

A low-carbohydrate diet in place of SGLT2i therapy in a patient with diabetic cardiomyopathy

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Summary

In patients with diabetes mellitus, the toxic milieu caused by abnormal glucose and free fatty acid handling can lead to heart failure (HF). Referred to as diabetic cardiomyopathy (DMCM), this syndrome often exists in the absence of conventional risk factors for HF such as history of myocardial infarction or hypertension. Low-carbohydrate diets (LCDs) have recently been endorsed as an efficacious therapeutic dietary approach to prevent and reverse cardiometabolic disease including type 2 diabetes mellitus (T2DM). LCDs improve systemic insulin resistance (IR), reverses cardiac remodelling in a rodent model and downregulates the expression of sodium-glucose co-transporter 2 (SGLT2) receptors in the kidney. It is therefore conceivable that a lifestyle approach such as adopting an LCD can be offered to patients with DMCM. The reported case is that of a 45-year-old man with a 15-year history of non-ischaemic cardiomyopathy, T2DM and obesity. The patient volunteered to engage in a 16-week low-carbohydrate dietary intervention trial and then self-selected to remain on this diet for 1 year. The whole-food LCD was based on simple 'traffic light' style food lists and not designed to restrict calories, protein, fat or salt. After 1 year, the patient had lost 39 kg and his cardiometabolic markers had significantly improved. LCDs present a potentially beneficial approach for patients with DMCM and could be considered as a lifestyle intervention before SGLT2i therapy is commenced.

Learning points

- Diabetic cardiomyopathy (DMCM) is a syndrome precipitated mainly by the detrimental effects of glucose metabolism disorders such as insulin resistance and diabetes.
- Low-carbohydrate diets (LCD) mimic many effects of sodium-glucose co-transporter 2 inhibitors (SGLT2i).
- LCDs are a dietary pattern which can have significant and beneficial effects on metabolic and anthropometric markers in patients with DMCM.
- LCDs and SGLT2i therapy could be combined and may achieve better clinical outcomes for patients with DMCM.
- Combination therapy may be carried out under close supervision as the real risk for diabetic ketoacidosis remains.



Background

Type 2 diabetes mellitus (T2DM) and heart failure (HF) commonly coexist in a syndrome termed diabetic cardiomyopathy (DMCM). The pathophysiology of DMCM is complex, and a detailed description, which is beyond the scope of this case report, can be found elsewhere (1, 2, 3). DMCM is defined by left ventricular hypertrophy and dysfunction occurring independent of established coronary artery or valvular disease and hypertension (4). Glucose metabolism disorders such as diabetes and insulin resistance (IR) create a mismatch in myocardial energy supply, which is the typical feature associated with DMCM pathogenesis (1, 2, 3). This cause-and-effect relationship is significant, as the reversal of IR suggests therapeutic potential. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are able to improve the broken energy metabolism in DMCM by modulating glucose metabolism and prioritising free fatty acid (FFA) utilisation (5). Further, SGLT2i decrease disease-specific symptom burden and hospitalisations; however, SGLT2i can have serious side effects, such as urogenital infections and increased risk of lower limb amputations (6). Recent reviews indicate that SGLT2i-like effects can be achieved with low carbohydrate diets (LCDs) (7), the former by excreting glucose through the kidney, the latter by avoiding carbohydrate in the diet (8). These findings propose a place for LCDs as an alternative to SGLT2i treatment for patients who are intolerant or have made an autonomous decision to trial lifestyle intervention prior to medical therapy. Currently, these drugs and LCDs are not recommended in combination, with the rationale being the increased risk of diabetic ketoacidosis (DKA), a life-threatening metabolic emergency (9). Based on this evidence, we present the case of a patient with DMCM who declined SGLT2i medication and instead engaged in an LCD for 1 year.

Case presentation

A 45-year-old information technology specialist with non-ischaemic cardiomyopathy and T2DM self-selected to continue an LCD after he was first enrolled in a 16-week randomised controlled trial investigating the effect of an LCD compared to usual care on HF symptoms and quality of life (QoL) in February 2022 (10). The patient was first diagnosed with DMCM in October 2021 when he presented with laboratory findings of T2DM (fasting blood glucose levels over 20 mmol/L and a glycosylated haemoglobin (HbA1c) of 7.9% (63 mmol/mol)) and mild

signs of heart failure. In addition to DMCM, the patient had prior diagnoses of right heart failure secondary to a massive pulmonary embolism requiring thrombolysis, obstructive sleep apnoea, a transient ischaemic attack, hypertension and obesity. Medications taken at the time of study enrolment included atorvastatin 20 mg, furosemide 40 mg, spironolactone 25 mg, bisoprolol 5 mg, irbesartan 75 mg, metformin 500 mg and lifelong warfarin 7 mg daily. Anthropometric measurements were height 186 cm, weight 236 kg, body mass index (BMI) 68.2 kg/m². An assessment undertaken as part of a nurse practitioner HF clinic appointment showed mild peripheral oedema. The patient denied orthopnoea, paroxysmal nocturnal dyspnoea, chest pain and/or palpitations during this consultation. He was assessed as New York Heart Association (NYHA) class III. The patient disclosed a long history of frequent dieting. When first diagnosed with non-ischaemic cardiomyopathy in 2008 he was able to lose 135 kg with the help of OPTIFAST™ shakes. The shake diet was not sustainable for the patient; therefore, long-term weight loss was not achieved. His hobby as an instructor at a recreational facility, which requires him to walk frequently, was compromised by his ability to only mobilise 500–750 m. In February 2022, he was offered an SGLT2i (dapagliflozin 10 mg daily) but declined the medication, as SGLT2i therapy was an exclusion criterion for enrolment into the 16-week LCD trial, which the patient wished to commence. He was able to continue all other medication for the duration of the trial, pending ongoing routine HF clinic reviews.

Investigation

Baseline biochemical parameters before commencement of the LCD are described in Table 1. Pancreatic insulin reserve by means of C-peptide was not established. A Doppler echocardiogram revealed normal valve morphology.

Treatment

The LCD intervention of the initial 16-week clinical trial was developed with the help of an expert dietitian and nutritionist in line with the clinical guidelines for therapeutic carbohydrate restriction (11), the details of which have been previously published (10). In brief, the trial participants were encouraged to eat a whole-food diet including a variety of above-ground and green leafy vegetables, small quantities of fruit and legumes, nuts and seeds. Different kinds of plant and animal protein (eggs, meat, fish, tofu, tempeh) were suggested to be

Table 1 Change and comparison of clinical and biochemical measures over time.

	Baseline	1 year
Weight (kg)	236	197
BMI	68.2	56.9
Systolic blood pressure (mm Hg)	135	129
Diastolic blood pressure (mm Hg)	72	71
Fasting blood glucose levels (mmol/L)	7.6	5.4
HbA1c (%) (mmol/mol)	6.7 (50)	5.6 (38)
Triglycerides (mmol/L)	3	1.9
Total cholesterol (mmol/L)	3.5	3.2
LDL cholesterol (mmol/L)	1.4	1.5
HDL cholesterol (mmol/L)	0.8	0.8
Estimated LVEF (%)*	45	51
Average E/e' ratio*	6.2	6

BMI, body mass index; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction.

*Serial echocardiograms were performed by different technicians and reported by different medical officers, which may introduce reporting and/or user errors.

consumed *ad libitum*. Dietary fat, salt and calories were not restricted. Participants engaged in the diet with the help of 'traffic light' food lists on which foods

and drinks were categorised into always/everyday (green list), sometimes (orange list) and avoid (red list). The level of engagement was assessed with the help of food frequency questionnaires and 3-day food recalls. Participants received a total of nine LCD education sessions throughout the 16-week study intervention period which focused on improving nutrition literacy and the implementation of long-lasting change. At the end of the 16-week trial, the patient had undergone significant behavioural change and decided to continue with the diet without supervision. Table 2 illustrates an abbreviated version of the traffic light food lists and additional advice given to participants during the 16-week RCT.

Outcome and follow-up

The patient engaged in the LCD for over 1 year. He reported that for celebrations, such as birthdays or Christmas he enjoyed 'a day off the LCD' but would usually return to an LCD eating pattern within the next couple of days. During the 16 weeks of the LCD trial the patient was able to lose 30 kg (12.7% of body weight)

Table 2 Abbreviated version of the low-carbohydrate diet food lists*, including additional advice given to the patient.

Always	Sometimes**	Avoid	Additional advice given
Green leafy vegetables	Cashew nuts	Baked beans	Do not count calories
Cruciferous vegetables (broccoli, cauliflower, celery, brussels sprouts)	Fruits (apple, banana, kiwifruit, peach, pear, pineapple)	Sweeteners (agave, aspartame, date sugar, maple syrup, corn syrup, sorbitol)	Only eat when hungry (intermittent fasting is encouraged)
Above-ground vegetables (green beans, cucumber, eggplant)	All berries	Any flours/grains: corn, wheat, rye, potato, oatmeal	Prioritise protein
Sauerkraut	Mussels	Low fat dairy	Do not restrict salt
Seaweed	Honey	Condensed milk	Do not snack between meals
Pumpkin (Jap, Kent, Grey)	Beetroot	Ice cream	Be careful with dairy
Garlic	Carrot	Flavoured yoghurt	
Horseradish	Corn (fresh)	Rice/soy/oat milk	
Ginger	Parsnip	Margarine, vegetable oils	
Onion	Potato (including sweet potato)	Soft drinks	
Avocado	Chickpeas	Cordials	
Tomato	Lentils	Energy drinks	
Olives	Soybeans	Fruit juices	
Almonds	Melon	Pasta	
Coconut	Chestnut	Rice	
Eggs	Kidney beans	Breakfast cereals (all)	
Full-fat dairy and cheese	Tomato (semi-/sun-dried)	Premade sauces (barbeque sauce)	
Fish – fresh and tinned	Artichoke	Commercial salad dressings	
Prawns	Fig (fresh)	Cold processed meats	
Meat (beef, pork, venison, mutton, lamb, offal, all poultry, kangaroo)		Take-away foods (burgers, pizza, crumbed meat, sushi, noodles)	
Butter		Alcohol (beer, cider, spirits)	
Pure black coffee, tea, water		All dried fruit	

*Food lists adapted with permission from The Noakes Foundation (<http://www.thenoakesfoundation.org>).

**Only one serving to be consumed per day of one (1) food from the list; servings further defined for the patient.

and achieved normalisation of blood glucose levels and diabetes remission (Fig. 1). Renal and hepatic function remained stable throughout. After 1 year of follow-up, the patient had lost an additional 9 kg and remained free of diabetes. Follow-up Doppler echocardiogram showed an left ventricular ejection fraction of 51%, and NYHA was II. The changes and a comparison of clinical and biochemical measures over time are outlined in Table 1. After specialist review, the patient was able to decrease the Lasix dose from 40 mg daily to 20 mg daily. The warfarin dose had to be increased to 9 mg/day from the initial 7 mg/day, likely due to an increase in dietary vitamin K intake on the LCD.

Discussion

The toxic effects of glucose and FFA on the myocardium are a hallmark of DMCM. This energetic crisis can be successfully targeted with SGLT2i, which increase urinary sodium and glucose excretion and in doing so improves blood pressure, glycaemic control and enhances ketone production (5). Significantly, many of the energetic changes seen with SGLT2i can also be achieved with an LCD, where minimal sugar and/or starch is ingested, hence glucolipotoxicity is reduced. Both SGLT2i and LCDs create a metabolic state which mimics fasting and so promote nutrient deprivation signalling characterised by ketogenesis, reduced generation of reactive oxygen species and improved cellular (including myocardial) survival (12). In recent literature, there

is limited experimental evidence to corroborate the findings of our case study; however, clinical trials evaluating the outcomes of an LCD in HF in the absence of SGLT2i have been registered on several clinical trial registration platforms and results are pending.

The risk of (euglycaemic) DKA when combining SGLT2i and an LCD is documented in the literature and physicians should exercise caution before recommending LCDs to patients who are treated with SGLT2i therapy (13). For this reason, the patient described in this case report was given the choice between starting on the LCD or commencing SGLT2i therapy. Notably, new research has emerged proposing beneficial synergistic, rather than adverse effects, when combining SGLT2i therapy with an LCD. Kusakabe *et al.* (14) investigated the effects of Canagliflozin therapy (a class of SGLT2i) and an LCD on metabolic health in an obesity and T2DM mouse model (*db/db* mice). Six-week-old *db/db* mice were randomised into four groups: 1) normal diet (ND), 2) ND plus Canagliflozin (CANA); 3) LCD; and 4) LCD plus CANA. The authors observed that mice fed either an ND or LCD plus CANA demonstrated sustained lowered serum glucose levels. IR (as measured by Morinaga Ultra Sensitive Mouse Insulin ELISA kit) improved only in mice subjected to LCD feeds in combination with CANA but worsened in mice post CANA administration alone. Interestingly, both LCD and CANA individually but also LCD and CANA combined feeding conditions led to significantly improved plasma total cholesterol levels compared to the ND arm ($P < 0.05$). Lastly, the LCD was

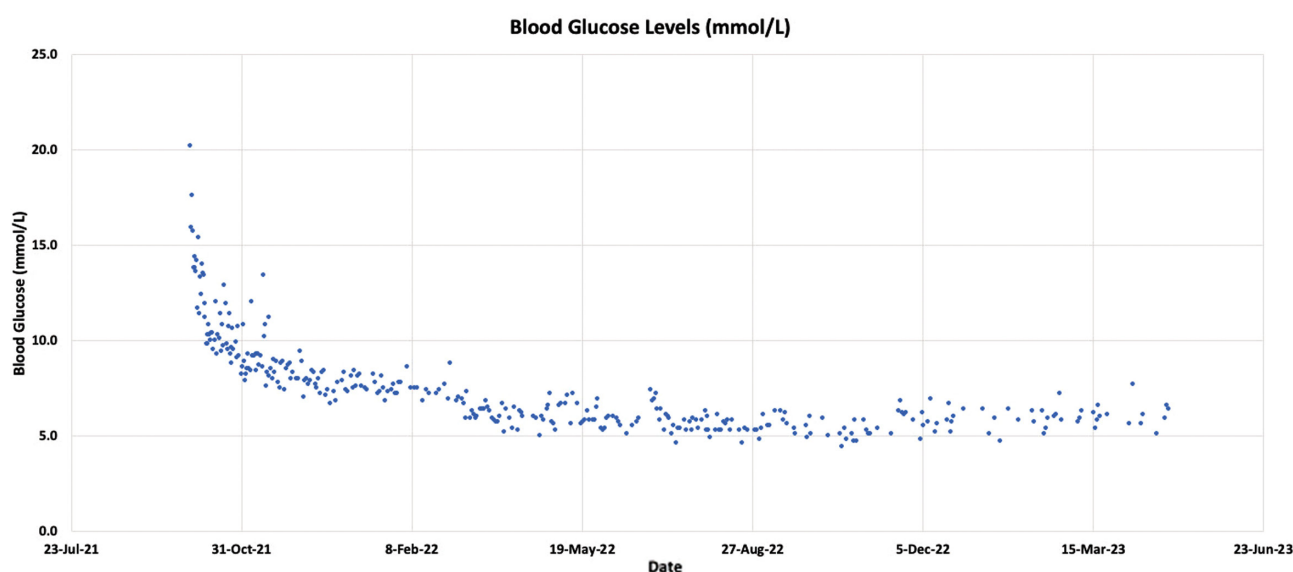


Figure 1
Blood glucose levels over time.

able to improve fatty liver, while CANA alone did not address liver lipid accumulation. Kusakabe *et al.* (14) concluded that combining the LCD with SGLT2i therapy may be superior for the management of T2DM and obesity than SGLT2i alone. Although mice share a large percentage (92%) of human genes, they differ from us in terms of gut microbiota and xenobiotic metabolism. As such results from rodent models should be interpreted with caution.

Of interest are also results of a human study. In the DAPA-DIET study, a 12-month cohort study in a secondary care setting, Hanson *et al.* (15) explored the effect of dapagliflozin combined with an LCD on weight loss, energy expenditure and appetite in patients with T2DM and obesity. The authors found that the combination therapy of SGLT2i and LCD led to significant and substantial weight loss, and reduced serum leptin levels in study participants. Intriguingly, Hanson *et al.* (15) suggested that the LCD intervention may curb carbohydrate cravings often associated with SGLT2i therapy, which may help to optimise sustainable weight loss.

Two factors seem to predispose patients on a combination of LCD and SGLT2i to develop DKA: Insulinopenia and/or dehydration (13). In addition to this, the amount of ingested carbohydrate may also play an important role in the development of this metabolic emergency. LCDs greatly reduce serum insulin levels thus may trigger DKA. For this reason, LCDs rather than a ketogenic diet should be recommended for patients who wish to engage in a carbohydrate restriction dietary approach but also want to continue SGLT2i therapy. In the DAPA-diet study, participants consumed approximately 100 g of carbohydrate/per day while on the LCD, whereas ketogenic diets recommend the intake of 50 g or less of dietary carbohydrate (11). While the authors acknowledged the possible risk of DKA to the patients, no adverse events were observed throughout the study period.

In summary, we propose here that an LCD can mimic SGLT2i therapy in a patient with DMCM. SGLT2i and LCDs share analogous mechanisms of action leading to weight loss, improved glycaemic control, and diuresis. Well-formulated, whole-food-based LCDs present a nutrient-replete dietary approach that can be safely offered to patients with DMCM. For both LCDs and SGLT2i therapy, compliance with treatment is key to beneficial outcomes, and patients may express preference for one therapeutic avenue over the other. While it may be difficult for patients to engage in an LCD all

the time, patients may also have to cease SGLT2i due to surgical procedures or illness. Results from clinical trials continue to highlight the profound benefits of SGLT2i, however these drugs have side effects and patients may be intolerant. Dietary trials investigating the effects of LCDs on HF outcomes should now be undertaken so that LCDs can be offered to patients who are unable or prefer not to take SGLT2i. LCDs not only offer a healthy lifestyle option but allow patients to regain control over their health and clinical care, which may promote self-efficacy and improve health outcomes (16). It is possible, that SGLT2i and LCDs can be administered in combination provided this is explored under tight supervision and clinical guidance. An option which could also be explored with the patient in this report.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the case study reported.

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Patient consent

Written informed consent for publication of their clinical details was obtained from the patient after full explanation of the purpose and nature of the article.

Patient's perspective

I wish to thank the researchers for allowing me to participate in the trial which introduced me to the low carb diet. At the time of being accepted I was still relatively recently diagnosed with type 2 diabetes and was still learning what an appropriate diet consisted of. Since reviewing my blood sugar levels from before I started the diet there has been a significant consistent change with an average of a 2 mmol/L decrease. From a well-being perspective, I have seen a significant improvement in general well-being, I'm able to exercise for longer periods of time before feeling short of breath (100 m vs a few kilometres now) and feeling less lethargic. From my most recent echo, there has also been a significant improvement with heart function. I did find the change in diet a challenge to begin with as being of European descent, breads and pastas do make up a significant portion of my food intake. What I have found interesting is there are alternatives available with no or low carb content. This trial has also made me more aware of the hidden carbs/sugars that exist in the normal foods that I would normally consume. I have decided to try to continue on with the traffic light style food list as I personally see an improvement in my health.

Author contribution statement

SK-M was responsible for the review of patient data and writing of the original draft. AD, BR, AO and CZ all provided the supervision, critical

feedback and support to shape the manuscript for this case report. All authors and the patient read and approved the final version of the manuscript.

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References

- 1 Parim B, Sathibabu Uddandao VV & Saravanan G. Diabetic cardiomyopathy: molecular mechanisms, detrimental effects of conventional treatment, and beneficial effects of natural therapy. *Heart Failure Reviews* 2019 **24** 279–299. (<https://doi.org/10.1007/s10741-018-9749-1>)
- 2 Yang CD, Pan WQ, Feng S, Quan JW, Chen JW, Shu XY, Aihemaiti M, Ding FH, Shen WF, Lu L, *et al.* Insulin resistance is associated with heart failure with recovered ejection fraction in patients without diabetes. *Journal of the American Heart Association* 2022 **11** e026184. (<https://doi.org/10.1161/JAHA.122.026184>)
- 3 Nakamura K, Miyoshi T, Yoshida M, Akagi S, Saito Y, Ejiri K, Matsuo N, Ichikawa K, Iwasaki K, Naito T, *et al.* Pathophysiology and treatment of diabetic cardiomyopathy and heart failure in patients with diabetes mellitus. *International Journal of Molecular Sciences* 2022 **23** 3587. (<https://doi.org/10.3390/ijms23073587>)
- 4 Paolillo S, Marsico F, Prastaro M, Renga F, Esposito L, De Martino F, Di Napoli P, Esposito I, Ambrosio A, Ianniruberto M, *et al.* Diabetic cardiomyopathy: definition, diagnosis, and therapeutic implications. *Heart Failure Clinics* 2019 **15** 341–347. (<https://doi.org/10.1016/j.hfc.2019.02.003>)
- 5 Wang X, Ni J, Guo R, Li L, Su J, He F & Fan G. SGLT2 inhibitors break the vicious circle between heart failure and insulin resistance: targeting energy metabolism. *Heart Failure Reviews* 2022 **27** 961–980. (<https://doi.org/10.1007/s10741-021-10096-8>)
- 6 Pittampalli S, Upadyayula S, Mekala HM & Lippmann S. Risks vs benefits for SGLT2 inhibitor medications. *Federal Practitioner* 2018 **35** 45–48.
- 7 Murray SW, Mckelvey S, Heseltine TD, Henderson G, Singh J, Unwin D & Brady AJB. The “discordant doppelganger dilemma”: SGLT2i mimics therapeutic carbohydrate restriction - food choice first over pharma? *Journal of Human Hypertension* 2021 **35** 649–656. (<https://doi.org/10.1038/s41371-021-00482-y>)
- 8 Chasis H, Jolliffe N & Smith HW. The action of phlorizin on the excretion of glucose, xylose, sucrose, creatinine and urea by man. *Journal of Clinical Investigation* 1933 **12** 1083–1090. (<https://doi.org/10.1172/JCI100559>)
- 9 Cucuzzella M, Riley K & Isaacs D. Adapting medication for type 2 diabetes to a low carbohydrate diet. *Frontiers in Nutrition* 2021 **8** 688540. (<https://doi.org/10.3389/fnut.2021.688540>)
- 10 Kleissl-Muir S, Zinn C, Rasmussen B, Owen A & Driscoll A. Low carbohydrate diet for diabetic cardiomyopathy: protocol for a randomised controlled trial. *Journal of Insulin Resistance* 2022 **5** 1–8. (<https://doi.org/10.4102/jir.v5i1.73>)
- 11 Hite AH, Cavan D, Cywes R, Ede G, Fettke G, Lenkes B, Noakes TD & Scher B. Schpritzler F, Westman EC & Yancy WS Jr. Clinical guidelines for therapeutic carbohydrate restriction. *LowCarb USA*, pp. 1–20 2019. Available at: <https://www.lowcarbusa.org/clinical-guidelines/>
- 12 Packer M. Critical reanalysis of the mechanisms underlying the cardiorenal benefits of SGLT2 inhibitors and reaffirmation of the nutrient deprivation signaling/autophagy hypothesis. *Circulation* 2022 **146** 1383–1405. (<https://doi.org/10.1161/CIRCULATIONAHA.122.061732>)
- 13 Mistry S & Eschler DC. Euglycemic diabetic ketoacidosis caused by SGLT2 inhibitors and a ketogenic diet: a case series and review of literature. *AACE Clinical Case Reports* 2021 **7** 17–19. (<https://doi.org/10.1016/j.aace.2020.11.009>)
- 14 Kusakabe T, Yokota S, Shimizu M, Inoue T, Tanaka M, Ohue-Kitano R, Muranaka K, Yamakage H, Wada H, Hasegawa K, *et al.* Differential effects of sodium-glucose cotransporter 2 inhibitor and low-carbohydrate diet on body composition and metabolic profile in obese diabetic db/db mice. *BMJ Open Diabetes Research and Care* 2020 **8** 1–11. (<https://doi.org/10.1136/bmjdr-2020-001303>)
- 15 Hanson P, Randeve H, Cuthbertson DJ, O'Hare PJ, Parsons N, Chatha K, Reidy G, Weickert MO & Barber TM. The DAPA-DIET study: metabolic response to Dapagliflozin combined with dietary carbohydrate restriction in patients with type 2 diabetes mellitus and Obesity—A longitudinal cohort study. *Endocrinology, Diabetes and Metabolism Case Reports* 2022 **5** e381. (<https://doi.org/10.1002/edm2.381>)
- 16 Sarkar U, Ali S & Whooley MA. Self-efficacy as a marker of cardiac function and predictor of heart failure hospitalization and mortality in patients with stable coronary heart disease: findings from the heart and soul study. *Health Psychology* 2009 **28** 166–173. (<https://doi.org/10.1037/a0013146>)

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