension, diabetes, and dyslipidaemia. Hence, for some of these people, the first medication may not be an anti-hypertensive medication (for example) but an anti-obesity medication.

The other important point is that medications to treat these conditions should not worsen the underlying obesity, hence awareness of the potential weight effects when selecting pharmacologic agents for the treatment for these conditions is important. For example, sulphonylureas promote weight gain and should be avoided in patients with obesity as far as possible.

IMPORTANCE OF A MULTI-LEVEL AND INDIVIDUALISED MULTI-PRONGED APPROACH TO TREATING OBESITY

It is now known that the simple calculations underlying the traditional adage of "eat less, exercise more" are fatally flawed.[26] Aiming for a 500 kcal deficit (energy expenditure more than energy intake) per day, cumulating to 3,500 kcal per week (equivalent to ~0.5 kg of fat) will not result in a 0.5 kg/week weight loss indefinitely, because this calculation does not consider the homeostatic mechanisms that will resist further weight loss, and in fact, will conspire to regain weight to restore the original "set point".[7,8,26] Additionally, it is important to note that the same diet and exercise plan (often prescribed once in the beginning) will not suffice to maintain that 500 kcal deficit per day as a declining weight will mean declining energy expenditure.[26]

Nonetheless, the point here is that asking all people with obesity to just "eat less and exercise more" overly simplifies the obesity problem. An understanding of the biology of weight regulation and the appreciation of the complex and multifactorial nature of how this regulation can go wrong resulting in obesity would indicate that there is no one-size-fits-all intervention or solution[27] and would necessitate a multi-level and individualised multi-pronged approach to treating obesity. Multi-level, apart from the individual, would include the social and community, physical (environment), and economic levels of interventions,[27] while a multi-pronged approach at the individual level would encompass not just the lifestyle and behavioural modifications but also the possible combination with pharmacologic and even bariatric surgical procedures based on individualised risk-benefit assessment.[10,24]

DIETARY APPROACHES TO OBESITY TREATMENT

Lifestyle management remains a cornerstone in a multi-pronged approach to the treatment of obesity, and dietary modification is foundational in this management. General dietary advices that have Randomised Controlled Trials (RCT) level of evidence include decreasing sugar-sweetened beverages and portion control (e.g., plate concept),[28] both of which can be routinely advocated. More specific dietary approaches can be broadly categorised into energy-focused (e.g., use of meal replacements, low/very low energy diets), macronutrient-focused (e.g., low carbohydrate diet, low fat diet), dietary pattern-focused (e.g., DASH diet, Mediterranean diet), and dietary timing-focused (e.g., intermittent fasting, time-restricted feeding).[28] These diets usually involve some form of controlled intake and will on average induce weight loss if followed strictly.[10,28] Hence, adherence to diet seems to be key as long-term diet trials have not shown a clear superiority of one diet over another with respect to average weight loss.[10,26]

However, while patient preference plays a part in adherence, the preceding discussion on the biology of weight regulation informs us that homeostatic mechanisms such as increased hunger and cravings will be triggered upon weight loss, posing a challenge to diet adherence in the long term. Therefore, the satiating effect of a diet may become particularly important for long-term dietary adherence and weight maintenance. For example, diets with high amounts of protein (protein has a greater satiating effect compared with carbohydrates and fats), especially when the overall diet has a low glycaemic index, has been shown to be more beneficial for maintaining weight loss,[26] and there is the suggestion that meals containing carbohydrates may have a weaker satiating effect on individuals with impaired glucose metabolism. Hence, obese individuals with impaired glucose

metabolism may benefit more from a diet with higher fat and protein.[29,30]

FINALLY: A BRIEF UPDATE ON INTERMITTENT FASTING

Recent years have seen a surge in popularity of timing-focused dietary approaches whereby such eating patterns involve restricting energy intake by varying degrees for a pre-defined period and eating *ad libitum* (i.e., to satisfy appetite) at all other times.[31] These can range from complete (no energy containing foods or beverages consumed) alternate day fasting, to modified fasting regimens that allow the consumption of 20-25 percent of energy needs on scheduled fasting days (e.g., alternate days, two days per week [the "5:2 diet"]), to time-restricted feeding (which allows *ad libitum* energy intake within specific time frames inducing regular, extended fasting periods), and finally, to a variety of fasting regimens undertaken for religious or spiritual purposes.[32]

Based on the current available evidence in humans, it appears that almost any intermittent fasting regimen can result in some weight loss and improvements in multiple health indicators including insulin resistance and reductions in risk factors for cardiovascular disease, through multiple pathways including reducing oxidative stress, optimisation of circadian rhythms, and ketogenesis, with no significant harm demonstrated.[32-34] However, human studies have largely been limited to observational studies of religious fasting, cross-sectional studies of eating patterns associated with health outcomes, and experimental studies with modest sample sizes.[32] Hence, large-scale randomised trials of longer duration (>1 year) are needed for more conclusive evidence on efficacy and potential harm so that sound recommendations can be made.[32]

In any case, consistent with points made in the preceding sections, intermittent fasting could potentially be a treatment option but unlikely to be that "silver bullet", and the treatment of obesity would still require a multi-level and individualised multi-pronged approach.

CONCLUSION

Obesity is now recognised as a disease and has been described as a complex, chronic medical condition with a major negative impact on human health. Several associations and organisations, including the World Health Organisation (WHO), have now declared obesity as a disease, and this is an important first step to tackling the problem of obesity. An understanding of the biology of weight regulation and the appreciation of the complex and multifactorial nature of how this regulation can go wrong resulting in obesity would indicate that there is no one-size-fits-all intervention or solution and would necessitate a multi-level and individualised multi-pronged approach to treating obesity and its related conditions.

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LEARNING POINTS

- **Obesity is now recognised as a chronic disease that needs chronic treatment to treat or prevent obesity-related complications.**
- **The complex and multifactorial nature of obesity means that there is no one-size-fits-all intervention or solution and would necessitate a multi-level and individualised multi-pronged approach to treating obesity and its related conditions.**
- **Dietary approaches such as intermittent fasting could potentially be a treatment option but it is unlikely to be that "silver bullet".**

Obesity Updates: Understanding Obesity as a Disease and Its Management

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Abstract

Obesity is now recognized as a chronic disease requiring long-term care to treat or prevent adiposity-induced and obesity-related complications. This article discusses the biology of weight regulation as a basis for understanding obesity as a disease, and for appreciating the complex and multifactorial nature of the obesity problem. Finally, the article highlights a clinical approach to obesity care that starts with accurate diagnosis and severity assessment (including clinical vs preclinical obesity), then outlines a multi-pronged treatment strategy, and provides brief updates on pharmacotherapy and the future direction of obesity care.

Keywords: Obesity. Chronic Disease. Body Weight Regulation. Obesity Management.

Introduction

Over the last 40 years, the prevalence of obesity has risen substantially in almost all regions of the world, such that there are now more than 600 million people with obesity worldwide (1,2). This increasing burden of obesity affects all regions (1), including Singapore. The National Health Survey (NHS 1992 – 2010) reports that 10.8% of adult Singaporeans had obesity in 2010, more than double the prevalence in 1992 (3). Results from recent national health surveys, including the latest National Population Health Survey (NPHS 2023 – 2024), suggest a continuation of this trend after a brief period of stabilisation from 2010 to 2017 (4).

Biology of Weight Regulation

The body's adipose tissue represents energy stores to survive energy-scarce conditions. Hence, it would not be surprising that that body weight (or more accurately, adipose tissue in the body) is tightly regulated by an extremely complex neuroendocrine energy balance circuitry, which is composed of specific nuclei in various brain regions, most prominently the hypothalamic arcuate nucleus (ARC), the paraventricular nucleus, the lateral hypothalamic area and the nucleus of solitary tract of the hindbrain (5–7) (**Figure 1**). Under relatively constant environmental conditions, this regulatory system senses and processes various metabolic signals regarding the current energetic status and adjusts the metabolic responses to maintain a stable weight without conscious control (5,8). This homeostatic regulation of body weight is similar to the regulation of other physiologic parameters, such as body temperature, blood pressure, or blood glucose, where a 'set point' seems to exist and deviation from this 'set point' elicits a compensatory response in an opposite direction to restore this body weight 'set point'. Therefore, weight regain after weight loss is physiological (9,10) and not necessarily due to a failure of conscious efforts (to lose weight).

Figure 1: Key hypothalamic nuclei involved in the regulation of appetite and energy balance. Figure taken from (7).

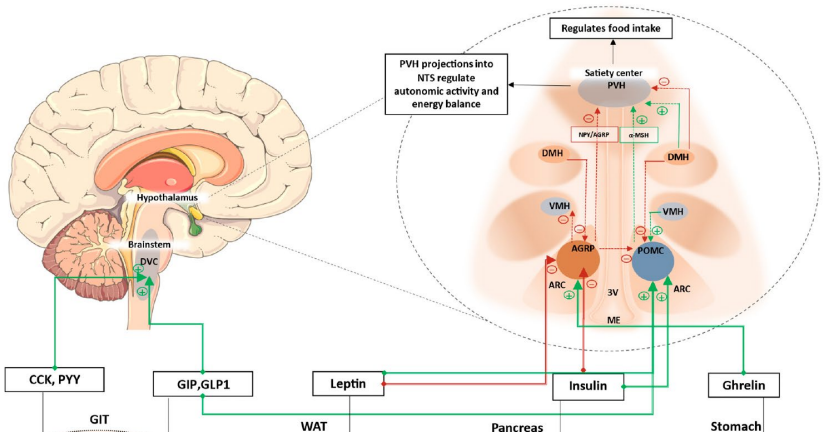


Figure 1. Key hypothalamic nuclei involved in the regulation of appetite and energy balance. ARC, comprising AGRP and POMC neurons, is located next to the median eminence. This region comprises permeable capillaries, thereby allowing access to circulating signals. These signals can modulate ARC neuronal populations, which then have extensive projections to PVH and other hypothalamic nuclei. PVH is the major hypothalamic satiety center. POMC neurons activate MC4R neurons in the PVH to decrease appetite, while AGRP neurons inhibit PVH-MC4R neurons to increase appetite. Additionally, AGRP neurons also inhibit POMC neurons via stimulation of inhibitory GABAergic input to POMC neurons. Anorexigenic signals such as leptin and GLP1 increase satiety by acting on POMC neurons, whereas orexigenic signals such as ghrelin can increase appetite by acting on AGRP neurons. Other hypothalamic neuronal populations have extensive projections to and from adjacent nuclei. While DMH has predominantly inhibitory projections to PVH and POMC, it also has been shown to also have activate inhibitory GABAergic neurons projecting to the AGRP neurons in the ARC. VMH mainly has excitatory projections to the POMC neurons, while AGRP neurons has inhibitory projections to VMH. Additionally, postprandial satiety signals from the enteroendocrine cells of the GIT can also act on DVC located in the brainstem to suppress appetite. AGRP: Agouti-related protein; POMC: Pro-opiomelanocortin; ARC: Arcuate nucleus; ME: median eminence; VMH: Ventromedial nucleus of the hypothalamus; DMH: Dorsomedial hypothalamus; PVH: Paraventricular nucleus; 3V: Third ventricle; DVC: Dorsal vagal complex; CCK: cholecystokinin; GIP: Glucose-dependent insulinotropic polypeptide; GLP1: Glucagon-like peptide-1; WAT: White adipose tissue; GIT: Gastrointestinal tract. Green dotted lines/arrows represent activation. Red dotted

Additionally, there exist a different set of neuroendocrine signals which guides food intake based upon the reward value of the food, also known as the reward or 'hedonic' system (5,11). The brain regions responsible for this reward system are dispersed in the corticolimbic structures, and a primary characteristic of this system is its ability to override the signals from the homeostatic circuits as described (5). Hence, the reward system is non-homeostatic with regard to energy balance. This system integrates basic midbrain and hindbrain functions with more complex cortical functions involving arousal at the sight of palatable food items and the procurement of food, mediating the 'liking' (level of pleasure or reward) and 'wanting' (the motivation or drive to consume food), which are subconscious processes (5). In human studies, functional MRI (fMRI) studies have shown overactivation of reward-encoding brain regions and/or deficiency in cortical inhibitory networks in people with obesity (5).

Obesity as a Disease: Pathophysiology and Health Consequences

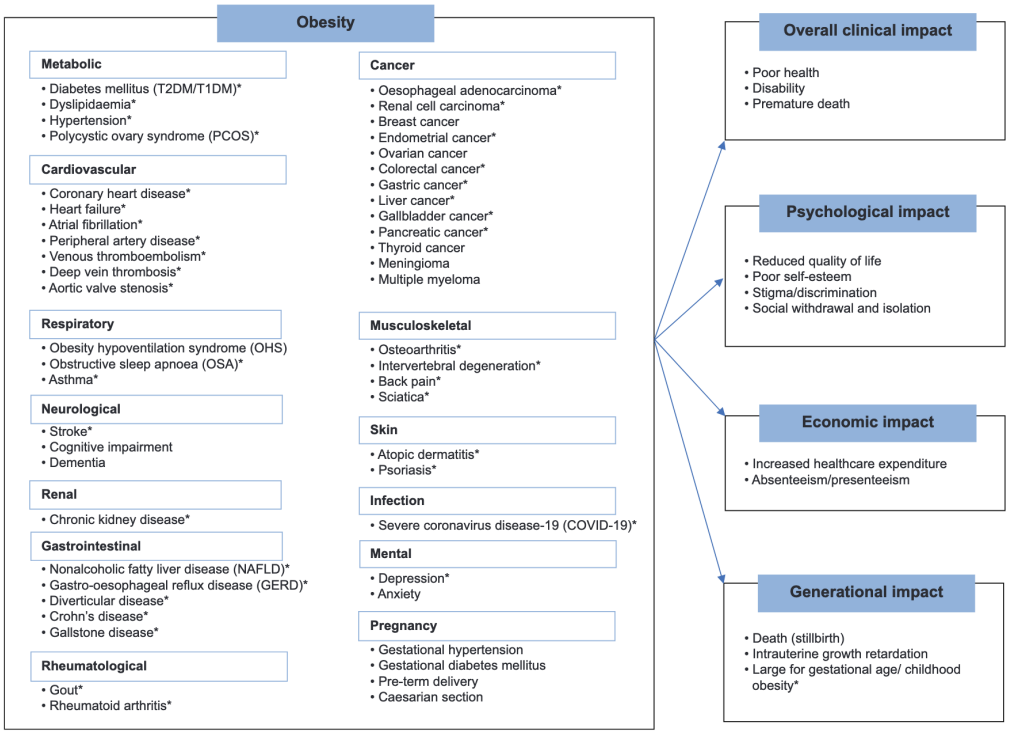
With the understanding of the biology of weight regulation, obesity (defined as a disproportionate body weight for height with an excessive accumulation of adipose tissue (12)) is now understood to signify an abnormal physiological state whereby there has been a surplus intake of energy and an elevated body weight set point is now defended (5,13). The factors known to cause this are complex and multiple, and they range from genetic to environmental to emotional factors, which are well-known to be potent modulators of appetite (11). Twin, family, and adoption studies show that the rate of heritability of BMI is high, ranging from 40 to 70% (14), demonstrating a major genetic component. In addition to syndromic and monogenic forms of obesity, genome-wide association studies (GWAS) have identified more than 700 independent loci associated with BMI and/or obesity (15–17). Environmental and lifestyle factors favouring a positive energy balance and weight gain include increasing per capita food supplies and consumption, particularly of highly processed, energy-dense and palatable food that are often served in large portions; decreasing time spent in occupational physical activities and displacement of leisure-time physical activities with sedentary activities such as television watching and use of electronic devices; growing use of medicines that have weight gain as a side effect; stress and inadequate sleep (14).

More recent studies have identified a potential role for the microbial content of the gut in determining a broad range of metabolic abnormalities, including obesity (18,19). The evidence supporting causation includes animal studies which show that obesity, as a phenotype, is transmittable via the transfer of gut microbiota from the obese (mice/humans) to germ-free mice (20,21), and mechanistic studies which demonstrate the possible mechanisms linking the gut microbiota with obesity (18,22). These specific obesogenic factors can, in turn, be influenced by broader environmental context, such as the physical environment (built environment, atmospheric temperature), socio-economic conditions (education, income), the psychosocial environment, cultural influences, and biological factors such as age, menopause, and coexisting health conditions (23,24). In addition, gene-environment interactions can occur, such as environmental and lifestyle factors modifying gene expression (25,26), lifestyle and genetic factors attenuating each other (27,28), and genetic factors influencing the propensity for certain lifestyle traits (29). Therefore, the development of obesity is truly complex, potentially involving a multitude of interactions between genetic and environmental/lifestyle factors.

Obesity is not benign. The failure of adipose tissues to continually expand leads to pathological changes in the adipose tissue which is characterized by macrophage invasion and/or increased release of pro-inflammatory adipokines and decreased release of anti-inflammatory adipokines such as adiponectin (12). Also, this failure to further expand and act as a 'metabolic sink' results in harmful ectopic fat deposition in lean tissues such as the heart, liver, pancreas and kidneys (12). These two phenomena contribute to a pro-inflammatory and insulin-resistant milieu, giving rise to metabolic complications such as type 2 diabetes mellitus (T2DM), metabolic-dysfunction associated steatotic liver disease (MASLD, previously known as non-alcoholic fatty liver disease) and cardiovascular disease (CVD) (12,30,31). Additionally, the physical forces as a result of excessive adipose tissue can give rise to biomechanical

consequences (such as Obstructive Sleep Apnea (OSA) and low back pain), and obesity as a condition has been associated with various psychosocial issues, impacting on mental health (31,32). All these adverse consequences affect quality of life, increase healthcare costs, and finally, increase mortality (31,33) (**Figure 2**). Therefore, based on the current knowledge that the development of obesity results from established pathophysiology, with attending health consequences (adiposity-induced/obesity-related complications, and mortality), obesity fulfils the criteria for a disease state and is now determined to be a disease (13), rather than just a lifestyle risk factor. Several associations and organisations, including the World Health Organisation (WHO), have now declared obesity as a disease (**Box 1**), and this is an important first step to tackling the problem of obesity, which has emerged as an epidemic that poses an unprecedented public health challenge (13).

Figure 2: Summary of diseases and conditions associated with obesity and the potential impacts. Figure taken from (31).



*Supported by Mendelian randomisation studies. T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus.

Figure 3 : Associations or organisations that have declared obesity is a disease. Figure taken from (13).

Box 1
Associations or organizations that have declared obesity is a disease

- National Institutes of Health
- US Food and Drug Administration
- Federal Trade Commission
- American Medical Association
- World Health Organization
- American College of Physicians
- American Association of Clinical Endocrinologists
- American College of Cardiology
- The Endocrine Society
- American Academy of Family Physicians
- Institute of Medicine
- The Obesity Society
- World Obesity Federation
- American Heart Association
- American Diabetes Association
- American Academy of Family Physicians
- American Society for Reproductive Medicine
- American Urologic Association
- American College of Surgeons

Data from Kahan S, Zvenyach T. Obesity as a disease: current policies and implications for the future. Curr Obes Rep 2016;5(2):291–7; and Bray GA, Kim KK, Wilding JPH. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev 2017;18(7):715–23.

Clinical Approach to Obesity Care

As with any disease, effective obesity care starts with an accurate diagnosis. Obesity is fundamentally a state of excess adiposity, so diagnosis should not rely on BMI alone (34), which is best used as a screening tool or population-level risk marker (34). Where feasible, excess adiposity should be confirmed using direct body-fat assessment, or at least one additional anthropometric measure such as waist circumference or waist-to-height ratio alongside BMI (34); in people with very high BMI ($\geqslant$40 kg/m^2), excess adiposity can generally be assumed, so additional adiposity measurement is usually not required to confirm the diagnosis (34). This emphasis on diagnosing obesity based on adiposity rather than BMI alone is a key point highlighted in the recently published 'The Lancet Diabetes & Endocrinology Commission on the definition and diagnostic criteria of clinical obesity' (34).

After diagnosis, as with the management of other chronic diseases, complications and health impact should be assessed to determine disease severity and guide treatment intensity. Since 2013, the field has been shifting from a BMI-centric model (treat to a generic 5–10% weight-loss target) toward a complications-centric approach, where treatment intensity is driven by the risk, presence, and severity of both adiposity-induced and obesity-related complications, and weight loss is primarily a means to improve those outcomes (35). This direction is reinforced by the recently published 'The Lancet Diabetes & Endocrinology Commission on the definition and diagnostic criteria of clinical obesity', which proposes a more clinically meaningful framework—distinguishing preclinical obesity (excess adiposity with preserved organ function) from clinical obesity (a chronic, systemic illness with adiposity-related organ dysfunction and/or substantial functional limitation) (34). Clinical obesity, by definition, warrants active treatment, and the aggressiveness of therapy should scale with the number, severity, and trajectory of complications (34,35). For example, when MASLD and/or OSA are present, $\geqslant$10% weight loss may be needed for meaningful improvement (35), making "modest" loss (5–10%) potentially inadequate and supporting escalation to more intensive options when the expected benefit outweighs risk.

Building on this paradigm, management should increasingly address the underlying obesity as a driver of many adiposity-driven cardiometabolic conditions, rather than treating each complication in isolation. This is consistent with a consensus document published by the Working Group on Obesity, Diabetes and the High-risk Patient from the European Society for Hypertension and the European Association

for the Study of Obesity, which highlights practice guidance for obesity-related hypertension, diabetes, and dyslipidaemia, and calls for treating obesity itself in affected individuals (36). For some patients, this means the first-line pharmacotherapy may reasonably be an anti-obesity medication rather than, for example, an antihypertensive, when obesity is a major contributor to the condition. Equally important, medications used to treat these conditions should not worsen obesity, so clinicians should consider weight effects when selecting agents; for instance, sulphonylureas can promote weight gain and should be avoided where possible in people with obesity (36).

Importance of a Multi-level and Individualized Multi-pronged Approach to Treat Obesity

It is now known that the simple calculations underlying the traditional adage of 'eat less, exercise more' are fatally flawed (37). Aiming for a 500 kcal deficit (energy expenditure more than energy intake) per day, cumulating to 3,500 kcal per week (equivalent to ~0.5kg of fat) will not result in a 0.5kg/week weight loss indefinitely, because this calculation does not consider the homeostatic mechanisms that will resist further weight loss, and in fact, will conspire to regain weight to restore the original 'set point' (9,10,37). Also, it is important to note that the same diet and exercise plan (often prescribed once in the beginning) will not suffice to maintain that 500kcal deficit per day as a declining weight will mean declining energy expenditure (37). Nonetheless, the point here is that asking all people with obesity to just 'eat less and exercise more' overly simplifies the obesity problem. An understanding of the biology of weight regulation and the appreciation of the complex and multifactorial nature of how this regulation can go wrong resulting in obesity would indicate that there is no one-size-fits-all intervention or solution (38) and would necessitate a multi-level and individualized multi-pronged approach to treating obesity. Multi-level, apart from the individual, would include the social and community, physical (environment) and economic levels of interventions (38), while a multi-pronged approach at the individual level would encompass not just the lifestyle and behavioural modifications, which remain the cornerstone, but also the possible combination with pharmacologic, and even bariatric surgical procedures based on individualized risk-benefit assessment (12,35).

Dietary strategies with RCT-level evidence that can be routinely advised include reducing sugar-sweetened beverages and practising portion control (e.g., the plate concept) (39). More structured approaches can be grouped into energy-focused (meal replacements, low/very low energy diets), macronutrient-focused (low carbohydrate, low fat), dietary pattern–focused (DASH, Mediterranean), and timing-focused (intermittent fasting, time-restricted feeding) interventions (39). When adhered to, most approaches produce weight loss, and long-term trials have not shown consistent superiority of one diet over another—making adherence the key determinant of outcomes (12,39). However, weight loss activates homeostatic counter-regulation (increased hunger and cravings), which undermines long-term adherence and weight maintenance; therefore, the satiating quality of the diet becomes particularly important. Higher-protein, low–glycaemic index diets appear more favourable for weight-loss maintenance (37), and individuals with impaired glucose metabolism may experience weaker satiety from carbohydrate-containing meals and potentially benefit from relatively higher fat/protein patterns (40,41). Timing-focused regimens, such as time-restricted feeding, are increasingly popular and, across available human data, can yield some weight loss and cardiometabolic improvements with no clear signal of harm (42–44). Yet evidence is still limited by small trials and observational designs, and larger, longer-duration RCTs (>1 year) are needed before firm recommendations can be made (42). Beyond diet, lifestyle management should also prioritise regular physical activity—combining aerobic training with resistance exercise—to support fat loss, preserve lean mass, and improve cardiometabolic fitness (45); adequate sleep duration and quality (45), given consistent associations between short/poor sleep and higher adiposity (46–48); and practical stress-management strategies (e.g., mindfulness, problem-solving, social support) (45), as chronic stress can undermine healthy eating, sleep, and activity routines (49,50).

Update on the Pharmacologic Management of Obesity

For many years, obesity pharmacotherapy achieved only modest weight loss, including the first glucagon-like peptide-1 receptor agonist (GLP-1RA) indicated for obesity, liraglutide (51). More recently, higher-potency incretin therapies have shown markedly greater efficacy, with semaglutide and tirzepatide—a dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) agonist—achieving ~15% and ~20% mean weight loss, respectively, in pivotal trials (52,53). These agents reduce energy intake by slowing gastric emptying (increasing post-meal fullness) and by acting on appetite centres in the hypothalamus and brainstem to increase satiety and reduce hunger (54). The most common adverse

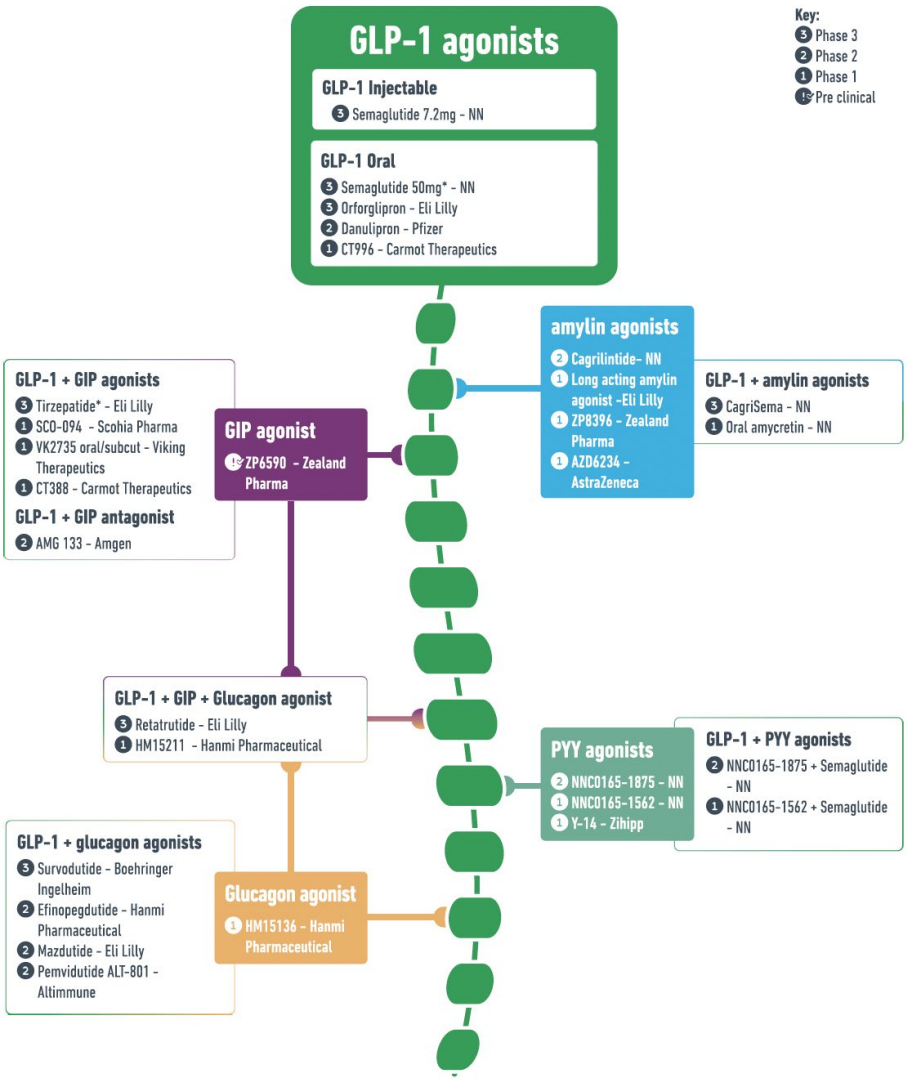
effects are gastrointestinal (nausea, vomiting, diarrhoea/constipation), while key cautions include avoidance in people with personal or family history of medullary thyroid carcinoma (MTC), in people with multiple endocrine neoplasia syndrome type 2 (MEN2), and in those with a history of pancreatitis (54). Reassuringly, although thyroid C-cell tumours are seen in rodents, a causal increase in human thyroid cancer risk remains unproven (54). Suicidality was previously highlighted as a caution, but accumulated evidence has not supported a causal link (55), prompting the U.S. Food and Drug Administration (FDA) to request removal of suicidal ideation/behaviour warnings from GLP-1RA weight-management labels (56).

Two frequently cited concerns are lean-mass reduction and durability of treatment. Some lean-mass reduction is expected with substantial weight loss, but emerging data suggest part of the observed change reflects reduced intramuscular fat (potentially improving muscle quality), rather than a simple loss of functional muscle tissue (57). Weight regain is common after stopping therapy, consistent with the idea that GLP-1RAs are treating an ongoing pathophysiology, and may be more rapid than after behavioural programmes, possibly because behavioural programmes leave patients with coping skills that persist beyond treatment (58). Importantly, the clinical value of GLP-1–based therapy extends beyond weight loss, with benefits across cardiometabolic and obesity-related disease (including liver outcomes, heart failure, and sleep apnoea) (54) and emerging signals for reduced risks in areas such as dementia (59), obesity-associated cancers (60), and alcohol/substance abuse (54,55,61).

Future of Obesity Management

The obesity-treatment pipeline is expanding rapidly, with glucagon-like peptide-1 (GLP-1)–based therapy remaining the “backbone” for many next-generation agents (**Figure 4**) (62). Newer multi-agonists are pushing efficacy closer to (and in some cases beyond) what was historically seen with bariatric surgery—for example, retatrutide (a GIP/GLP-1/glucagon triple agonist) achieved ~24.2% mean weight loss at 48 weeks in phase 2 data (63). In parallel, oral GLP-1 options are advancing beyond oral semaglutide; in a phase 2 obesity trial, the oral non-peptide GLP-1RA orforglipron produced dose-dependent weight loss up to ~14.7% at 36 weeks (64), potentially improving scalability and long-term acceptability. The pipeline is also diversifying beyond entero-pancreatic hormones, with agents targeting central appetite/reward pathways and other mechanisms in various phases of development (62,65). As efficacy increases, newer strategies are also aiming to optimise body composition, including approaches designed to mitigate excessive lean-mass loss (e.g., via myostatin–activin pathway modulation) (66). Procedural innovation is advancing alongside pharmacotherapy (67), including modified operations such as “sleeve-plus” procedures that build on sleeve gastrectomy to improve durability and metabolic outcomes (68). The likely end-state is not “drug vs surgery”, but combination, stepped, complications-driven care—pairing lifestyle therapy with pharmacotherapy (often in combinations) and using endoscopic/surgical options when needed to achieve durable, individualised health goals. In summary, deeper understanding of obesity pathophysiology is translating into a rapidly expanding range of therapies with increasing efficacy, supporting more individualised, complications-driven care and improved durability of outcomes.

Figure 4: Glucagon-like peptide-1 as the backbone of the pipeline for gut hormone-based obesity treatments. Figure taken from (62).



GLP-1 glucagon like peptide-1, GIP glucose-dependent insulinotropic polypeptide, PYY peptide YY, NN: novo nordisk, *completed phase 3 trials for obesity.

Conclusion

Obesity is now recognized as a disease and has been described as a complex, chronic medical condition with a major negative impact on human health. Several associations and organisations, including the World Health Organisation (WHO), have now declared obesity as a disease, and this is an important first step to tackling the problem of obesity. An understanding of the biology of weight regulation and the appreciation of the complex and multifactorial nature of how this regulation can go wrong resulting in obesity would indicate that there is no one-size-fits-all intervention or solution and would necessitate a multi-level and individualized multi-pronged approach to treating obesity and its related conditions. Lifestyle intervention remains the cornerstone of obesity management and should be integrated with pharmacologic, endoscopic, and surgical options when indicated. Finally, a deeper understanding of obesity pathophysiology is translating into a rapidly expanding range of therapies with increasing efficacy, supporting more individualised, complications-driven care and improved durability of outcomes.

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Learning Points

1. Obesity is now recognized as a chronic disease requiring long-term care to treat or prevent adiposity-induced and obesity-related complications.
2. The complex and multifactorial nature of obesity means that there is no one-size-fits-all intervention or solution, and would necessitate a multi-level and individualized multi-pronged approach to treating obesity and its related conditions.
3. A deeper understanding of obesity pathophysiology is translating into a rapidly expanding range of therapies with increasing efficacy, supporting more individualised, complications-driven care and improved durability of outcomes.

Dietary strategies with RCT-level evidence that can be routinely advised include reducing sugar-sweetened beverages and practising portion control (e.g., the plate concept) (31). More structured approaches can be grouped into energy-focused (meal replacements, low/very low energy diets), macronutrient-focused (low carbohydrate, low fat), dietary pattern–focused (DASH, Mediterranean), and timing-focused (intermittent fasting, time-restricted feeding) interventions (31). When adhered to, most approaches produce average weight loss, and long-term trials have not shown consistent superiority of one diet over another—making adherence the key determinant of outcomes (12,29). However, weight loss activates homeostatic counter-regulation (increased hunger and cravings), which undermines long-term adherence and weight maintenance; therefore, the satiating quality of the diet becomes particularly important. Higher-protein, low–glycaemic index diets appear more favourable for weight-loss maintenance (29), and individuals with impaired glucose metabolism may experience weaker satiety from carbohydrate-containing meals and potentially benefit from relatively higher fat/protein patterns (32,33). Timing-focused regimens, such as time-restricted feeding, are increasingly popular and, across available human data, can yield some weight loss and cardiometabolic improvements with no clear signal of harm (35–37). Yet evidence is still limited by small trials and observational designs, and larger, longer-duration RCTs (>1 year) are needed before firm recommendations can be made (35).

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Unit No. 4

INITIATION OF URATE LOWERING THERAPY (ULT)

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ABSTRACT

Gout is an inflammatory crystal arthritis characterised by hyperuricaemia and deposition of monosodium urate crystals (MSU) into joints and soft tissues. Urate-lowering therapy (ULT) is the cornerstone of long term managing chronic hyperuricemia and recurrent flares in patients with chronic tophaceous gout. Early ULT results in suppression of serum uric acid (SUA) and dissolution of deposited MSU crystals and tophi, thus preventing joint erosion complications.[1]

Keywords: ULT, prophylaxis, colchicine, treatment targets

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INDICATIONS FOR STARTING URATE LOWERING THERAPY (ULT)

ULT should be considered and discussed with every patient with a definite diagnosis of gout. ULT is indicated in patients with recurrent flare (≥2 times/year), tophi, urate arthropathy, and/or renal stones.[1]

Patients with gout should be counselled and involved in decision-making concerning the use of ULT.

ULT allows for dissolution of crystal deposits and the disappearance of gout features, provided that uric acid levels are treated to target. Effective ULT reduces the size and number of tophi and facilitates their disappearance, thereby improving quality of life, which can be seriously impaired.[2,3]

TIMING OF INITIATION OF ULT

Should urate-lowering drugs be initiated during a flare or wait until a fortnight later? Two small trials suggest that allopurinol initiation during an acute gout attack neither prolongs the duration of flares nor worsens its severity as compared with delayed initiation. Early treatment in patients with comorbidities is supported by a study of a large cohort of gout patients in whom hypertension, ischaemic heart disease, and CKD were associated with increased risk of recurrence of flare.[4]

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There is a need to start ULT early, particularly in patients with comorbidities and/or Serum Uric Acid (SUA) level >8 mg/dL (476 umol/L). Support to treat patients with high SUA level earlier is based on studies showing an association of hyperuricaemia with increased flare frequency.

TREATMENT TARGETS FOR ULT

For patients on ULT, the SUA level should be monitored, treated to <6 mg/dL (360 umol/L) and maintained. The exceptions are the elderly with limited life expectancy or when the patient has indicated a preference not to treat to target SUA and only for symptom control.

A lower SUA target (<5 mg/dL; 300 umol/L) is recommended for patients with tophaceous gout.

ULT should be stopped when the SUA level is <3 mg/dL (174 umol/L) as this is not recommended in the long term.

Some studies suggest that uric acid might protect against various neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis.[5,6]

HOW TO INITIATE

Types Of ULT:

1. Xanthine oxidase inhibitors: XOI

Allopurinol (1st line)

Risk factors of allopurinol-induced serious cutaneous adverse reactions (SCAR) include the presence of HLA-B* 5801 allele, starting dose of allopurinol, and renal impairment. The frequency of HLA-B* 5801 prevalence is estimated at 18.5 percent in Singapore; 1 in 5 Chinese, 1 in 15 Malays, and 1 in 25 Indians. HLA-B* 5801 genotyping is available in Singapore but is not mandatory for patients starting allopurinol. It is important to bear in mind that this test needs to be interpreted correctly. Among 100 allopurinol users with positive HLA-B* 5801, only two patients may develop serious cutaneous adverse reactions (SCAR), while among 100 patients who test negative, almost all are not at risk of developing allopurinol-induced SCAR. Therefore, the test may deny many people who will not have developed SCAR from allopurinol a cheap and effective means to lower uric acid.

For patients with renal impairment or of an older age group and are deemed to be at higher risk of allopurinol-induced serious adverse reactions, the option of genotyping maybe a consideration. For patients who have already tolerated well to long-term allopurinol treatment, genotyping is not required.

Allopurinol should be started at a low dose (100 mg/day) even in patients with normal kidney function to reduce the likelihood of an early gout flare. A high starting dose increases the risk of SCAR.[7,8] An optimal dose of allopurinol 300 mg/day achieves the SUA target of 6 mg/dL (360 umol/L) in about 70-80 percent of patients.

Treatment with allopurinol can be titrated up to 600-900 mg/day. Compliance must be ascertained prior to escalating doses.

Allopurinol may be combined with a uricosuric agent (e.g., Probenecid) if target SUA cannot be attained in the presence of continued flares. Febuxostat or a uricosuric agent as an addition agent is indicated if allopurinol cannot be tolerated.

In patients with renal impairment, allopurinol should start low at 50 mg OM. Titration of the dose should be much slower to achieve and maintain the same target SUA as in patients with normal renal function.

Renal failure is associated with an increased risk of SCARs and poor outcome. Decreased renal function results in decreased clearance and higher serum levels of oxypurinol, which can induce a cytotoxic T-cell response and trigger hypersensitivity reactions in SCARs.

Febuxostat

Febuxostat is a potent non-purine selective xanthine oxidase inhibitor, which is metabolised in the liver and not excreted via the kidneys. Therefore, it can be considered for use in patients with allopurinol allergy or moderate to severe renal impairment. The normal daily dose of febuxostat is 80 mg.

Febuxostat has been found to be more effective in patients with CKD than allopurinol given at doses adjusted to creatinine clearance. Febuxostat should be avoided, or used with particular caution, in patients with high cardiovascular risk.

2. Uricosuric agents

Probenecid (1-2 g/day)

Do not use in patients with renal stones or renal impairment (creatinine clearance <30 ml/min).

Benzbromarone (50-200 mg/day)

This is not commonly used in the primary care setting and may not be effective when creatinine clearance <30 ml/min.

A review for side effects is recommended after 4-6 weeks with slow upward titration of ULT in every patient.

Prophylaxis with colchicine is recommended during the first six months of ULT. Recommended prophylaxis is colchicine, 0.5-1 mg/day, in which the dose should be reduced in patients with renal impairment. Clinicians should be aware of potential neurotoxicity and/or muscular toxicity with prophylactic colchicine in renal impairment or statin treatment. Co-prescription of colchicine with strong P-glycoprotein and/or CYP3A4 inhibitors should be avoided. If colchicine is not tolerated or is contraindicated, low dose prednisolone may be used but caution is needed in diabetics. Occasionally, as needed NSAIDs may be sufficient. As renal impairment increases the risk of colchicine toxicity, consider reducing colchicine dose or increasing dosing interval in patient with eGFR <30 mL/min/1.73 m^2.

REVIEW OF PATIENT AFTER 4-6 WEEKS

Side effects from medications and breakthrough gout flares should be monitored with full blood count (FBC), uric acid, alanine aminotransferase (ALT), and creatinine level (refer to **Table 1**). The patient can be counselled by a dietitian and nurse manager on lifestyle and diet.

Table 1: Side Effects of Allopurinol

Side effects	Warning signs	Things you need to do
Allergic reaction, especially skin reactions (if it occurs, it usually does so within the first few weeks to three months).	Skin rashes, itching, redness, burning sensation Fever, sore throat, red eyes, mouth sores, flu-like symptoms such as bodyaches or feeling unwell may be early symptoms	Stop medication and see a doctor immediately as this may be a serious allergy If the rash is mild, your doctor may re-introduce Allopurinol at a lower dose at another time
Reduced blood counts (rare)	There may be no warning signs but unusual bleeding or bruising, lip or mouth ulcers with flu-like symptoms may occur	Inform your doctor immediately if these symptoms occur Go for regular blood tests
Liver abnormalities	Usually none, jaundice may occur	Go for regular blood tests
Nausea, loss of appetite, or diarrhoea		Take medication after food or divide the dose into two to be taken within the day

Clearly document counselling and monitoring for side effects.

1. Instruct ACTION PLAN if patient develops any of the above:
   - Stop Allopurinol immediately. DO NOT take the next dose.
   - Stop taking medications (there is no need for permission from doctors).
   - Seek medical attention (A&E) and inform any doctor of new drug, allopurinol (even if it was started in the past 3-4 months).
2. Explain the SEVERITY (What happens if drug is not stopped in time):
   - Allergic reaction can affect internal organs like the liver and kidneys, and if the reaction is severe, death can occur.
3. End counselling on a reassuring note that you are accessible.
   - Call the clinic if those symptoms occur, and inform the patient that you will provide close monitoring.

COMMON FAQS:

1. **What if I miss a dose?**
   If you miss a dose or forget to take your medicine, take it as soon as you remember it. If it is almost time for your next dose, skip the missed dose and continue with your regular schedule. **Do not** double the dosage to make up for the missed dose.
2. **Should I continue or stop taking Allopurinol during an acute gout attack?**
   If you have been taking Allopurinol regularly, you should continue taking it during an acute gout attack, along with other medications to treat the acute gout attack.
3. **Can I drink alcohol while taking Allopurinol?**
   Avoid or limit alcohol intake while on this medicine as alcohol can increase the amount of uric acid in your blood. Alcohol consumption can trigger acute gout attacks.
4. **Are there any medications to avoid while on Allopurinol?**
   Allopurinol may increase the effects of warfarin, Azathioprine, and Mercarptopurine, and may increase the incidence of skin rashes in patients taking Ampicillin.

ACUTE TREATMENT FOR GOUT FLARES

An acute gout flare is an intensely painful and disabling inflammatory arthritis, usually involving a single joint, but occasionally involving two or more joints (refer to **Table 2**).

Acute flares should be treated as early as possible. Fully informed patients can be taught to self-medicate at the first warning symptoms.

Choose drug(s) based on contraindications, the patient's previous experience with treatments, time of initiation after flare onset, and the number and type of joint(s) involved.

Table 2: Gout Classification Criteria

Criteria (2015 ACR-EULAR)[9]		**Categories** ***Please select the highest category ever noted for each criterion.***
CLINICAL	Pattern of joint/bursa involvement during symptomatic episode(s) ever	Joint(s) *or* bursa(e) other than ankle, midfoot or 1st MTP (or their involvement only as part of a polyarticular presentation)
		Ankle *or* midfoot (as part of monoarticular or oligoarticular episode without 1st MTP involvement)
		MTP (as part of monoarticular or oligoarticular episode)
	Characteristics of symptomatic episode(s) ever: (i) Erythema overlying affected joint (patient-reported or physician-observed) (ii) Can't bear touch or pressure to affected joint (iii) Great difficulty with walking or inability to use affected joint	No characteristics
		One characteristic
		Two characteristics
		Three characteristics

	Time-course of episode(s) ever: Presence (ever), irrespective of anti-inflammatory treatment: (i) Time to maximal pain <24 h (ii) Resolution of symptoms in ≤14 days (iii) Complete resolution (to baseline level) between symptomatic episodes	No typical episodes
		One typical episode
		Recurrent typical episodes
	Clinical evidence of tophus: Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g., Achilles)	Absent
		Present

Recommended therapeutic options for acute flare include:

1. Colchicine
2. NSAIDs
3. Corticosteroids

Colchicine

Colchicine may be used (within 12 hours of flare onset) at a loading dose of 1 mg followed by 0.5 mg an hour later on day 1 and/or colchicine tablets of 0.5 mg BD/TDS.

Use colchicine with caution in patients with severe renal or liver impairment.

Drug interactions between colchicine and strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporin or clarithromycin and simvastatin may mean that it is safer to avoid colchicine.

In patients with frequent flares and contraindications to colchicine, use NSAIDs or corticosteroid (oral and injectable).

Combination therapy, such as colchicine and NSAID or colchicine and corticosteroids, can be prescribed for patients with particularly severe acute gout.

IL-1 blockers are prohibitively expensive and rarely used for treating prolonged refractory flares in the tertiary care setting. Acute infection is a contraindication to their use.

COX1 and COX2 Inhibitors

Avoid using in patients with renal impairment CKD 3 and active peptic ulcer disease.

Caution is needed in patients with known cardiovascular disease as an increased risk of myocardial infarction, stroke, and heart failure has been associated with these drugs, although whether such risk is increased in patients receiving short courses of NSAID for a gout flare is unknown.

There is no preference of one particular NSAID over others. Common NSAIDs (COX-1), indomethacin 50 mg TDS, naproxen 550 mg BD, and diclofenac sodium 50 mg TDS or (COX-2) Etoricoxib 90 or 120 mg OM (maximally for a week) can be used.

The total duration of NSAID therapy for a gout flare is five to seven days.

Corticosteroids

Oral corticosteroids may be used, especially in patients with renal impairment or drug allergies. Use prednisolone 30-35 mg/day for 3-5 days.

GENERAL ADVICE

1. Adequate hydration and rest
2. Removal of medication triggers, e.g., diuretics
3. Avoid high purine foods, sugar sweetened drinks, and alcohol (beer)
4. Apply ice packs

Case Study

Mr Tan, 60, is a smoker with diabetes mellitus (DM), hypertension, and chronic kidney disease (CKD) Stage 3, and recurrent gout flares lasting five weeks with increasing intensity and duration. He assumes it is due to frequent travel and lack of exercise. He comes today for routine review of his chronic diseases. Current laboratory results are creatinine 106mmol/l, eGFR 56 mL/min/1.73 m^2, uric acid 490 μmol/L, HbA1c 7.3%, random hypocount 8.5 mmol/L. He is on glipizide 5mg BD, metformin 250mg BD, amlodipine 5 mg OM. He complains of severe gout pain. He had always been reluctant to start definitive treatment, which you had previously mentioned. What will you do next?

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LEARNING POINTS

- **ULT is indicated in patients with recurrent flare >2 times per year, tophi, urate arthropathy, and/or presence of renal stones.**
- **While different xanthine oxidase inhibitors and uricosuric agents can be used, the indication for starting medication, action plan, and side effects must be explained to the patient.**
- **Prophylaxis (colchicine or low dose oral corticosteroids for those who cannot take colchicine) should be commenced during the early months of initiating ULT to reduce the risk of additional flares, which are common early in the course of ULT. Allopurinol should be continued during acute attacks for patients already on this.**
- **Management of comorbidities and risk factors, including chronic renal disease, obesity, diabetes, dyslipidaemia, and hypertension is crucial as part of holistic management including dietary and health lifestyle advice.**

CHRONIC DISEASE MANAGEMENT 2025
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Unit No. 5

ASSESSMENT AND MANAGEMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE

Dr Desmond Wai

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease in the world. Overall improvement in public health, active screening of blood products, and universal vaccination against hepatitis B have led to a drop in incidence of hepatitis B and C worldwide. NAFLD is strongly associated with metabolic syndrome. With an increase in overweight status and obesity worldwide, it is not surprising that NAFLD is on the rise. Diagnosis of NAFLD requires confirmation of fatty infiltration in liver, as well as liver damage such as elevated liver enzymes and the presence of fibrosis. Currently, the best treatment for NAFLD is weight loss, and the proven method would be dieting with regular exercises. Vitamin E and pioglitazoles are promising medications for treating NAFLD, but each has their shortcomings. Until more studies are conducted, lifestyle modification remains the only reliable way to treat NAFLD. Family physicians also ought to look out for cardiovascular diseases, as well as be vigilant in cancer screening, as NAFLD is associated with higher risks of ischaemic heart disease and cancer.

Keywords: Fatty Liver, metabolic syndrome, diabetes mellitus, cirrhosis

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INTRODUCTION

WHAT IS NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)?

There must be evidence of fat in liver of ≥5 percent, usually confirmed by imaging studies, with no secondary causes such as significant alcohol consumption, medications, or genetic disorders.

NAFLD comprises of a spectrum of diseases, depending on the degree of inflammation, and extent of liver fibrosis.

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NAFLD can be categorised histologically into:

1. Non-alcoholic fatty liver (NAFL), which refers to presence of fat in liver without significant inflammation or fibrosis. Risk of progression to cirrhosis or liver failure is minimum.
2. Non-alcoholic steatohepatitis (NASH), which refers to presence of fat with inflammation. NASH can progress to cirrhosis.
3. NASH cirrhosis, which refers to cirrhosis with current or previous histological of steatosis or steatohepatitis.

HOW PREVALENT IS NAFLD?

No population study has been done in Singapore. But judging from some cohort studies, NAFLD is common locally. One local study showed that NAFLD is present in 56 percent of patients undergoing cholecystectomy. Another local study showed that among attendees to a public health forum, 40 percent had ultrasonic evidence of NAFLD. Note that these studies are biased and could have overestimated the prevalence of NAFLD in Singapore.

Population studies in Asia like Hong Kong, China, and Bangladesh showed NAFLD to be present in about 25-40 percent of the general population. Fortunately, less than 5 percent of NAFLD patients have significant fibrosis. Hence, we can postulate that NAFLD is prevalent in 25-40 percent of the Singapore population, with the majority (about 95 percent) without significant fibrosis.

NAFLD is particularly common in patients with metabolic syndrome. NAFLD is present in more than 95 percent of obese patients undergoing bariatric surgery. Two-thirds of diabetics and half of the patients with dyslipidaemia have NAFLD.

WHAT IS THE NATURAL HISTORY OF NAFLD?

Generally speaking, patients with NAFL alone have a very low risk of progression to liver cirrhosis. However, patients with steatohepatitis, especially those with fibrosis, may progress to cirrhosis or even liver cancer. The progression is believed to take more than a decade, with weight gain being an important predictor of progression.

Interestingly, longitudinal follow-up studies have showed that cancer and cardiovascular diseases are the top two causes of death in patients with NAFLD. Liver complications such as hepatocellular carcinoma, liver cirrhosis, and liver failure are only ranked as the third most common cause of death for patients with NAFLD.

Possible explanations include overweight status and metabolic syndrome, which are risk factors for certain cancers, such as pancreatic, breast, and colon cancer. Additionally, patients with NAFLD would have concurrent metabolic syndrome, which in itself is a risk factor for cardiovascular disease.

HOW DO I CONFIRM THE DIAGNOSIS OF NAFLD?

First, there must be documentation of fat in liver, which is usually diagnosed via ultrasound scan. Most of my patients with NAFLD have their disease diagnosed via routine screening. Fatty liver is rarely diagnosed on CT or even laparoscopy when patients undergo abdominal or pelvic surgeries.

Second, there may be liver inflammation, thus their liver profile may show elevated GGT or ALT.

Third, alternative causes of liver injuries, such as viral hepatitis B or alcohol, should be excluded. The safe limit of alcohol has been of much debate. The consensus is that the safe limit of alcohol consumption for a man is 21 units a week, and 14 units for a woman. One unit of alcohol is approximately one can of beer, one glass of wine, or one shot of hard liquor.

Fourth, NAFLD is almost always associated with metabolic syndrome, thus clinicians ought to look out for overweight status, hypertension, dyslipidaemia, diabetes, or pre-diabetes. On the other hand, in patients without any evidence of metabolic syndrome or significant alcohol consumption, a diagnosis of NAFLD is unlikely.

HOW CAN I STAGE SEVERITY OF NAFLD?

NAFLD progresses into the following stages: pure fat, steatohepatitis, fibrosis, then cirrhosis.

The ideal method to stage the disease is percutaneous liver biopsy, which could identify the degree of inflammation and stage of fibrosis. However, as biopsy is associated with a small risk of complications (about 1 percent) such as hemoperitoneum, patients rarely agree to it.

While transaminases such as ALT and GGT may reflect degree of liver inflammation, they can only act as a guide as they do not correlate accurately with inflammation in liver histology.

Several non-invasive methods of assessment for NAFLD are available commercially.

Hepatic steatosis can be accurately quantified by MR imaging. MR Elastography can also identify the amount of liver fibrosis, as well as identifying any focal liver lesions, but its limited availability and high cost make it difficult for general use in primary care.

Several panels utilise laboratory and clinical markers, such as platelets, albumin, BMI, age, ALT, etc to insert into a particular formula to estimate the risk of liver fibrosis. Some of these are available for use in Singapore.

Fibroscan®, which measures liver stiffness, is also available locally to estimate the amount of liver fibrosis. Fibroscan® is cheaper than MR Elastography. Note, however, that 10-25 percent of fibroscan studies may fail to obtain reliable readings due to patient factors. Besides, an appropriate probe size is needed for different patient sizes.

HOW SHOULD I MANAGE AT A PRIMARY CARE CLINIC?

Establishing the diagnosis, i.e., confirming presence of fat in liver, with exclusion of alternative liver diseases is the first line of management.

One also ought to look for other components of metabolic syndrome as they are almost always present in all patients with NAFLD.

The next step is to establish the severity of liver damage by non-invasive methods. Those with advanced fibrosis or cirrhosis should be referred for specialist care.

Lifestyle modification is the mainstay of treatment for NAFLD and should be done at the primary care level.

The most proven management of NAFLD is weight loss. Weight loss of 3-5 percent from baseline often leads to improvement in hepatic steatosis. Further weight loss of 7-10 percent would lead to improvement of inflammation and fibrosis histologically.

Exercising alone might not be sufficient in improving the stage of NAFLD, thus exercising should be combined with dieting. A hypocaloric diet, i.e., creation of a calorie deficit, plus moderate-intensity exercise, is likely to provide the best likelihood of sustaining weight loss.

My personal experience is that constant reminders and regular review of patients, providing insights, going through the patient's dietary and social history, are important in helping patients adhere to hypocaloric diet and a regular exercise regime.

Metformin has been discarded as a treatment of choice as meta-analysis showed no benefits in improvement in liver histology.

Pioglitazone, vitamin E at 800 IU/day have been showed to improve liver histology in NASH patients. However, Pioglitazone use is associated with weight gain and increased bone loss, as well as a small risk of bladder cancer. Therefore pioglitazone should be used only for those with biopsy proven NASH and with informed consent.

Vitamin E at a dose of 400 IU/day has been associated with an increased risk of prostate cancer and all-cause mortality in some studies. Hence, its benefits and risks ought to be

discussed with patients before starting it. Vitamin E is not recommended for NAFLD patients with liver biopsy, with cirrhosis, or with diabetes.

Newer diabetic medications like GLP-1 agonists have showed promising results in managing weight loss but its use in NAFLD is currently not recommended yet.

Bariatric surgeries, which lead to significant weight loss, can lead to improvement in liver histology. But careful patient selection, as well as long-term post-op support, are important in ensuring maintenance in weight loss.

HOW TO DO DIETING?

There is no simple answer to this. I often joke with my patients that if there is a simple method to lose weight, there will no fat doctors!

A few points can be written on losing weight, though.

First, there must be a calorie deficit whereby a patient's calorie intake is less than his requirement. The type of diet, be it in low carbo diet, ketogenic diet, Mediterranean diet, Subway diet, etc is not important. Studies have showed that these diets can all help to reduce weight. The most important part of dieting is its sustainability, as many studies showed that only a quarter to a third of participants have the discipline to complete a one-year programme to lose weight.

Many of my patients lost weight with a ketogenic diet. But being Asians, it is difficult to not consume rice or bread so most cannot sustain a ketogenic diet.

Second, the patient must have enough insight into the problem to improve self-motivation. Emotional support from his or her family members is essential for success.

Third, foods that contain simple sugar, like desserts, soft drinks, or snacks should be minimised or rationed.

Fourth, a low-calorie diet leads to reduced metabolic rate and muscle loss. Therefore, any form of dieting should be accompanied with a moderate amount of exercise to avoid loss of lean mass and maintenance of metabolic rate.

Finally, we as physicians must be aware of the adverse effects of different types of diets. For instance, intermittent fasting, i.e., eating for only eight hours over a 24-hour period can help in losing weight significantly. But patients often feel lethargic, cold, and dizzy when they first embark on intermittent fasting. Patients who operate heavy machinery or drive a taxi, for instance, may not be suitable for intermittent fasting. In addition, skipping breakfast has been shown to be associated with gallstone formation, hence we must first warn patients about all these before recommending it to them.

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LEARNING POINTS

- **NAFLD is currently the most common cause of liver disease in Singapore, as well as the rest of the world. It will emerge as the leading cause of cirrhosis, liver cancer, and liver-related mortality in time to come.**
- **NAFLD is associated with metabolic syndrome and the family doctor ought to look out for and treat different components of metabolic syndrome.**
- **There is currently no magic way to lose weight. Much effort in taking low-calorie diets and doing daily exercises must be preached to all patients constantly.**

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Unit No. 6

HEART FAILURE WITH NORMAL AND REDUCED EJECTION FRACTION – ASSESSMENT AND SHARED CARE MANAGEMENT

Dr Rohit Khurana

Keywords: Heart Failure, shared care management, reduced ejection fraction, preserved ejection fraction, BNP, therapy

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INTRODUCTION

Heart failure (HF) is a common clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. HF may be caused by disease of the myocardium, pericardium, endocardium, heart valves, vessels, or by metabolic disorders.

HF due to left ventricular dysfunction is categorised into HF with reduced ejection fraction (with Left Ventricular Ejection Fraction (LVEF) ≤50 percent, known as HFrEF; also referred to as systolic HF) and HF with preserved ejection fraction (with LVEF >50 percent; known as HFpEF; also referred to as diastolic HF[1]).

A reduced LVEF in systolic heart failure is a powerful predictor of mortality. As many as 40-50 percent of patients with heart failure have diastolic heart failure with preserved left ventricular function.

Overall, there is no difference in survival between diastolic and systolic heart failure that cannot be attributed to ejection fraction. Patients with diastolic heart failure are more likely to be women, to be older, and to have hypertension, atrial fibrillation, and left ventricular hypertrophy, but no history of coronary artery disease.[2,3] The pathogenesis of diastolic dysfunction involves abnormalities of active ventricular relaxation and passive ventricular compliance, which lead to ventricular stiffness and higher diastolic pressures. These pressures are transmitted through atrial and pulmonary venous systems, reducing lung compliance. A combination of decreased lung compliance and cardiac output leads to symptoms.[2]

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CLINICAL PRESENTATION AND DIAGNOSIS

Patients with HF usually present with the classic triad of symptoms – oedema, fatigue, and dyspnoea. Other typical symptoms may include orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance, and increased time to recover from exercise. Less typical signs include nocturnal cough, wheezing, bloated feeling, loss of appetite, confusion (especially in the elderly), depression, palpitations, dizziness, and syncope.[4]

However, symptoms are non-specific and non-sensitive, and therefore are less useful in discriminating HFrEF from HFpEF. In addition, atypical presentations should be considered when evaluating obese patients and older adults because of potentially different aetiology, clinical presentation, and outcome as compared to the general population.

Typical signs of HFrEF include elevated-jugular venous pressure, gallop rhythm, hepato-jugular reflux, and laterally displaced apical impulse. Less typical symptoms include weight gain, cachexia (tissue wasting), cardiac murmur, peripheral oedema (ankle, sacral, scrotal), pulmonary rales, tachycardia, irregular pulse, tachypnoea, hepatomegaly, ascites, cold extremities, oliguria, and narrow pulse pressure.[4]

The assessment of signs and symptoms is clinically significant to suggest the likelihood of HFrEF as well as to monitor response to therapy and stability overtime. In groups such as the obese, the elderly, and those with chronic lung disease, being confident of the symptoms and signs might be more difficult.

Persistent symptoms despite treatment often suggest the need for additional therapy and worsening of symptoms often suggest serious development and the need for prompt medical attention.

Heart failure is much more likely in the presence of a relevant medical history suggesting an increased risk of cardiac damage. In advanced economies such as Singapore, nearly 60 percent of patients diagnosed with acute heart failure have underlying coronary artery disease. In patients with acute coronary syndromes, myocardial ischaemia is often a precipitant risk factor, especially for *de novo* heart failure.[5] A prior diagnosis of heart failure, diabetes, hypertension, valvular heart disease, advanced age, the male sex, and obesity have all been found to predict fluid overload typical of congestive heart failure.

The symptoms and signs of heart failure are the consequence of systemic and pulmonary congestion, which result from increased left ventricular filling pressures. Even in the absence of overt clinical congestion, haemodynamic congestion may still occur, and this also predicts a worse mortality and re-

hospitalisation rate. Heart failure symptoms can occur with preserved or reduced ejection fraction (systolic or diastolic heart failure). The New York Heart Association classification system is the simplest and most widely used method to gauge symptom severity (refer to **Table 1**). The classification system is a well-established predictor of mortality and can be used at diagnosis and to monitor treatment response.

Table 1: American College of Cardiology/American Heart Association Recommendations by Stage of Heart Failure[13]

STAGE	RECOMMENDATION
A: Heart failure risk factors	Guideline-directed treatment of hypertension and hyperlipidemia
B: Diastolic dysfunction without symptoms	Treat hypertension with thiazide diuretics, ACE inhibitors, or nondihydropyridine calcium channel blockers
C: Symptomatic heart failure with preserved ejection fraction and hypertension	Treat volume overload with diuretics; consider use of beta blockers, ACE inhibitors
C: Symptomatic heart failure with preserved ejection fraction without hypertension	Treat volume overload with diuretics

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

Information from references 3 and 12.

ASSESSMENT

In patients with non-acute onset, presenting with symptoms and signs of heart failure in the primary care setting, the probability of heart failure should be determined by the history and symptoms supported by findings on clinical examination. Blood tests, an ECG, and a chest x-ray should be requested on all patients. During these steps, at least one element should be positive to consider the diagnosis and subsequently plasma natriuretic peptides and an echocardiogram should be requested. The diagnostic assessment, in accordance with the ESC 2016 guidelines, is summarised in **Table 2**.[4]

Table 2: Diagnostic assessment in patient with suspected heart failure (non-acute onset) – according to ESC guidelines[4]

Diagnostic assessment in patient with acute heart failure adapted from the ESC guidelines (2016)[1]

1. Measurement of plasma natriuretic peptide level (BNP, NT-proBNP or MR-proANP)*

2.
a) 12-lead ECG;
b) chest X-ray†
c) laboratory assessments: cardiac troponins, BUN (or urea), creatinine, electrolytes (sodium, potassium), glucose, complete blood count, liver function tests and TSH.

3. Echocardiography‡

* to help in the differentiation of acute heart failure from non-cardiac causes of acute dyspnea

† to assess signs of pulmonary congestion and detect other cardiac or non-cardiac diseases that may cause or contribute to the patient's symptoms

‡ recommended immediately in haemodynamically unstable patients with acute heart failure and within 48 hours when cardiac structure and function are either not known or may have changed since previous studies.

Brain Natriuretic Peptide (BNP)

BNP and N-terminal pro-BNP (the cleaved inactive N-terminal fragment of the BNP precursor) levels can be used to evaluate patients with shortness of breath suspected of having heart failure.[5] BNP is secreted by the atria and ventricles in response to stretching or increased wall tension. The hormone then causes fluid and sodium loss in the urine and mild vasodilation. BNP levels increase with age, is higher in women and patients of African origin, and can be elevated in patients with renal failure. BNP appears to have better reliability than N-terminal pro-BNP,[6] especially in older populations. Guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) recommend the use of natriuretic peptides for assessment of patients with symptoms of heart failure.

Most dyspnoeic patients with HF have plasma BNP values >400 pg/mL, while values <100 pg/mL have a very high negative predictive value for HF as a cause of dyspnea.[7] In the range between 100-400 pg/mL, plasma BNP concentrations are not very sensitive or specific for detecting or excluding HF. As BNP levels increase, the specificity increases and likewise the likelihood of a heart failure diagnosis. BNP levels also increase in level according to New York Heart Association classification. Elevations in plasma BNP can establish the presence of HF due to diastolic dysfunction with similar accuracy to systolic dysfunction. However, the values do not differentiate between systolic and diastolic dysfunction.

BNP levels are strong predictors of mortality at two to three months and cardiovascular events in acute heart failure, specifically when BNP level is >200 pg/mL or N-terminal pro-BNP level is >5,180 pg/mL.[7] Limited evidence supports monitoring reduction of BNP levels in the acute and outpatient settings. A 30 to 50 percent reduction in BNP level at hospital discharge showed improved survival and reduced re-hospitalisation rates. Optimising management for outpatient targets of a BNP level <100 pg/mL and an N-terminal pro-BNP level <1,700 pg/mL showed improvement in decompensations, hospitalisations, and mortality events.[7]

Echocardiography

Echocardiography should be performed in all patients with new onset HF and can provide important information about ventricular size and function.[8] The sensitivity and specificity of two-dimensional echocardiography for the diagnosis of systolic dysfunction are as high as 80 and 100 percent, respectively. Valvular structure and function in valve disease can be characterised.

A number of other important findings can be detected. Regional wall motion abnormalities are compatible with coronary artery disease. Pericardial thickening may be indicative of constrictive pericarditis. Infiltrative

cardiomyopathies are associated with an abnormal myocardial texture. Left ventricular diastolic function can be assessed by estimation of the pulmonary capillary wedge pressure via the ratio of tissue Doppler of early mitral inflow velocity (E) to early diastolic velocity of the mitral annulus (e'). An E/e' ratio of >15 suggests a Pulmonary capillary wedge pressure (PCWP) of >15 mmHg when e' is the mean of medial and lateral mitral annulus early diastolic velocities. There are limitations to the use of the E/e' ratio, which are beyond the scope of this article. Right atrial and pulmonary artery pressures are determined by the peak velocity of tricuspid regurgitation on Doppler echocardiography.

These findings correlate with the pulmonary artery wedge pressure, regardless of the aetiology of HF or severity of tricuspid regurgitation; they can be used to assess changes in left ventricular filling pressures resulting from therapy.

Treadmill Exercise Testing

Exercise testing should be part of the initial evaluation of virtually all patients with HF. In addition to detection of ischaemic heart disease, assessment of exercise capacity can be used for risk stratification and determining prognosis. Serial measurements can also assess the efficacy of therapy and clinical stability of patients over time.

With severe HF, measurement of the maximal oxygen uptake (VO_2max) provides an objective estimate of the functional severity of the myocardial dysfunction.[9] VO_2max is one of the best indices of prognosis in patients with symptomatic HF. However, peak VO_2 and exercise capacity can be affected by factors other than cardiac status, including deconditioning, pulmonary disease, and anaemia. One advantage of measuring VO_2max directly is that cardiac and non-cardiac causes of impaired exercise can be distinguished by assessing the anaerobic threshold and related indices.

PRINCIPLES OF MANAGEMENT

The 2016 ESC guidelines recommend both lifestyle interventions and pharmacological therapies.[4] HF with reduced ejection fraction has well-validated therapies to reduce morbidity (i.e., reducing symptoms, improving health-related quality of life and functional status, decreasing the rate of hospitalisation), and to reduce mortality. In contrast, HF with preserved ejection fraction lacks evidence-based treatment recommendations.

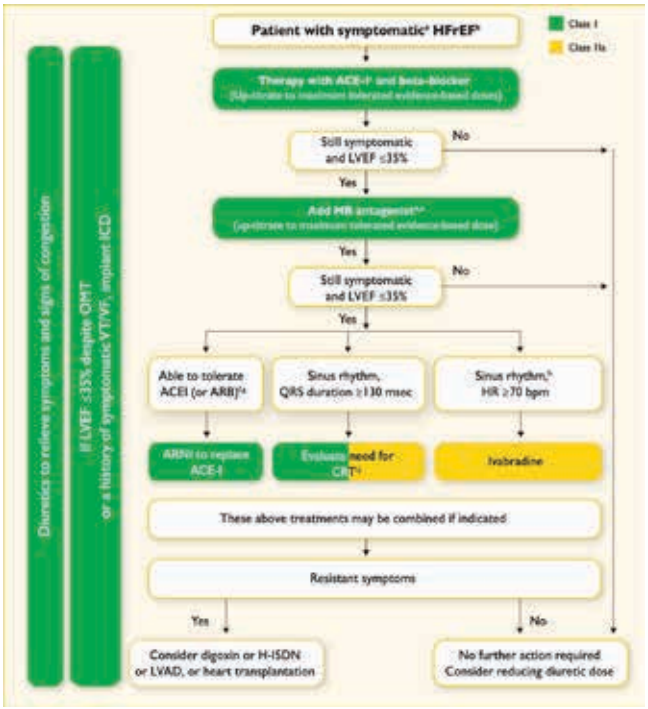
Diuretics are essential in relieving symptoms, but it has yet to be definitively established whether they provide long-term prognostic benefit.[10] They provide immediate relief of symptoms and help manage the chronic fluid status in stable patients, irrespective of whether it is HFrEF or HFpEF.

It is imperative that patients with heart failure understand their condition and are involved in their management decisions. Lifestyle interventions can improve patients' quality of life and prevent exacerbations. The role of dietary salt restriction and the importance of regular exercise to increase functional capacity should be reinforced. For patients with more advanced heart failure, daily weight measurements and fluid restriction with close supervision may be necessary. Formalised cardiac rehabilitation that combines exercise with ongoing educational and psychological support has proven benefits.

HF with Reduced Ejection Fraction

Management of heart failure with reduced ejection fraction (HFrEF) includes management of contributing factors and associated conditions, lifestyle modification, pharmacologic therapy, and, if indicated, device therapy (refer to **Figure 1**).

Figure 1. Therapeutic algorithm for a patient with symptomatic heart failure with reduced ejection fraction[4]



Cardiac resynchronisation therapy is indicated with patients with an ejection fraction of <35 percent and QRS duration of >130 ms. Contributing factors comprise hypertension, myocardial ischaemia or infarction, diabetes mellitus, thyroid dysfunction, and infection. Coronary disease and diabetes mellitus have become increasingly responsible for HF while hypertension and valve disease have become less common due to improvements in detection and therapy. However, almost all patients with HFrEF will require diuretics on a chronic basis to alleviate symptoms and signs of congestion.[11]

Other treatment generally starts with ACE inhibitors or angiotensin receptor blockers (ARBs), followed by beta-blockers. Beta blockers can also provide relief in patients with ischaemic heart disease presenting with angina and rate control in those with atrial fibrillation. If symptoms persist, as based on the NYHA functional classification of II-IV, mineralocorticoid receptor antagonists (MRA such as spironolactone or eplerenone may be added. Ivabradine may also be an option for some patients with HFrEF, if

they are in sinus rhythm and their resting heart rate is >70 bpm. Improved mortality has been demonstrated with beta blockers, ACE inhibitors, ARNI, hydralazine plus nitrate, and MRAs, with limited evidence of survival benefit for diuretics.

NOVEL TREATMENT OPTIONS IN HFREF

One new treatment strategy is the angiotensin receptor neprilysin inhibitor (ARNI), which comprises valsartan and sacubitril. This drug serves to reduce sympathetic tone, aldosterone levels, and sodium retention through inhibition of the overactive renin angiotensin system while simultaneously potentiating protective vasoreactive neuropeptides.

The first (and currently only commercially available) ARNI, formerly known as LCZ696 and marketed as Entresto, was evaluated in the PARADIGM-HF trial in comparison to enalapril 10 mg bd. After 27 months of follow-up, the trial was stopped early due to positive interim results.[12] All-cause mortality was 17 percent with the ARNI, as compared to 19.8 percent with enalapril, in HFrEF patients maintained on optimal background HF therapy. This yielded a hazard ratio of 0.84 ($p<0.001$) and a number needed to treat of 32.

The position of ARNI prescribing in primary care has also not been firmly established. Cardioselective beta-blockers may be prescribed in patients with co-morbid chronic obstructive pulmonary disease (COPD). More recently, the EMPA-REG OUTCOME and the DECLARE TIMI-58 trial reported that empagliflozin and dapagliflozin, respectively, which are both inhibitors of the sodium glucose co-transporter (SGLT-2) in the kidney when added to metformin, had beneficial prognostic cardiovascular outcomes compared to placebo in patients with cardiovascular risk factors and/or disease.[12] Subgroup analysis suggested the benefits were consistent for patients with and without HF.

HF with Preserved Ejection Fraction

In contrast with treatment of heart failure with HFrEF, there are fewer randomised controlled trials (RCTs) of patients with HFpEF. The ACC/AHA recommends using a stage-based approach to guide treatment of HFpEF.[13] The ESC recommends diuretics for treating fluid overload in patients with HFpEF.[4] However, it makes no recommendation regarding other medications for treatment. It recommends identifying and treating cardiovascular and non-cardiovascular comorbidities, because most deaths and hospitalisations in patients with HFpEF are not due to chronic heart failure. The ACC/AHA and ESC recommend combined endurance and resistance training for patients with HFpEF to improve exercise capacity, physical functioning, and diastolic function.

Hypertension should be treated according to appropriate guidelines. Although RCTs of several medications showed fewer heart failure hospitalisations, this benefit was offset by increases in hospitalisations for other reasons. Thus, in the absence of hypertension, the evidence does not support treating patients with HFpEF with any medication except diuretics. Additionally, RCTs of angiotensin receptor blockers, nitrates, and spironolactone raise concerns about adverse effects, and physicians should avoid using these medications if possible. Similarly, the use of digoxin should be avoided in patients 65 years and older. Comorbid atrial fibrillation or coronary artery disease should be treated.

Data from the PARAMOUNT trial comparing valsartan-sacubitril with valsartan in HFpEF showed that ARNI reduced NT-proBNP levels, left atrial volume index, and increased eGFR more so than valsartan alone and independent of its systolic blood pressure lowering effect. The long-term clinical outcomes of ARNI in HFpEF are being further investigated in the ongoing PARAGON trial.

SHARED CARE MANAGEMENT

Often, patients with HFrEF are managed in the hospital outpatient or specialist clinics for three to six months after diagnosis, to titrate medication to optimal doses. The optimal duration of these hospital-based programmes before transitioning patient care to the community has not been established, nor whether all or only higher risk patients benefit. However, there is evidence that, given the complexity of the HF syndrome and its co-morbidities, close collaboration between hospital and primary care practitioners is crucial in order to provide optimal, integrated care and improved outcomes.[14] It is important to realise that there is a wide variation in the disease trajectory of HF and the majority of patients do not generally follow a gradual decline. Some feel and function well but succumb to sudden fatality, while other patients may display improved functioning after a period of poor quality of life. Diverse and multiple co-morbidities further complicate the disease trajectory, warranting regular monitoring.

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LEARNING POINTS

- **It is imperative that patients with heart failure understand their condition and are involved in their management decisions; lifestyle interventions can improve patients' quality of life and prevent exacerbations.**
- **Given the complexity of the HF syndrome and its co-morbidities, close collaboration between hospital and primary care practitioners is crucial in order to provide optimal, integrated care and improved outcomes.**
- **Recent trials (EMPA-REG OUTCOME and the DECLARE TIMI-58) suggest that both empagliflozin and dapagliflozin, which are inhibitors of the sodium glucose co-transporter (SGLT-2) in the kidney, had beneficial prognostic cardiovascular outcomes when added to metformin compared to placebo in patients with cardiovascular risk factors and/or disease.**
- **Heart failure is increasingly common. Timely and accurate diagnosis is important since treatments can improve symptoms and improve prognosis.**
- **There are parallels with the diagnostic evaluation of heart failure with both preserved and reduced ejection fraction. Management approached overlap but the syndromes also require distinct treatment strategies.**
- **Primary care has a crucial responsibility to oversee the health status of a heart failure patient and associated co-morbid conditions using evidence-based pharmacotherapy and lifestyle interventions.**

FPSC 133
MCQS ON CHRONIC DISEASE MANAGEMENT 2026
SUBMISSION DEADLINE: 16 JUNE 2026, 12 noon
INSTRUCTIONS

- **To submit answers to the following multiple choice questions, you are required to log on to the College Online Portal (https://lms.wizlearn.com/cfps/)**
- **Please contact sfp@cfps.org.sg if you have not received an email on the LMS account.**
- **Attempt ALL the following multiple-choice questions.**
- **There is only ONE correct answer for each question.**
- **The answers should be submitted to the College of Family Physicians Singapore via the College Online Portal before the submission deadline stated above.**
- **There will be NO further extension of the submission deadline**

S/N	30 MCQs
1	The risk of antihypertensive drugs on rapid decline in eGFR in Japanese patients with Chronic Kidney Disease was studied by Kenta Fujimoto et al and their findings were published in Am J Hypertens, June 2025. Which of the following indicates a patient has rapid decline in eGFR? A. Annual reduction >10% B. Annual reduction >15% C. Annual reduction >20% D. Annual reduction >25% E. None of the above
2	In the 2024 European Society of Cardiology (ESC) hypertension clinical practice guidelines, which ONE of the following is the CORRECT definition of hypertension? A. BP ≥140/95 mmHg B. BP ≥140/90 mmHg C. BP ≥130/85 mmHg D. BP ≥130/80 mmHg E. BP ≥120/70 mmHg
3	Which ONE of the following organs can be damaged by prolonged elevated blood pressure? A. Eye B. Bone and joints C. Skin D. Hearing E. Hair and nails
4	A 50-year-old man presents with a blood pressure of 140/90 mmHg. In which ONE of the following is lowering of his blood pressure indicated? A. Heart failure B. Moderate CKD C. Severe CKD D. Type 2 diabetes mellitus E. All of the above

5	A 45-year-old woman is diagnosed with obstructive sleep apnoea. Which ONE of the following clinical features is likely to be ABSENT? A. Day-time sleepiness B. Snoring when sleeping C. Renal bruit D. Atrial fibrillation E. Obesity
6	The following statements are TRUE with regards to insulin initiation EXCEPT: A. Insulin therapy should be initiated in patients with symptomatic hyperglycaemia B. Insulin therapy should be initiated in patients who have uncontrolled HbA1c despite optimising treatment with oral hypoglycaemic agents C. Common barriers to insulin therapy include stigma and inconvenience, fear of injection and pain, misconception that insulin use will result in greater complications of diabetes D. The doctor should be prepared to spend time to work with the patient to handle the challenges faced with insulin therapy E. Insulin therapy should be reserved as a last resort when there are no other medication options
7	Which of the following is NOT a barrier to initiation of insulin therapy? A. Cost of insulin therapy B. Fear of needle and pain C. Inconvenience and disruption of patient's lifestyle D. Limited access to diabetes nurse educators E. Patient denial and limited understanding of diabetes and complications
8	When initiating patients on insulin therapy, the physician should advice the patients on the following EXCEPT: A. Discontinue all oral hypoglycaemic agents B. Insulin administration and storage C. Safe driving D. Sick day management E. Effects of fasting and exercise and changes in insulin requirements
9	The following strategies can be adopted to assist patients in overcoming the challenges to insulin therapy EXCEPT: A. Demonstrate how insulin is administered and the convenience of insulin pens B. Offer measures to reduce weight gain—lifestyle advice, concomitant use of insulin with metformin, SGLT-2 inhibitors, GLP-1RA C. Attribute the patients' uncontrolled DM to their lifestyle and diet D. Education to raise awareness and understanding of glycaemic levels and desired targets through SMBG training and interpretation E. Empower patients with the knowledge on hypoglycaemia management
10	If the patient has uncontrolled HbA1c and the basal insulin dose exceeds 0.5 units/kg/day, which of the following strategies will not be useful to further optimise their diabetes control? A. Intensifying the insulin regime to a basal-plus regimen B. Intensifying the insulin regime to a basal-bolus regimen

	C. Switching the patient to a pre-mixed insulin regime D. Addition of GLP-1RA to the patient's treatment regimen E. Increase the dose of basal insulin by 4–6 units
11	A 42-year-old man with obesity reports that after dinner, despite feeling physically full, he often eats dessert when exposed to highly palatable foods. He notes that this behaviour is most pronounced when stressed or tired. Which of the following best explains this pattern of eating behaviour? A. Failure of hypothalamic homeostatic circuits to sense current energy stores B. Activation of reward-related corticolimbic circuits that can override homeostatic satiety signals C. Absence of a defended body-weight set point D. Increased conscious decision-making mediated by cortical control E. Reduced peripheral metabolic signalling from adipose tissue
12	A 52-year-old man is seen in primary care for weight management. His BMI is 33.8 kg/m². He has hypertension and dyslipidaemia, both optimally controlled. He is physically active at work and reports no functional limitations. Which of the following statements best reflects the most appropriate diagnostic and severity assessment approach for his obesity? A. BMI alone is sufficient to confirm obesity and guide treatment intensity B. Obesity diagnosis should be deferred until complications develop C. Excess adiposity should be confirmed using an additional anthropometric or body-fat measure D. Treatment should target a generic 5–10% weight loss regardless of comorbidities E. Aggressive treatment is indicated only if BMI is ≥40 kg/m²
13	A 48-year-old woman with obesity (BMI 35.5 kg/m²) has metabolic dysfunction-associated steatotic liver disease (MASLD) and moderate obstructive sleep apnoea. She is currently taking lifestyle measures and has lost 5% of her body weight over six months. Her liver enzymes and sleep symptoms have improved minimally. Which is the most appropriate next step in management? A. Escalate obesity treatment, as greater weight loss may be required to improve her complications B. Continue lifestyle therapy only, as 5% weight loss is adequate for most patients C. Focus on treating MASLD and OSA separately rather than targeting obesity D. Add medications for each complication before addressing obesity directly E. Avoid anti-obesity pharmacotherapy until BMI exceeds 40 kg/m²
14	A 50-year-old woman with obesity and impaired fasting glucose has struggled with weight regain after multiple diet attempts. She reports intense hunger when following low-calorie, high-carbohydrate meals. She

	asks whether a different dietary approach might help her maintain weight loss. What is the best next dietary recommendation to improve adherence and reduce hunger-related relapse? A. Advise her to “push through” the hunger as the key issue is compliance, since no specific diet is superior long-term B. A low-glycaemic index, higher-protein dietary pattern may improve weight-loss maintenance C. Time-restricted feeding should be routinely recommended due to strong long-term RCT evidence D. Very-low-energy diets are preferred for all patients because they overcome biological resistance E. Carbohydrate-restricted diets should be avoided in individuals with impaired glucose metabolism
15	A 54-year-old woman with obesity asks about newer weight-loss medications after reading about “incretin therapies” online. She is concerned about safety, durability and long-term value beyond weight loss. Which of the following statements best reflects the current evidence regarding GLP-1–based anti-obesity pharmacotherapy? A. Their primary mechanism of action is increasing basal metabolic rate B. Concerns about suicidality have led to strengthened regulatory warnings C. Lean-mass loss with these agents reflects predominantly functional muscle loss D. Weight regain after discontinuation suggests these drugs treat an ongoing pathophysiology E. Their clinical benefits are limited mainly to weight reduction
16	Mr X, a 40-year-old smoker with hypertension sees you for routine review. He reports two gout flares in the past two months, relieved with three days of Arcoxia for each episode. You perform some blood tests, which results in the following: Creatinine 95 umol/L, eGFR >90 mL/min Uric acid 460 mmol/L HbA1c 5.4% Random hypo-count 7.5 mmol/L He is currently on Amlodipine 5 mg OM. He does not drink alcohol except one glass of wine once or twice a year on special occasions. His BMI is 25kg/m^2. Which is the most appropriate next step? A. Offer dietary advice B. Offer dietary advice and advise regular exercise C. Discuss and offer to initiate urate lowering therapy, ideally with colchicine prophylaxis D. Prescribe NSAIDs standby for gout flare E. Prescribe prednisolone standby for gout flare

17	Mr Y**,** a 45-year-old man, reports three recent gout attacks involving the ankle and knee. His BP is 144/94 mmHg. On examination, there is a small tophus over the left elbow. He volunteers that two years ago he had taken allopurinol 100 mg daily for one month, then 200 mg daily for three months, but stopped as it "did not help his gout and there was no improvement." He did not follow up with his GP. Two weeks ago, he was admitted for a gout flare. Blood tests showed: • Uric acid: 620 µmol/L • Creatinine: 95 µmol/L • eGFR: 65 mL/min Which is the CORRECT advice? A. Reassure him that urate-lowering therapy is unnecessary unless he develops more than five attacks per year B. Advise that allopurinol should not be restarted since it previously failed, and initiate febuxostat or probenecid instead C. Advise that urate-lowering therapy should be restarted with gradual dose titration to achieve a serum urate target of <300 µmol/L, with regular monitoring, and consider colchicine prophylaxis during titration D. Advise that urate-lowering therapy should only be started after complete resolution of tophi with target of uric acid <360 µmol/L E. Start allopurinol immediately at 300 mg daily without prophylaxis, as renal function is acceptable
18	You are seeing Mr Y TWO months later. At your last visit, he declined colchicine prophylaxis as he did not want to take "too many tablets". He has since started and is adherent to his urate-lowering therapy. Last month, his serum uric acid had decreased to 390 mmol/L. He experienced a gout flare last week and has come today to ask about colchicine prophylaxis. Which is the CORRECT advice regarding colchicine prophylaxis? A. Colchicine prophylaxis is not useful once urate-lowering therapy has already been started B. Colchicine prophylaxis can reduce the risk of gout flares, particularly during the first 3–6 months after initiating urate-lowering therapy C. Colchicine prophylaxis should be stopped permanently after any episode of diarrhoea D. Colchicine prophylaxis inevitably causes renal impairment even in patients with normal renal function E. Colchicine prophylaxis should only be started if serum uric acid is above 600 mmol/L
19	Mr Y, a 60-year-old mechanic, was recently started on allopurinol 100 mg two months ago and increased to 200 mg three weeks ago in your clinic. He came down with flu four days ago and developed rashes after being given Klacid, fluimucil, and loratidine by another GP. Today, he returns to your clinic.

	Which is the most appropriate next step? A. Stop Klacid and continue the chronic medications B. Prescribe paracetamol for pain relief and switch to Levofloxacin 500 mg bd instead C. Continue medications and check for Dengue serology D. Stop Klacid, fluimucil, and loratidine E. Stop all medications and refer for possible SJS
20	A 40-year-old accountant on allopurinol 100 mg OM for the past one year reports two recent gout attacks in the last one year. He has no other known past medical history. His BMI 25 kg/m², BP 144/94 mm Hg. He is having a gout attack now. He tells you that his gout attacks are usually aborted with colchicine TDS for two days. Whilst on colchicine, he does not experience diarrhoea except perhaps one episode of loose stools after which he stops colchicine. Which is the most appropriate next step? A. Continue allopurinol at 100 mg OM despite the attack and start colchicine. Consider checking a baseline creatinine if not recently done B. Stop Allopurinol during this acute gout attack and start colchicine. Consider checking a baseline creatinine if not recently available C. Increase the allopurinol to 200 mg OM today and start colchicine. Consider checking a baseline creatinine if not recently done D. Start hydrochlorothiazide for hypertension E. Start Losartan for hypertension
21	Which of the following factors is NOT associated with metabolic dysfunction associated fatty liver disease (MAFLD)? A. Smoking B. Elevated uric acid C. Overweight status D. Hypertension E. Elevated triglycerides
22	Proven and recommended 1st-line treatment for patients with compensated cirrhosis from MAFLD is: A. Liver transplant B. Bariatric surgery C. Vitamin E D. Weight loss E. Metformin
23	Assessment of MAFLD at primary care clinic includes all of the following except: A. Fibroscan B. FIB-4 assessment C. Liver biopsy D. Liver function test E. Fasting lipids

24	Which of the following is NOT a major cause of death among patients with MAFLD over the long term? A. Pancreatic cancer B. Hepatitis flares C. Cerebrovascular accident D. Acute myocardial infarct E. Heart failure
25	Which of the following is NOT a common abnormal laboratory marker in patients with MAFLD? A. Elevated uric acid B. Elevated triglycerides C. Elevated MCV D. Elevated GGT E. Elevated fasting glucose
26	The following are first-line tests in the assessment of suspected heart failure, EXCEPT: A. **Electrocardiogram (ECG**): important for identifying evidence of acute or prior myocardial infarction or acute ischaemia, as well as rhythm abnormalities such as atrial fibrillation B. **Chest x-ray**: characteristic findings are cardiac-to-thoracic width ratio above 50%, cephalisation of the pulmonary vessels, Kerley B-lines, and pleural effusions C. **Blood test**: Cardiac troponin (T or I), complete blood count, serum electrolytes, blood urea nitrogen, creatinine, liver function test and brain natriuretic peptide (BNP). BNP (or NT-proBNP) level adds greater diagnostic value to the history and physical examination than other initial tests mentioned above D. **Ambulatory blood pressure**: to determine overall mean blood pressure control and diurnal variability E. **Transthoracic Echocardiogram:** to determine ventricular function and haemodynamics
27	A 65-year-old gentleman with known chronic heart failure presents to your clinic with worsening shortness of breath. His current medication regimen comprises an ACE-inhibitor, beta blocker, and a loop diuretic. He has mild ankle oedema, an elevated jugular venous pressure, and bibasal crepitations. His blood pressure is 145/82 mmHg. Which of the following would be the next appropriate management? A. Add digoxin B. Add spironolactone C. Discontinue the beta blocker D. Discontinue the ACE-inhibitor E. Add rosuvastatin
28	A 67-year-old lady with stable reduced ejection fraction chronic heart failure presents to your clinic requesting a review of her medications. She has a history of ischaemic heart disease as a cause of her heart failure. She wants to reduce her pill burden. Which of the following medications has no proven mortality benefit? A. Entresto (sacubutril/valsartan)

	B. Nitrates and hydralazine C. Digoxin D. Spironolactone E. Bisoprolol
29	As a primary care physician, you refer your patient with suspected heart failure for a direct access transthoracic echo to determine the left ventricular ejection fraction (EF). Which of the following is the correct formula for calculating the EF? A. EF = [end systolic volume (ESV) − end diastolic volume (EDV)] ÷ EDV B. EF = [Heart rate (HR) × end diastolic volume (EDV)] ÷ end systolic volume (ESV) C. EF = [Heart rate (HR) × end systolic volume (ESV)] ÷ end diastolic volume (EDV) D. EF = [end diastolic volume (EDV) − end systolic volume (ESV)] ÷ EDV E. EF = [end diastolic volume (EDV) − end systolic volume (ESV)] ÷ Heart rate (HR)
30	Very common causes of decompensation in a stable patient with heart failure include all of the following except: A. Excess intake of sodium in the diet B. Inappropriate reduction in medications C. Lack of physical activity D. Lack of medication compliance E. Reduced intake of water

FPSC133 – 10 Readings
FPSC 133 – Sat 7th and Sun 8th March 2026, 2.00 pm – 5.30 pm (via Zoom)
A Selection of Ten
A Selection of 10 Readings on topics related to
Chronic Disease Management 2026
All are in Free Full Text
Selection of readings made by A/Prof Goh Lee Gan

READING 1 – EVALUATION OF IMPLEMENTATION OF AN INSULIN PATIENT DECISION AID

Tong WT(1)(2), Ng CJ(3)(4)(5), Lee YK(3), Lee PY(6). Evaluation of the implementation of an insulin patient decision aid for patients with type 2 diabetes in an academic primary care clinic in Malaysia: a mixed method study. BMC Health Serv Res. 2025 Mar 27;25(1):450. PMID: 40148948.

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ABSTRACT
BACKGROUND: Literature surrounding patient decision aid (PDA) focus on testing effectiveness such as measuring patient or practice outcomes, while few studies looked into evaluation of implementation outcomes. It is important to assess implementation outcomes because in order for PDA to deliver its intended effects, they should first be effectively implemented. This study aimed to evaluate the implementation of an insulin PDA in an academic primary care clinic specifically measuring implementation outcomes.

METHODS: A mixed-methods sequential explanatory design was used. This study was conducted at a primary care clinic in an academic hospital from April - November 2018. The insulin PDA was implemented using a tailored implementation intervention, which comprised of 11 strategies aiming to overcome 13 prioritised implementation barriers. Evaluation data were collected from: healthcare administrators such as the head of department, the clinic coordinator, and the nursing officer who oversees the clinic operations, doctors whose tasks were to deliver the insulin PDA to patients, nurses who were responsible for making sure the insulin PDAs were available, and patients with

type 2 diabetes who were offered the insulin PDA. The study commenced with the quantitative approach to assess 'Reach', 'Adoption', 'Implementation' and 'Maintenance'of the insulin PDA. Subsequently, qualitative approach was employed and qualitative interviews were conducted with the relevant stakeholders to explain the quantitative outcomes. A total of six IDIs and six FGDs were conducted with healthcare providers (healthcare policymakers: 3, doctors: 35, and staff nurses: 5), and 62 IDIs were conducted with patients.

RESULTS: For 'Reach', 88.9% (n = 48/54) of doctors and 55% (n = 11/20) of nurses attended the insulin PDA training workshops. This was attributed to their self-motivation and the mandate from the Head of Department. The PDA reached 387 patients and was facilitated by the doctors who delivered the PDA to them and their own desire to know more about insulin. Doctors' 'Adoption' of the PDA was high (83.3%, n = 45/54) due to the positive personal experience with the usefulness of the PDA. Only 65.7% (n = 94/143) of patients who received the PDA read it. The degree of 'Implementation' of the PDA varied for different tasks (ranged from 19.2 to 84.9%) and was challenged by patient and system barriers. For 'Maintenance', 80% of the doctors were willing to continue using the PDA due to its benefits.

CONCLUSION: This study highlighted that the implementation of an insulin PDA in a primary care setting is promising. Addressing the issues of social hierarchy, and healthcare providers' roles and responsibilities can further improve implementation outcomes.

READING 2 -- BENEFITS AND POTENTIAL RISKS OF METFORMIN ACROSS DIVERSE POPULATIONS, WITH A PARTICULAR EMPHASIS ON WOMEN IN THE PERIMENOPAUSAL PHASE.

Lim BSY(1), Chen M(2), Li HY(3), Li LJ(4)(5)(6)(7). Metformin use in prediabetes: A review of evidence and a focus on metabolic features among peri-menopausal women. Diabetes Obes Metab. 2025 Jun;27 Suppl 3(Suppl 3):3-15. PMID: 40329646.

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ABSTRACT

The prevalence of prediabetes has more than doubled over the past two decades. Although hormones associated with the menstrual cycle may offer some protection against diabetes by enhancing insulin sensitivity and suppressing gluconeogenesis, the prevalence of diabetes among women remains high at 10.5%. Notably, among the perimenopausal population, the prevalence catches up to-and even surpasses-that of men starting from the 70-74 age group, according to the 2021 International Diabetes Federation (IDF) report.

This narrative review examines the benefits and potential risks of metformin across diverse populations, with a particular emphasis on women in the perimenopausal phase. Metformin's interaction with hormonal regulation significantly influences both its therapeutic efficacy and long-term side effect profile, contributing to sex-specific differences in treatment response.

Consequently, its effectiveness varies among women at different stages of menopause, potentially due to differential impacts on inflammatory markers and modulation of the hypothalamic-pituitary-ovarian (HPO) and hypothalamic-pituitary-thyroid (HPT) axes.

Emerging evidence also highlights metformin's potential in managing conditions such as polycystic ovary syndrome (PCOS), breast tissue inflammation and endometrial disorders within this demographic.

Given these potential and multifaceted benefits, this review highlights the need for further randomized controlled trials (RCTs) to investigate metformin's role among perimenopausal and menopausal women and to better understand how menopausal status may influence its efficacy.

READING 3 – SARCOPENIA AND SARCOPENIC OBESITY IN CARDIOVASCULAR DISEASE

Tan LF(1)(2), Sia CH(2)(3), Merchant RA(2)(4). Sarcopenia and sarcopenic obesity in cardiovascular disease: a comprehensive review. Singapore Med J. 2025 Aug 1. PMID: 40759432.

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ABSTRACT

Sarcopenia is the loss of muscle strength, mass and function. It is often exacerbated by chronic comorbidities such as cardiovascular diseases (CVDs).

There is a bidirectional relationship between sarcopenia and CVD. Sarcopenia can lead to increased adiposity, insulin resistance and chronic inflammation, predisposing adults to developing cardiovascular events.

Chronic inflammation and decreased physical activity observed in cardiac patients can lead to accelerated muscle loss and the development of sarcopenia.

Sarcopenia is linked to faster CVD progression, higher mortality and reduced quality of life. The co-occurrence of obesity with sarcopenia is termed sarcopenic obesity (SO). This condition is associated with worse outcomes than either condition individually. Early detection is crucial, as interventions can slow or reverse sarcopenia and improve cardiovascular outcomes.

This review summarises evidence on the interplay between CVD and sarcopenia, discusses diagnostic approaches and management strategies, and identifies knowledge gaps for future research.

READING 4 – IS TYPE 2 DIABETES A MODIFIABLE RISK FACTOR OR CAUSATIVE FACTOR FOR HEART FAILURE WITH A PRESERVED EJECTION FRACTION (HFPEF) ?

Packer M(1), Lam CSP(2), Butler J(3), Zannad F(4), Vaduganathan M(5), Borlaug BA(6). Is Type 2 Diabetes a Modifiable Risk Factor for the Evolution and Progression of Heart Failure With a Preserved Ejection Fraction? J Am Coll Cardiol. 2025 Nov 18;86(20):1917-1931. PMID: 40960442.

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ABSTRACT

BACKGROUND: Type 2 diabetes is associated with an increased risk of heart failure with a preserved ejection fraction (HFpEF), but it is not clear whether this metabolic disorder is causal or represents a modifiable risk factor. Mechanisms by which diabetes may be associated with HFpEF can be grouped into the following: 1) those related to hyperglycemia and amenable to antihyperglycemic drugs; and 2) those related to the association of type 2 diabetes with obesity and visceral adiposity, and thus, treatable with interventions that reduce adipose tissue mass or improve adipocyte biology.

EVIDENCE AGAINST A ROLE FOR HYPERGLYCEMIA: Experimentally, acute and chronic hyperglycemia caused by islet cell destruction can lead to cardiac dysfunction, but these models resemble type 1 (not type 2) diabetes. Heightened levels of environmental glucose can cause enzymatic or nonenzymatic modification of proteins and signaling through the polyol pathway, but interference with these mechanisms has not produce clinical benefits in patients with heart disease and type 2 diabetes. Furthermore, lowering of blood glucose in type 2 diabetes with insulin, sulfonylureas, dipeptidyl peptidase-4 inhibitors and thiazolidinediones has not reduced the risk of heart failure.

EVIDENCE FOR A MEDIATING ROLE FOR ADIPOSITY: In marked contrast, experimental models that link type 2 diabetes to HFpEF are typically accompanied by excess adiposity. Epidemiological studies demonstrate that the association between type 2 diabetes and HFpEF is mediated primarily through a common link with central obesity and an expanded visceral fat mass. Changes in the biology of adipocytes as a result of visceral adiposity are sufficient to cause systemic insulin resistance and diabetes. Interestingly, the primary metabolic defect in the diabetic heart is lipid overload, not an impairment in glucose uptake or insulin resistance. Adiposity can promote HFpEF through the secretion of proinflammatory adipokines that lead to sodium retention and cardiac steatosis and fibrosis. Additionally, excess adiposity can drive the production of and enhance cardiac sensitivity to advanced glycation end products. Glucagon-like peptide receptor agonists and sodium-glucose cotransporter reduce the risk or progression of HFpEF, but this benefit is not related by the presence of diabetes or to the glucose-lowering effects of these drugs. Instead, their favorable cardiac effects may be mediated by their action to induce or mimic a state of caloric deprivation, thus restoring adipokine balance and alleviating the state of cardiac steatosis. Similarly, bariatric surgery alleviates both visceral adiposity and type 2 diabetes and reduces the risk of HFpEF.

CONCLUSIONS: Taken together, these findings suggest that diabetes-associated HFpEF is mediated primarily through its association with excess adiposity. Diabetes is a modifiable risk factor if treatment is directed toward adiposity rather than hyperglycemia. .

READING 5 – HIGHER PROPORTION OF DAYS COVERED (PDC) FOR ANY DM DRUG WAS ASSOCIATED WITH IMPROVED HBA1C RESULTS

Higher PDC for any DM drug and oral DM drugs during the observation period was significantly associated with clinically relevant HbA1c improvements.

Chan SL(1)(2), Yap CJQ(3), Xu Y(4), Chia SY(5), Mohamed Salim NNB(5), Lim DM(6), Choke E(7), Carmody D(8), Tan GCS(9), Goh SY(8), Bee YM(8), Chong TT(3). **Relationship between anti-diabetic medication use and glycaemic control: a retrospective diabetes registry-based cohort study in Singapore. BMJ Open. 2025 Sep 18;15(9):e098650. PMID: 40973363.**

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ABSTRACT

OBJECTIVE: This study aimed to determine the association between diabetes mellitus (DM) medication use and glycaemic control.

DESIGN: This was a retrospective diabetes registry-based cohort study.

SETTING: Singapore.

PARTICIPANTS: Patients aged 18 and above with incident DM in the SingHealth Diabetes Registry from 2013 to 2020 were included. The entire study period included a 1 year baseline period, a 1 year observation period and a 3 month outcome period.

OUTCOME MEASURES: Drug use was measured using the proportion of days covered (PDC), and the changes in glycated haemoglobin (HbA1c) between the outcome and baseline periods were assessed. The associations between baseline HbA1c and PDC ≥0.80 and between PDC and change in HbA1c were analysed using logistic regression and the Kruskal-Wallis test, respectively.

RESULTS: Of 184 646 unique patients in the registry from 2013 to 2020, 36 314 met the inclusion and exclusion criteria and were included in the analysis. The median PDC for any DM drug, oral DM drugs and insulin during the observation period was 20.3%, 16.8% and 0%, respectively. Those who had good glycaemic control at baseline were less likely to receive DM drugs and those with poor baseline glycaemic control or

missing baseline HbA1c were more likely to be consistent users (PDC >80%) (p<2.2 × 10-16).

CONCLUSION: The relationship between DM drug use and glycaemic control is complex and non-monotonic. Higher PDC for any DM drug and oral DM drugs during the observation period was significantly associated with clinically relevant HbA1c improvements.

READING 6 -- INDIVIDUAL EMPOWERMENT, IN PARTNERSHIP WITH COMMUNITY AND HEALTHCARE PROVIDERS AND SUPPORTED BY RESEARCH AND INNOVATION OF CARE DELIVERY, IS KEY TO BUILDING A HEALTHIER AND STRONGER NATION.

Khoo J(1)(2), Lim RLC(3), Ng LP(3), Phoon IKY(3), Gani L(1), Puar THK(1)(2), How CH(2)(4), Loh WJ(1)(2). Metabolic health and strategies for a Healthier SG. Singapore Med J. 2025 Oct 1;66(Suppl 1):S30-S37. PMID: 41090312.

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ABSTRACT
This review examines strategies for the prevention and management of obesity, hypertension, type 2 diabetes mellitus and dyslipidaemia, conditions that are increasing in Singapore, as components of individualised health plans in 'Healthier SG' and beyond. We describe cardiometabolic disease prevention and management initiatives in Changi General Hospital (CGH), including collaborations with SingHealth Polyclinics, Active SG, Exercise is Medicine Singapore and community partners in the Eastern Community Health Outreach programme, and highlight advances in curable hypertension (e.g., primary hyperaldosteronism) and novel cardiovascular risk markers such as lipoprotein(a).

We also outline technology-based interventions, notably the CGH Health Management Unit, which demonstrate the utility and convenience of telemedicine, and digital therapeutics in the form of apps that have been shown to improve treatment adherence and clinical outcomes.

Individual empowerment, in partnership with community and healthcare providers and supported by research and innovation of care delivery, is key to building a healthier and stronger nation.

READING 7 – FITTERLIFE (A COMMUNITY-BASED VIRTUAL WEIGHT MANAGEMENT PROGRAMME FOR OVERWEIGHT ADULTS) WAS EFFECTIVE IN ACHIEVING CLINICALLY SIGNIFICANT SHORT-TERM WEIGHT LOSS IN A REAL-WORLD SETTING.

Ge L(1), Lim FS(2), Lin S(3), Molina JAC(1), Pereira MJ(1), Manohari A(1), Tan D(2), Tan E(3). Effectiveness of FitterLife: A Community-Based Virtual Weight Management Programme for Overweight Adults. Nutrients. 2025 Dec 19;18(1):17. PMID: 41515134

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ABSTRACT

Background: The high prevalence of overweight and obesity in Singapore necessitates scalable primary prevention strategies. This study evaluated the short-term effectiveness of FitterLife, a 12-week, digitally delivered, group-based behavioural weight management programme targeting at-risk adults without diabetes or hypertension in the community.

Methods: In a retrospective matched cohort study, we compared 306 FitterLife participants (enrolled from October 2021 to January 2025) with 5087 controls identified from a population health data mart, matched on age, sex, ethnicity, and baseline body mass index (BMI). The primary outcome was achieving ≥5% weight loss or a ≥1 kg/m2 BMI reduction at 12 weeks. Programme effectiveness was analysed using propensity score matching (1:1) and inverse probability weighted regression. Mixed-effects models assessed weight/BMI trajectories and modified Poisson regression identified behavioural factors associated with success.

Results: After matching, FitterLife participants were more likely to achieve the weight loss target than controls (45.7% vs. 13.7%, coefficient = 0.32, 95% confidence interval [CI]: 0.26-0.38) and were over three times as likely to succeed (Adjusted incidence rate ratio [aIRR] = 3.37, 95% CI: 2.87-3.93). The programme group showed significant reductions in weight (-2.23 kg, 95% CI: -2.57 to -1.90) and BMI (-0.86 kg/m2, 95% CI: -0.95 to -0.73) at the end of programme. Higher session attendance and improved behavioural factors were associated with success.

Conclusions: FitterLife was effective in achieving clinically significant short-term weight loss in a real-world setting. The findings demonstrate the potential of a scalable, behavioural theory-informed, virtual group model as a viable primary prevention strategy within national chronic disease management efforts.

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READING 8 -- ALBUMINURIA EMERGED AS AN IMPORTANT PREDICTOR OF FRACTURE RISK. ESPECIALLY IN NON-OBESE INDIVIDUALS.

Xiong X(1)(2)(3)(4), Lui DTW(5)(6), Ju C(3), Liu X(2)(7), Wei L(2)(3)(8), Chandran M(6)(9)(10), Wong CKH(2)(11)(12). Associations of Albuminuria and Metabolic Syndrome Traits With Fracture Risk in Patients With Type 2 Diabetes: A Population-Based Cohort Study. J Cachexia Sarcopenia Muscle. 2026;17(1):e70215. PMID: 41630354

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ABSTRACT

BACKGROUND: Type 2 diabetes is associated with an increased risk of fragility fractures. While obesity may protect against fractures, individuals with type 2 diabetes often exhibit other metabolic syndrome (MetS) traits and albuminuria. We evaluated their roles and synergistic implications on incident fractures, stratified by obesity status.

METHODS: Patients with type 2 diabetes were identified from territory-wide electronic health records in Hong Kong (2000-2018). MetS-related traits included albuminuria and individual MetS traits (obesity, hypertension, low HDL-cholesterol and hypertriglyceridemia). Outcomes were hip and major osteoporotic fractures (MOF). Patients were followed until fracture, death or 31 December 2020. Adjusted hazard ratios (aHRs) were estimated using multivariable Cox models.

RESULTS: Among 165 289 patients with type 2 diabetes (median age: 60.0 years; 54.2% men), 1583 (0.96%) experienced hip fractures, and 3393 (2.05%) had MOF over a

median follow-up of 5.3 years. Albuminuria was the strongest risk factor for hip fractures (obese: aHR 1.33, 95% CI 1.11-1.60; non-obese: 1.54, 1.33-1.78) and MOF (obese: 1.13, 1.01-1.26; non-obese: 1.28, 1.15-1.43). Hypertension was a significant risk factor only in non-obese patients. In the non-obese group, each additional MetS-related trait was associated with an increased risk of hip fracture and MOF. When stratified by diabetes duration, albuminuria remained a significant risk factor across different diabetes durations, while suboptimal glycaemic control became a significant risk factor particularly when diabetes duration ≥ 5 years.

CONCLUSIONS: In this large population-based cohort of patients with type 2 diabetes predominantly of Asian descent from Hong Kong, albuminuria emerged as an important predictor of fracture risk. MetS traits compound this risk, especially in non-obese individuals. These findings could be instrumental in shaping screening initiatives for fracture risk optimization in type 2 diabetes.

READING 9 -- NO STATISTICALLY SIGNIFICANT DIFFERENCE IN THE RISK OF CARDIOVASCULAR EVENTS WAS OBSERVED IN PEOPLE WITH CHRONIC KIDNEY DISEASE WHO WERE NEWLY PRESCRIBED FEBUXOSTAT COMPARED WITH THOSE NEWLY TREATED WITH ALLOPURINOL.

Inoue R(1), Yamaguchi S(1), Okada A(1), Yamauchi T(2), Kadowaki T(1)(2)(3), Nangaku M(4). Allopurinol Versus Febuxostat Use and the Risk of Cardiovascular Disease in People With Chronic Kidney Disease: A New-User Active Comparator Cohort Study. Nephrology (Carlton). 2025 Nov;30(11):e70149. PMID: 41262068

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ABSTRACT
AIM: Hyperuricaemia, a common comorbidity among people with chronic kidney disease, is widely treated with uric acid-lowering agents such as allopurinol and febuxostat. Cardiovascular outcomes of people with chronic kidney disease receiving allopurinol or febuxostat have been controversial. The present study evaluated the risk of cardiovascular events associated with allopurinol or febuxostat treatment in people with chronic kidney disease.

METHODS: We conducted a new-user active comparator cohort study using a nationwide insurance claims database in Japan. Individuals with an estimated glomerular filtration rate < 60 mL/min/1.73 m2 who were newly prescribed allopurinol or febuxostat were included. The primary outcome was a composite of cardiovascular events, including fatal and non-fatal acute myocardial infarction, fatal and non-fatal

stroke, and all-cause death. Hazard ratios were estimated using a multivariate Cox regression model. A sensitivity analysis was performed using an inverse probability of treatment weighting (IPTW) Cox regression model. RESULTS: A total of 1673 and 7805 individuals were included in the allopurinol and febuxostat treatment groups, respectively. The febuxostat group had a similar incidence of the composite outcome as the allopurinol group (hazard ratio 0.93, 95% confidence interval: 0.79-1.08, p = 0.33). The hazard ratio for febuxostat compared with allopurinol treatment did not vary across different estimated glomerular filtration rate levels. The sensitivity analysis using IPTW showed similar results.

CONCLUSION: In conclusion, no statistically significant difference in the risk of cardiovascular events was observed in people with chronic kidney disease who were newly prescribed febuxostat compared with those newly treated with allopurinol.
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READING 10 – TREATMENT WITH DAPAGLIFLOZIN RESULTED IN A HIGHER PROPORTION OF PARTICIPANTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) IMPROVEMENT

Lin J(1)(2)(3)(4), Huang Y(5)(3)(4), Xu B(1)(2)(3)(4), Gu X(6), Huang J(1)(2)(3)(4), Sun J(7), Jia L(8), He J(9)(10), Huang C(1)(2)(3)(4), Wei X(1)(2)(3)(4), Chen J(11), Chen X(12), Zhou J(13), Wu L(14), Zhang P(15)(2)(3)(4), Zhu Y(8), Xia H(6), Wen G(16), Liu Y(1)(2)(3)(4), Liu S(1), Zeng Y(1), Zhou L(1), Jia H(1), He H(17), Xue Y(1), Wu F(1), Zhang H(15)(2)(5)(3)(4). **Effect of dapagliflozin on metabolic dysfunction-associated steatohepatitis: multicentre, double blind, randomised, placebo controlled trial. BMJ. 2025 Jun 4;389:e083735. PMID: 40467095.**

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ABSTRACT

OBJECTIVE: To assess the efficacy and safety of the sodium-glucose cotransporter 2 inhibitor dapagliflozin in participants with metabolic dysfunction-associated steatohepatitis (MASH).

DESIGN: Multicentre, double blind, randomised, placebo controlled trial.

SETTING: Six tertiary hospitals in China from 23 November 2018 to 28 March 2023.

PARTICIPANTS: 154 adults with biopsy diagnosed MASH, with or without type 2 diabetes.

INTERVENTIONS: All participants were randomly assigned to receive 10 mg orally of dapagliflozin or matching placebo once daily for 48 weeks.

MAIN OUTCOME MEASURES: The primary endpoint was MASH improvement (defined as a decrease of at least 2 points in non-alcoholic fatty liver disease activity score (NAS) or a NAS of ≤3 points) without worsening of liver fibrosis (defined as without increase of fibrosis stage) at 48 weeks. The secondary endpoints included the MASH resolution without worsening of fibrosis and fibrosis improvement without worsening of MASH. Analyses used the intention-to-treat dataset. RESULTS: MASH improvement without worsening of fibrosis was reported in 53% (41/78) of participants in the dapagliflozin group and 30% (23/76) in the placebo group (risk ratio 1.73 (95% confidence interval (CI) 1.16 to 2.58); P=0.006). Mean difference of NAS was -1.39 (95% CI -1.99 to -0.79); P<0.001). MASH resolution without worsening of fibrosis occurred in 23% (18/78) of participants in the dapagliflozin group and 8% (6/76) in the placebo group (risk ratio 2.91 (95% CI 1.22 to 6.97); P=0.01). Fibrosis improvement without worsening of MASH was reported in 45% (35/78) of participants in the dapagliflozin group, as compared with 20% (15/76) in the placebo group (risk ratio 2.25 (95% CI 1.35 to 3.75); P=0.001). The percentage of individuals who discontinued treatment because of adverse events was 1% (1/78) in the dapagliflozin group and 3% (2/76) in the placebo group.

CONCLUSION: Treatment with dapagliflozin resulted in a higher proportion of participants with MASH improvement without worsening of fibrosis, as well as MASH resolution without worsening of fibrosis and fibrosis improvement without worsening of MASH, than with placebo.