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Review

Repurposing metabolic drugs as anti-inflammatory agents

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Dysregulation of bodyweight systemic metabolism is intrinsically linked to an inflammatory phenotype, with each underpinning the other. Over the past decade, new classes of drug, such as glucagon-like peptide-1 (GLP-1)-based therapies and sodium glucose co-transporter 2 (SGLT2) inhibitors, have entered the clinical management of bodyweight and metabolic disease with great success. With their expanded use, it is emerging that the benefits of these drugs extend beyond metabolic improvements into changes in chronic inflammation, potentially independent of those in metabolism. In this review, we discuss the impact of metabolic drugs on inflammatory comorbidities of metabolic disorders and beyond. We highlight the molecular mechanisms via which these drugs exert their anti-inflammatory actions and discuss their potential repurposing as direct anti-inflammatory agents.

Highlights

Recent evidence from clinical use is highlighting the anti-inflammatory properties of two classes of metabolic drugs, glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium glucose co-transporter 2 (SGLT2) inhibitors.

The molecular underpinnings of the anti-inflammatory actions of these medications are emerging and suggest improvements in systemic metabolism paired with direct anti-inflammatory mechanisms, but large gaps in our understanding remain.

Understanding the mechanisms underlying the anti-inflammatory effects may reveal potential therapeutic opportunities outside of metabolic diseases.

Metabolic disorders and inflammation

Obesity is a complex chronic and progressive disease [1], which impacts over a billion individuals worldwide, a number that is rapidly increasing, with a prediction that over 50% of the world's population will be living with overweight or obesity by 2035 [2]. The economic cost to global health systems worldwide is estimated to be US$4.32 trillion per annum [3]. The primary driver of this cost is embedded in the fact that obesity is strongly associated with numerous comorbidities, ranging from metabolic conditions, such as cardiovascular disease (CVD) and **type 2 diabetes mellitus (T2DM)** (see Glossary), to 13 different malignancies [4]. As a result, obesity can decrease the number of healthy-life years, and can reduce life expectancy by up to 14 years [5]. In 2019, higher than optimal bodyweight was linked to an estimated 5 million deaths from non-communicable obesity-related diseases, such as CVD, diabetes, and cancer [6]. The increases in morbidities and mortality are multifaceted [7] and, for many, include a genetic component, and environmental drivers.

However, one of the primary mechanisms underpinning obesity-related comorbidities is the presence of **chronic inflammation**, not only within dysfunctional adipose tissue depots, but also systemically, across the life-course. Over three decades ago, the first evidence emerged linking obesity, inflammation, and metabolic, with the observation that tumour necrosis factor (TNF) was elevated in obese adipose tissue and could directly drive insulin resistance [8]. Since then, numerous studies have linked obesity to elevated levels of many inflammatory cytokines, including TNF, interleukin (IL)-6, and IL-17 [9–13]. Similarly, research has linked obesity-related inflammation to the development of comorbidities [14] (Figure 1).

The clinical management of obesity has focussed on trying to reduce weight using lifestyle modification, pharmacotherapy, and surgical interventions [15–17]. With the continued use of these approaches, there is burgeoning evidence that their benefits extend far beyond improvements

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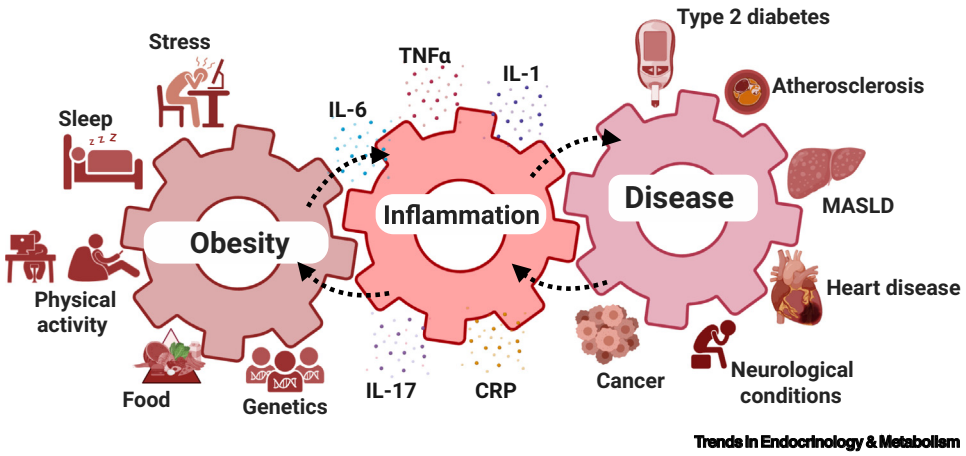

Figure 1. Bi-directional interplay between obesity, inflammation, and comorbid diseases, such as type 2 diabetes mellitus, cardiovascular disease, metabolic liver disease, and dementia. Established drivers/contributors of obesity include genetics, poor food environment, reduced physical activity, reduced sleep hygiene and elevated stress. Low-grade chronic inflammatory mediators include interleukin (IL)-1, IL-6, IL-17, and tumour necrosis factor (TNF). Abbreviations: CRP, C-reactive protein; MASLD, metabolic dysfunction-associated steatotic liver disease. Figure created with BioRender.

in bodyweight and metabolic profiles, including improvements in cardiovascular, hepatic, and renal health, with reduced dementia and cancer risk. In parallel, a significant body of evidence is emerging detailing that the protective mechanisms of these obesity-focussed interventions extend beyond weight loss and improvements in metabolic profiles, with reduced inflammation a major component. Given this growing evidence and the evolving therapeutic landscape of anti-obesity medications, we focus here on two pharmacotherapies widely used in the setting of obesity and metabolic disease; GLP1-based therapies and SGLT2 inhibitors. We discuss their current clinical use, modes of action, and focus on the emerging benefits, and their direct anti-inflammatory effects.

GLP-1-based medications

GLP-1 is a gut-derived multifaceted incretin peptide hormone first discovered in 1987 [18], which has a broad role in systemic metabolism, from controlling glucose metabolism through regulation of insulin secretion, gastrointestinal motility, food intake, and energy expenditure [19–21]. The classical actions (regulation of glucose homeostasis and food intake) of GLP-1 are mediated via the canonical GLP-1 receptor (GLP-1R), which is widely expressed across multiple sites, including the islet β cells and CNS [22]. In glucose metabolism, GLP-1 signalling can promote insulin secretion while inhibiting glucagon secretion, and loss of GLP-1R signalling increases glycaemic excursion after oral glucose challenge [23]. This effect is mediated locally in β cells, given that loss of CNS GLP-1R signalling only transiently impairs glucose homeostasis [24,25]. Mechanistically, GLP-1R signalling drives a cAMP-dependant crosstalk with membrane ion channels to support intracellular glucose metabolism [22]. Conversely, GLP-1R regulation of food intake is mediated centrally, as first reported in 1996 [20], and knockdown of GLP-1 CNS attenuates the impact of GLP-1R **agonist** (GLP-1RA) treatment on food intake and bodyweight [25]. The actions of GLP-1 in the CNS are complex, with widespread distribution of GLP-1R across the CNS, especially the hypothalamus [22]. One study, which genetically knocked out GLP-1R on specific hypothalamic feeding cells, concluded that classic homeostatic control regions of food intake are sufficient, but not individually necessary, for the effects of GLP-1RA [26]. In its native form, GLP-1 is rapidly cleaved by dipeptidyl peptidase-4 (DPP-4) [27]. Glucose metabolism improved in mice lacking DPP-4, or treated with DPP-4 inhibitors, highlighting the

Glossary

Agonist: compound that activates a receptor, mimicking a biological molecule.
Cardiovascular events: incident that damages the heart or blood vessels.
Chronic inflammation: non-resolving condition underpinned by excessive inflammation, which damages tissues, organs, and/or systems.
First-line drug: first/preferred treatment for a disease, usually effective at controlling the condition.
Glycaemic control: maintenance of blood glucose levels within a desirable range to prevent both hypoglycaemia and hyperglycaemia.
Glycosuria: abnormal excretion/presence of glucose in the urine.
Mitochondrial output: production of energy in the form of ATP via cellular respiration.
Type 2 diabetes mellitus (T2DM): condition in which blood glucose levels are higher than normal because the body cannot use insulin effectively or cannot produce it enough.

therapeutic potential of targeting GLP-1 activity [28]. The first generation of GLP-1-targeted medications focussed on GLP-1RAs such as Exendin-4, a peptide isolated from Gila monster venom, and their beneficial impact on glucose metabolism [29]. Subsequent efforts focussed on the development of long-acting GLP-1RAs, which are resistant to DPP-4 enzymatic activity, such as liraglutide [30,31].

Over the past decade, we have observed the rapid expansion of GLP-1 therapies, with current generations including semaglutide and tirzepatide. As patient exposure to these medications increases, their benefits have extended beyond **glycaemic control** and weight regulation. For example, their impressive cardio and hepatic protective properties have resulted in numerous investigations assessing their independent benefits in the management of CVD and metabolic-associated liver disease. In parallel with the large body of clinical evidence for extra-metabolic benefits is the burgeoning evidence for their anti-inflammatory effects.

GLP-1RAs and cardiovascular health

The cardioprotective effects of GLP-1RAs have been extensively studied in numerous clinical trials, including randomised studies. The international, multicentre trials LEADER, SUSTAIN-6, REWIND, and SUMMIT [32–35] demonstrated the superiority of liraglutide, semaglutide, dulaglutide, and tirzepatide, respectively over placebo in terms of prevention of major adverse cardiac events in individuals with T2DM with both high risk and prior history of CVD. Benefiting from large sample sizes of 3200–9000, these trials provided robust evidence of GLP-1RA efficacy in primary and secondary prevention of **cardiovascular events**, and led to the recommendation of GLP-1RAs as **first-line drugs** in T2DM for primary and secondary prevention of cardiac events in recent collaborative European guidelines published by the European Society of Cardiology and the European Association for the Study of Diabetes [36].

Numerous studies demonstrated evidence for alternative cardioprotective mechanisms of action (Figure 2), including impairing pathological activation of macrophages by exendin-4, with associated reduction in atherosclerotic plaque development [37]; the amelioration of baseline chronic inflammation by liraglutide in individuals with T2DM, reflected by decreased serum C-reactive protein (CRP) levels following initiation of therapy [38]; improvement of basal cardiometabolic risk factors by reducing body mass index when administered in conjunction with lifestyle interventions [39]; and attenuation of atherosclerotic plaque development through a reduction in lipid deposition, in circulating inflammatory cytokines and leukocyte recruitment [40]. The anti-inflammatory effects of GLP-1RA are furthered supported by evidence from murine models of obesity, where GLP-1RAs reduced adipose tissue macrophage populations, as well as the expression and production of IL-6, TNF, and monocyte chemoattractant protein-1 (MCP-1) [41]. Similarly, in individuals with T2DM, the inflammatory macrophage marker soluble CD163 and production of TNF and IL-1 were reduced after 3 months of GLP-1RA therapy [42]. Mechanistically, GLP-1 treatment induced STAT3 expression, resulting in increases in alternatively activated (M2-like) macrophage-related molecules, such as IL-10, CD163, and CD204 [43]. This was further supported in a murine model of atherosclerosis, where GLP-1Ras, via increased STAT3 expression, polarised macrophages to the M2-like phenotype, leading to a reduction in IL-6 levels and improvements in atherosclerotic plaques [44] (Figure 3).

GLP-1RAs and liver health

Another major comorbidity of obesity and metabolic dysfunction is now termed ‘metabolic dysfunction-associated steatotic liver disease’ (MASLD) [45]. In addition to metabolic dysfunction, such an insulin resistance and dyslipidaemia, inflammation has been strongly linked to both the development and progression of MASLD [46]. Overwhelming clinical evidence has

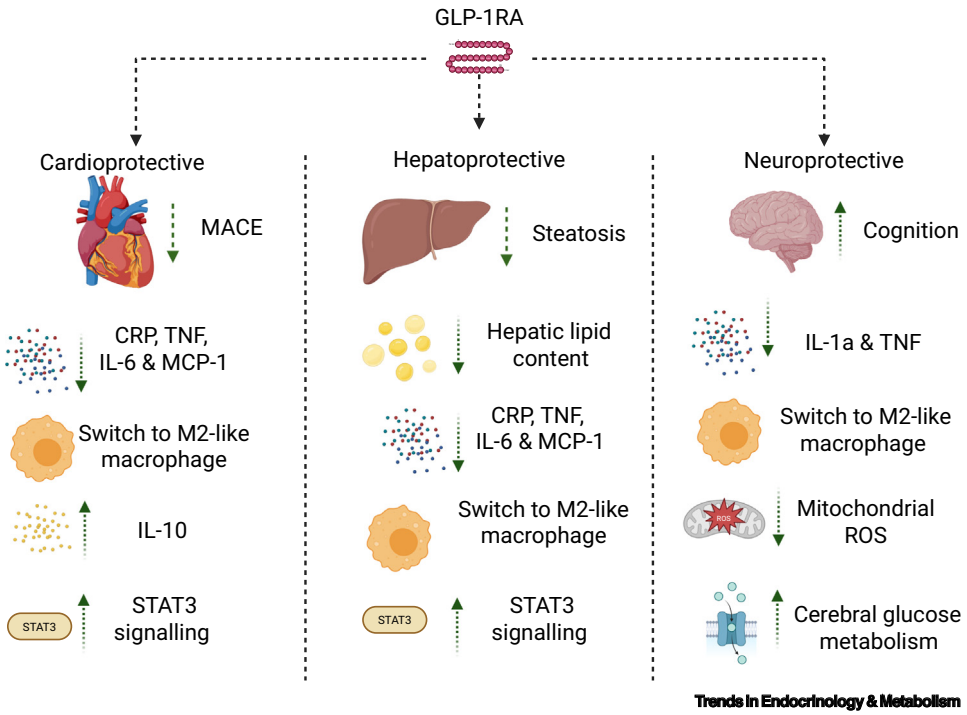

Figure 2. Overview of glucagon-like peptide 1 receptor agonist (GLP-1RA)-related protection in cardiovascular, hepatic, and neurological health. GLP-1RA use is linked to reduced major adverse cardiovascular events (MACEs) and hepatic steatosis in the setting of obesity and metabolic disease, and improved cognitive function in neurodegenerative diseases. Mechanistically, improvements in tissue and systemic metabolism, paired with reduced inflammation and macrophage polarisations, are the major drivers of benefits associated with GLP-1RAs. Abbreviations: CRP, C-reactive protein; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; ROS, reactive oxygen species; TNF, tumour necrosis factor. Figure created with BioRender.

demonstrated the benefits of GLP-1RAs on liver steatosis [47–50]: in LEAN, a randomised double-blind study, 39% of individuals randomised to liraglutide had resolution of definite steatohepatitis [48]; similarly, a Phase 2 trial showed that semaglutide treatment resulted in a significantly higher percentage of patients with resolution of metabolic dysfunction-associated steatohepatitis (MASH) compared with placebo [50]. SURPASS-3 MRI, a multicentred trial investigating the effect of the tirzepatide on liver fat content, showed significant reduction in liver fat content in individuals with T2DM compared with insulin [51]. In a 2024 retrospective analysis, GLP-1RA usage was associated with a lower risk of progression to cirrhosis and mortality among patients with MASLD and T2DM [52].

The underlying mechanisms are likely multifaceted (Figure 2), including improvements in systemic insulin resistance. It is also proposed that GLP-1 is likely affecting hepatocytes directly, given that GLP-1R activation on hepatocytes promotes the expression of genes associated with lipid oxidation [53]. In addition, inflammation is a major contributor to MASLD; therefore, GLP-1-mediated reduction in inflammation is another mechanism underpinning improvements. Retrospective analysis of individuals with obesity and T2DM showed that those treated with liraglutide had reduced levels of the liver-derived inflammatory marker CRP [54]. In murine models of lipid-driven hepatic dysfunction, treatment with exendin-4 revealed GLP-1R-dependent reductions in hepatic macrophage infiltration and inflammation [37]. In another murine study, liraglutide treatment improved hepatic inflammation in a methionine choline-deficient (MCD) dietary model of liver disease; specifically, the authors noted a reduction in signatures associated with hepatic inflammatory

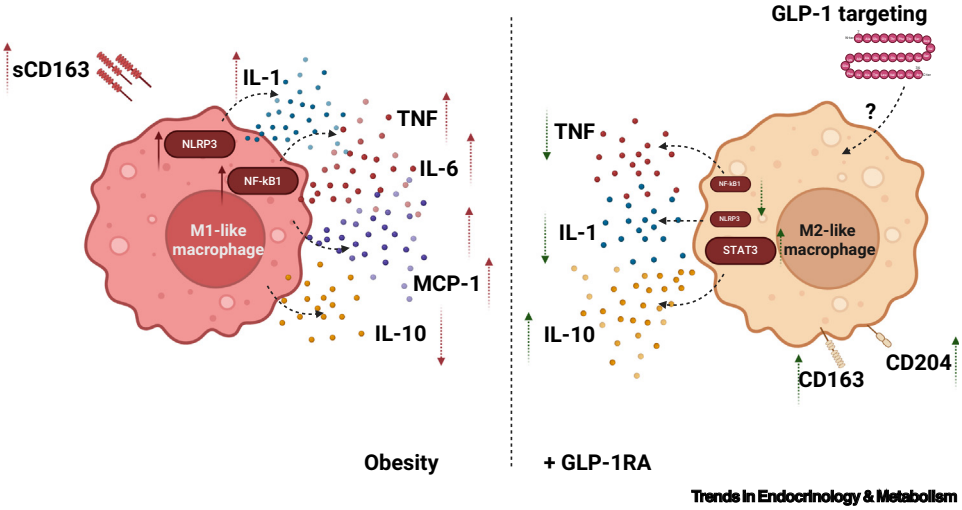

Figure 3. Impact of obesity on macrophage biology and the reported changes achieved with glucagon-like peptide 1 receptor agonist (GLP-1RA) therapy. Obesity is associated with an increased frequency of inflammatory macrophages (M1-like), which contribute to elevated levels of interleukin (IL)-1, IL-6, monocyte chemoattractant protein-1 (MCP-1), and tumour necrosis factor (TNF) via increased NF-κB and NLRP3 signalling, with a reduction in IL-10 production. Data show that GLP-1RA therapy increases M2-like macrophages, leading to reduced IL-1 and TNF, with an increase in IL-10 production mediated by reduced inflammatory (NF-κB and NLRP3) signalling and increased STAT3 signalling. Figure created with BioRender.

macrophages and TNF transcripts [55]. Conversely, an increase in M2-like hepatic macrophage polarisation was observed upon liraglutide treatment, whereby *in vitro* treatment of Kupffer cells with liraglutide polarised them toward an M2-like phenotype via a cAMP–STAT3 signalling cascade [56]. In a pilot study of individuals with T2DM and MASLD, liraglutide treatment resulted in decreased histological hepatic-inflammation in most patients [57].

GLP-1RAs and neuroprotection

The presence of a central GLP-1 secretory system that may act independently of gastrointestinal production [58] has directed research toward the potential role of GLP-1RAs in the central and peripheral nervous systems. Evidence for central GLP-1 anti-inflammatory actions comes from the observation that GLP-1R activation reduced TNF production in a murine model of sepsis; mechanistically, this was not mediated by haematopoietic or endothelial GLP-1Rs, but required central neuronal GLP-1R signalling [59]. As a central player in the modulation of neuroinflammation, GLP-1 receptor activation was demonstrated to block the release of proinflammatory cytokines, such as TNF and IL-1a, from neurotoxic phenotype A1 astrocytes [60], which have themselves been shown to be key drivers of conditions with neurodegenerative elements, such as Parkinson's (PD) and Alzheimer's diseases (AD), the risk of developing each of which is elevated in individuals with T2DM [61].

Clinical data supporting GLP-1RAs as a treatment for PD have been encouraging, with randomised placebo-controlled trials of weekly exenatide in patients with moderate PD and daily lixisenatide in patients with early PD improving motor and cognition clinical assessment scores and delaying loss of motor skills, respectively compared with placebo [62,63]. The fact that improvements persisted after a medication washout period raises interesting questions about the precise nature and duration of the mechanism of action of GLP-1RAs in PD. Murine models treated with GLP-1 drugs, such as liraglutide, in the setting of AD demonstrated both general anti-inflammatory capacity, in the diminishing of deleterious reactive oxygen species (ROS) via dampening of oxidative

phosphorylation with beneficial effects for astrocytes, and more disease-specific activity in their protection against amyloid plaque and neurofibrillary tangle formations that are pathognomonic of the disease [64,65]. However, small-scale studies in humans, underpowered to demonstrate potential impacts on neuropsychiatric symptom control, showed positive effects on pathogenic pathways, such as slowing the decline in cerebral glucose metabolism and enhancing glucose transfer across the blood–brain barrier [66,67]. The Phase 2b ELAD study reported improved clinical and cognitive scores in patients with AD treated with liraglutide as well as a protective effect on brain volume compared with placebo; a caveat exists in that these represented secondary outcomes as per the trial protocol and the results await final publication [68] (Figure 2).

GLP-1RAs and other inflammatory conditions

In addition to their beneficial effects in cardiovascular and metabolic liver diseases, GLP-1 drugs have been explored in a range of inflammatory conditions, including psoriasis, an inflammatory skin condition [69,70]. GLP-1-based therapy modulates invariant natural killer T (iNKT) cells infiltration into psoriatic plaques, paired with an increase in the circulation. *In vitro* studies demonstrated that GLP-1 (both native peptide and liraglutide) treatment could trigger cAMP responses and subsequently reduce iNKT cell production of cytokines. Subsequent studies of GLP-1 and psoriasis noted a significant reduction in dermal γδT cell frequencies and levels of IL-17, IL-23, and TNF, three causative inflammatory cytokines in psoriasis [71,72]. iNKT cells are involved in the regulation of adipose tissue [73], and obesity exerts a deleterious impact on the frequencies (peripheral and adipose tissue) and functional responses (including regulation of bodyweight) of these cells across the lifespan [73]. In murine models of obesity and cohorts of people with obesity, GLP-1-based therapy reversed obesity-related defects in iNKT cell frequencies, and promoted IL-10 production by these cells, further supporting its anti-inflammatory actions [74].

Acute kidney disease (AKD) and chronic kidney disease (CKD) are rising in incidence globally, with T2DM identified as an independent risk factor for both [75]. In cohorts of individuals with kidney disease, GLP-1 drug usage was associated with reduced major adverse kidney disease, and CKD-related deaths [76]. Mechanistically, in addition to the direct effect of GLP-1 on the kidney [77], GLP-1 modulation of macrophage phenotype and function has been implicated in the protective effects of GLP-1 in CKD [78]. In murine models of kidney disease, GLP-1 treatment significantly improved renal outcomes by decreasing the renal infiltration and proliferation of T cells, which resulted in decreased macrophage infiltration. Furthermore, *in vitro*, T cells stimulated in the presence of liraglutide showed decreased proliferation of both T helper (Th)-1 and Th17 cells [79] (Figure 4).

Emerging evidence is highlighting the potential benefits of GLP-1 therapies in the setting of cancer. Given that obesity is among the most significant drivers of cancers [80], a class of drugs that improve obesity might be expected to improve cancer outcomes. In a large retrospective cohort study with a 15-year follow up, GLP-1 drug usage was associated with a significant risk reduction in ten of 13 obesity-associated cancers [81]. Mechanistically, the reduction in insulin resistance and inflammation is likely a primary driver of this reduced risk. In addition, GLP-1 therapy can significantly improve natural killer (NK) cell anticancer functions [82], a critical immune population that is strongly limited by obesity [83,84]. Conversely, a later study highlighted the potential inhibitory role of GLP-1 on T cells, postulating that it might act as a T cell-negative co-stimulatory molecule. Using murine models of colorectal cancer, the study demonstrated that antagonism of GLP-1R signalling triggered antitumour immunity [85]. Further detailed studies in humans are required to determine whether inhibiting GLP-1 signalling drives antitumour immunity. Another outstanding issue requiring clarity is the expression of the GLP-1 receptor on immune cells. Although robust expression of GLP-1R has been shown across multiple T cell populations [85], how GLP-1 exerts

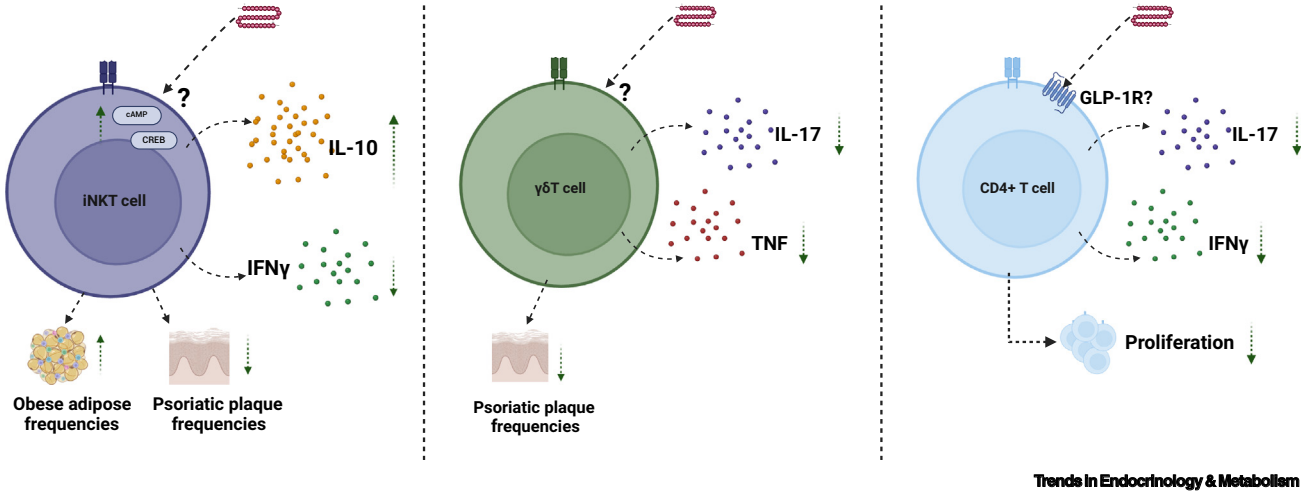

Figure 4. Glucagon-like peptide 1 (GLP-1) receptor agonist (GLP-1RA) therapy modulates conventional and unconventional T cell responses. Data show that GLP-1 therapy increases anti-inflammatory invariant natural killer T (iNKT) cells producing interleukin (IL)-10 in the setting of obesity. In addition, inflammatory iNKT and γδT cells are reduced in the plaques of patients with psoriasis, leading to decreases in IL-17 and tumour necrosis factor (TNF). Similarly, data show that GLP-1 can reduce CD4+ T cell production of inflammatory mediators, including IL-17 and interferon (IFN) γ. Figure created with BioRender.

its anti-inflammatory actions is incompletely understood, given that most immune cells do not express the GLP-1R, and its expression is limited to intestinal intra-epithelial lymphocytes [86].

Sodium glucose co-transporter 2 inhibitors

SGLT2 inhibitors are routinely used in the treatment of T2DM. SGLT2 is expressed within the renal proximal tubule and is responsible for the reabsorption of ~90% of filtered glucose [87]. Consequently, highly selective inhibitors, including canagliflozin, dapagliflozin, and empagliflozin, have been developed to prevent renal glucose uptake through SGLT2 and promote **glycosuria** to, ultimately, improve glycaemic control [88]. However, inhibiting SGLT2 only blocks the reabsorption of 30–50% of filtered glucose within the kidney [89]. As such, SGLT2 inhibitors administered either as a monotherapy or in combination with other glucose-lowering agents can regulate blood glucose levels in patients with T2DM [90]. The reduced plasma glucose concentrations resulting from SGLT2 inhibition also provide further clinical benefit to patients with T2DM, whereby the loss of calories from glucose excretion can intrinsically reduce patient body weight [91–93].

SGLT2 inhibitors have now been revealed to have novel roles beyond glycaemic control. For example, their impressive cardioprotective and renoprotective properties have resulted in them becoming synonymous with the management of heart failure and CKD [94–96] (Figure 5). Chronic inflammation has a central role in the pathogenesis of T2DM [97], CVD [98], and CKD [99], thus suggesting the potential of SGLT2 inhibitors to resolve inflammatory disease. Moreover, other T2DM drugs have previously demonstrated anti-inflammatory functions, whereby metformin has shown promise in the treatment of autoimmune disease [100]. Consequently, research is beginning to reveal the immunomodulatory properties of SGLT2 inhibitors, detailing their impact on the immune response [101].

SGLT2 medications and cardiovascular health

The cardioprotective effects of SGLT2 inhibitors is a class-wide attribute, whereby canagliflozin [102], dapagliflozin [103], and empagliflozin [104] have been shown to reduce the severity of cardiovascular comorbidities in patients with T2DM. These findings led to a clinical trial, which showed that SGLT2 inhibitors reduced the risk of adverse cardiovascular outcomes in patients with heart failure, regardless of their diabetes status [96,105,106]. As a result, SGLT2 inhibitors

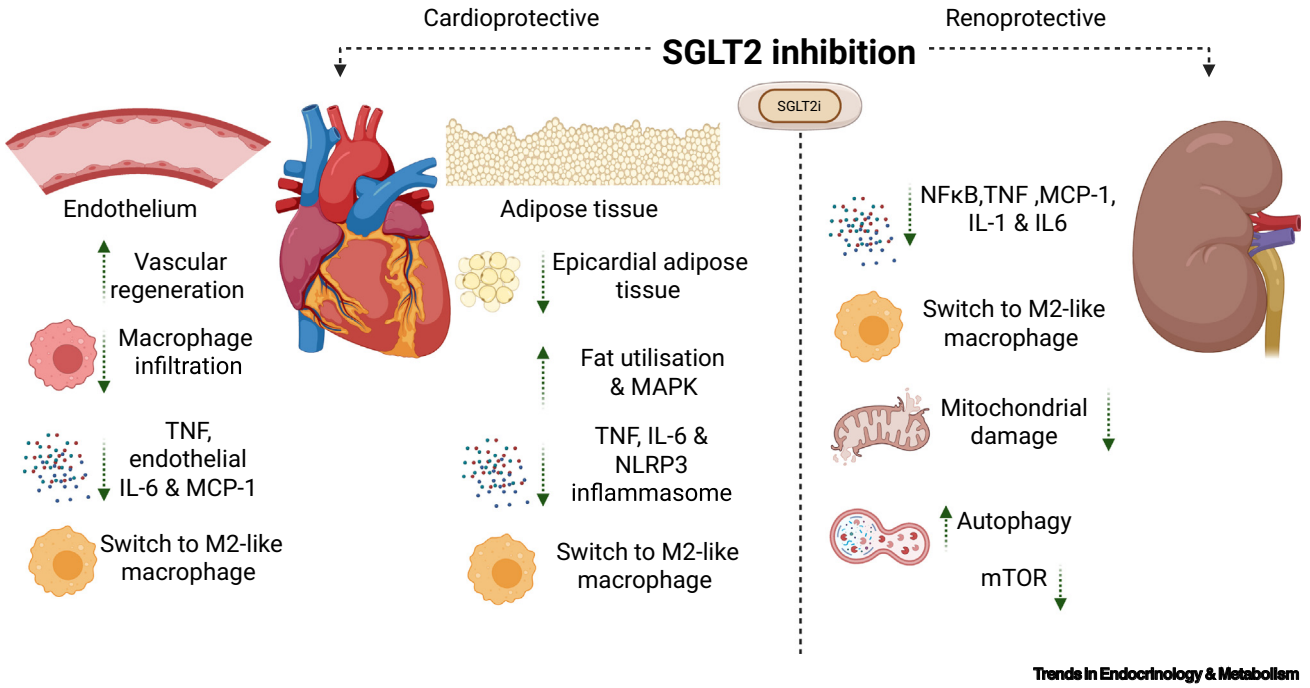

Figure 5. Protective effects of sodium glucose co-transporter 2 (SGLT2) inhibitors on obesity-related comorbid diseases. SGLT2 inhibitor use is linked to reduced major adverse cardiovascular events (MACEs) and kidney disease in the setting of obesity and metabolic disease. Mechanistically, improvements in tissue and systemic metabolism, paired with reduced inflammation and macrophage polarisations, are the major drivers of benefits associated with SGLT2 inhibitors. Abbreviations: IL, interleukin; MCP-1, monocyte chemoattractant protein-1; mTOR, mammalian target of rapamycin; TNF, tumour necrosis factor. Figure created with BioRender.

are increasingly integrated into treatment strategies against chronic heart failure. However, the glucose-lowering function of SGLT2 inhibitors is unlikely to be the main driver of their cardioprotective function [102]. Instead, distinct anti-inflammatory processes, independent of glycaemic control, contribute to improved cardiovascular health.

Ectopic fat deposition within the heart and adjacent vasculature induces local tissue inflammation. Interestingly, dapagliflozin was reported to reduce epicardial adipose tissue (EAT) volume in patients with T2DM and obesity [107], which could contribute to risk reduction in cardiovascular events. Similar reductions in EAT volume have also been described in response to canagliflozin [108]. Other SGLT2 inhibitors, such as empagliflozin, have been shown to reduce adipose tissue inflammation by promoting fat utilisation and modulating resident macrophage function [109,110]. To this end, empagliflozin enhances energy expenditure within the adipose through activation of AMP-activated protein kinase (AMPK) and promotion of adipose tissue browning, consequently suppressing diet-induced weight gain [109,110]. In terms of altered macrophage function within adipose tissue, empagliflozin induces a switch toward an M2-like phenotype, with reduced levels of proinflammatory cytokines, such as TNFα, measured within local tissues [109,110]. In addition, increased adipokine signalling has also been implicated in the anti-inflammatory function of dapagliflozin and empagliflozin within adipose tissue, where they inhibit proinflammatory cytokine production [111] and NLRP3 inflammasome activation [112]. Interestingly, reduced NLRP3 inflammasome activation appears to have a metabolic underpinning, in that increased β-hydroxybutyrate levels following SGLT2 inhibition attenuate inflammasome activation in macrophages [113]. Together, these findings demonstrate how the versatile functions of SGLT2 inhibitors converge to ameliorate inflammation and manage obesity.

Other aspects of cardiovascular health are also impacted by SGLT2 inhibition. For example, dapagliflozin can restrain atherogenesis by inducing an anti-inflammatory microenvironment that minimises endothelial cell dysfunction [114]. Specifically, TNFα-mediated stimulation is attenuated by dapagliflozin, reversing diet-induced changes in endothelial cell function to restore normal levels of vasorelaxation and macrophage infiltration [114]. Similarly, canagliflozin limits signalling through the IL-1β pathway to regulate the production of IL-6 and MCP-1 by vascular endothelial cells [115], again linking vascular health and the immunoregulatory effect of SGLT2 inhibition. Moreover, empagliflozin has also been demonstrated to modulate macrophage function to mitigate adverse coronary events [116]. Following 6 months of treatment with empagliflozin, provascular progenitor cells and M2-like macrophages were more abundant in the circulation and were accompanied by a reduction in oxidative stress and inflammatory granulocyte function, together establishing a landscape permissive for vasculature regeneration [116]. There is evidence to suggest that proinflammatory cytokine production by endothelial cells and differentiated macrophages is inhibited by dapagliflozin through its repression of the NF-κB pathway [117]. These studies highlight the multifaceted approach through which SGLT2 inhibitors realise their cardioprotective function.

Interestingly, nutrient sensing is engaged in several of these immunomodulatory processes. One example is AMPK, which responds to nutrient deprivation. In the context of cardioprotective function, the anti-inflammatory effect of canagliflozin on endothelial cell cytokine secretion is dependent on AMPK activation and downstream signalling through this pathway [115]. The influence of AMPK is not unique to canagliflozin, given that the cardioprotective function of empagliflozin has been related to AMPK-induced changes in autophagy [118]. There is evidence to suggest that this impact on metabolism extends further, wherein empagliflozin improves **mitochondrial output** to overcome the dysfunction characterised within this organelle upon cardiac arrest [119]. Mechanistically, changes in mitochondrial function upon empagliflozin treatment are attributed to repression of mitochondrial fission to re-establish larger mitochondria with greater respiratory capacities [120]. However, activation of AMPK upon SGLT2 inhibition does not follow a class-wide mechanism. To this end, canagliflozin significantly inhibits complex I of the electron transport chain, leading to breakdown of mitochondrial respiration and subsequent AMPK activation [121,122]. By comparison, both dapagliflozin and empagliflozin have been shown to either have a lesser effect, or even no effect, on complex I activity versus canagliflozin [121,123]. In addition, canagliflozin has off-target effects on mitochondrial glutamate dehydrogenase, compounding the inhibition of mitochondrial metabolism and, thus, altering the balance of ATP levels to those favourable for AMPK activation [123]. Consequently, these studies highlight the importance of appraising the specific anti-inflammatory and antimetabolic properties of individual members within this drug class.

SGLT2 inhibitors and kidney health

Several clinical trials, including those exploring the cardioprotective effect of SGLT2 inhibition, have also revealed that canagliflozin [102], dapagliflozin [103], and empagliflozin [124] reduce the risk and severity of adverse renal outcome in patients with T2DM. Again, the renoprotective properties of SGLT2 inhibitors improve patient outcomes in CKD [125], resulting in new guidance recommending their use for the treatment of CKD and other renal disorders. Similar to the cardioprotective effects of SGLT2 inhibition, the renoprotective properties of these antidiabetic drugs are founded upon several anti-inflammatory mechanisms.

There are several common mechanisms that underpin the renoprotective and cardioprotective effects of SGLT2 inhibitors. For instance, empagliflozin has been shown to inhibit NF-κB activation, reduce proinflammatory cytokine production, and alleviate renal inflammation [126].

Macrophages treated with empagliflozin also display attenuated NF-κB signalling, which again inhibits the secretion of a range of proinflammatory cytokines [127]. Changes in mitochondrial metabolism also have a central role in mediating the renoprotection offered by SGLT2 inhibitors. Specifically, a marked reduction in the urinary levels of mitochondrial DNA and IL-1β following empagliflozin treatment suggests reduced mitochondrial damage and a concomitant amelioration of inflammation [128]. This is likely attributable to the mitochondrial biogenesis that empagliflozin promotes by preventing mitochondrial fragmentation within renal proximal tubular cells [129]. These changes in mitochondrial dynamics are coupled to AMPK activation [129,130], whereas dapagliflozin has been demonstrated to attenuate renal fibrosis in CKD by reversing MAPK-mediated alterations in mitochondrial function [131], again highlighting the importance of manipulating cellular metabolism to alleviate inflammation.

Research exploring changes in mitochondrial function SGLT2 inhibition also hint that mTOR activation is suppressed under these conditions [129]. Following dapagliflozin treatment, renal proximal tubular cells exhibit reduced mTOR activity, rewiring mitochondrial metabolism to drive itaconate synthesis, which then inhibits the activation of the NLRP3 inflammasome [132]. Moreover, dapagliflozin-mediated changes in the mTOR/AMPK signalling axis are central to its initiation of renal autophagy and subsequent anti-inflammatory function within the kidney [133]. Furthermore, canagliflozin and empagliflozin are also able to suppress mTOR in a range of human kidney cell types [134], indicating that there is a class-wide effect on mTOR activity. Collectively, there is a wealth of evidence describing the anti-inflammatory effects of SGLT2 inhibitors that contribute to both their renoprotective and cardioprotective function.

SGLT2 inhibitors and other inflammatory conditions

Given the burgeoning success of repositioning SGLT2 inhibitors into the treatment frameworks of CVD and CKD, exciting new studies have explored the use of canagliflozin, dapagliflozin, and empagliflozin in other inflammatory diseases. For instance, since autoimmunity is characterised by chronic inflammation arising from T cell hyperactivation, and canagliflozin has been shown to modulate human T cell function via metabolic reprogramming, the anti-inflammatory effects of SGLT2 inhibitors have been considered in this context [101]. Notably, early T cell receptor signalling events are impaired by canagliflozin, which impacts downstream signalling through the ERK/mTOR/MYC axis, preventing the metabolic rewiring required following T cell receptor-mediated activation [101]. Thereafter, T cell effector function, such as cytokine production, is heavily constrained by canagliflozin, which also retains this immunosuppressive function on autoimmune patient-derived T cells [101]. In the setting of immune thrombocytopenia (ITP), an autoimmune condition defined by autoreactive platelet destruction, empagliflozin has demonstrated immunomodulatory properties by skewing human T cell differentiation toward a regulatory phenotype [135]. Again, there was a metabolic foundation to these changes, whereby mTOR activity was impaired by empagliflozin, thus inhibiting the upregulation of glycolysis and shifting instead toward oxidative respiration [135]. Importantly, empagliflozin maintained these immunomodulatory functions in patient-derived T cells [135], further supporting the repurposing of SGLT2 inhibitors for the treatment of autoimmune disease. These findings are strengthened by emerging murine analyses, whereby canagliflozin alleviated an imiquimod-induced model of psoriasis by reducing cutaneous concentrations of inflammatory cytokines [136]. Excitingly, recent analyses in patients with T2DM and comorbid inflammatory skin conditions revealed that those receiving SGLT2 inhibitor treatment were at significantly less risk of developing new-onset alopecia areata, vitiligo, seborrheic dermatitis, and acne [137]. However, the risk of new-onset psoriasis was slightly increased by SGLT2 inhibitors [137], which perhaps advocates for further analyses of the efficacy of specific members within this class of drug in the treatment of autoimmunity, alongside research into individual autoimmune conditions on a case-by-case basis. Promisingly, similar research also

demonstrated that SGLT2 inhibitors have a protective effect against inflammatory skin conditions [138]. The marked reduction in the risk of developing vitiligo [138] is particularly interesting, given that T cell-mediated responses have a central role in the pathogenesis of this disease [139]. Outside of their influence on T cell function, SGLT2 inhibitors are also well tolerated in systemic lupus erythematosus [140], reducing the risk of nephritis and offering cardioprotective and renoprotective benefits in some patient cohorts [141]. Together, these findings provide a foundation for the clinical development of SGLT2 inhibitors as therapeutic agents in autoimmune conditions, particularly those burdened by heightened T cell function (Figure 6).

The use of SGLT2 inhibitors in other inflammatory conditions also warrants further investigation. Growing research is considering the use of SGLT2 inhibitors in conditions of hepatic inflammation, where they are well tolerated in patients with T2DM and concomitant liver cirrhosis [142], reducing the rate of mortality versus other antidiabetic drugs [143]. These findings are being expanded into conditions such as MASLD, in which SGLT2 inhibitors restrained steatosis and fibrosis in patients with T2DM and comorbid liver disease [144]. Once more, the therapeutic benefit of SGLT2 inhibition in conditions of hepatic inflammation has been linked to an immunomodulatory effect on T cell function. In this instance, empagliflozin was shown to alleviate MASH by inhibiting the activation of CD8+ T cells [145]. Interestingly, this immunosuppressive effect on pathogenic CD8+ T cell responses was again supported by metabolic reprogramming, whereby elevated rates of ketogenesis promoted the production of β-hydroxybutyric acid, in turn suppressing interferon regulatory factor 4 (IRF4), a key determinant of CD8+ T cell activation [145]. Other recent examples extend to the reduction in gout flare-ups in patients with T2DM receiving SGLT2 inhibitors [146], in addition to the alleviation of pathological aging through improved immune-mediated clearance of senescent cells following treatment with canagliflozin [147]. The potential mechanisms through which the already-described anti-inflammatory effects of SGLT2 inhibitors could benefit 'inflamm-aging' have also been extensively reviewed [148].

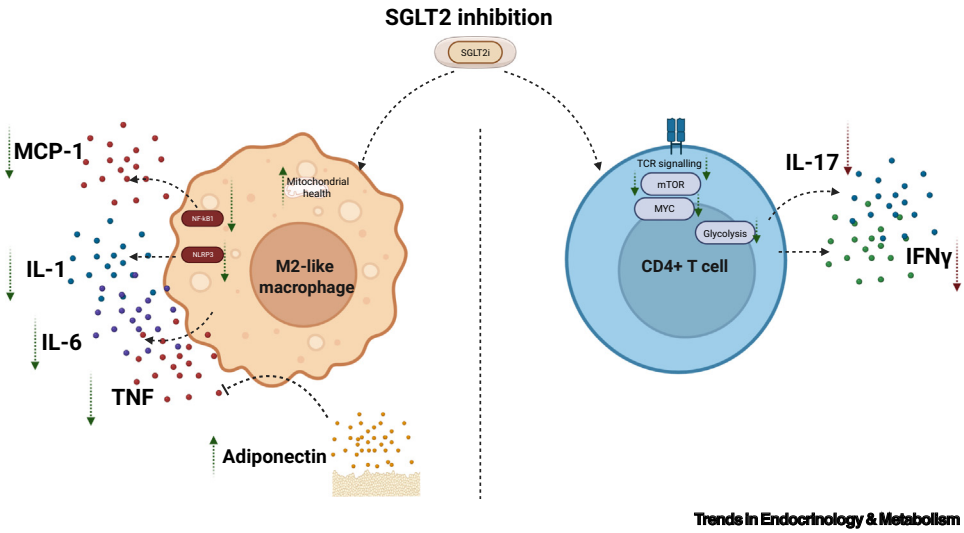

Figure 6. Impact of sodium glucose co-transporter 2 (SGLT2) inhibitors on macrophage and T cell biology. Data show that SGLT2 inhibitors increase anti-inflammatory M2-like macrophages producing interleukin (IL)-10, with notable reductions in IL-1, IL-6, monocyte chemoattractant protein-1 (MCP-1), and tumour necrosis factor (TNF) via reduced NF-κB and NLRP3 signalling. In addition, SGLT2 inhibitors can reduce CD4+ T cell production of inflammatory mediators, including IL-17 and interferon (IFN) γ, via reduced T cell receptor (TCR) signalling and metabolism. Abbreviation: mTOR, mammalian target of rapamycin. Figure created with BioRender.

Overall, these findings underline the ever-expanding uses of SGLT2 inhibitors in the treatment of inflammatory disease.

Concluding remarks and future perspectives

The emergence over the past 25 years of GLP-1RAs and SGLT2 inhibitors to manage T2DM has revolutionised treatment goals for patients living with the disease. Studies investigating these drugs are leading to a richer understanding of not only how obesity drives inflammation, but also how alterations in specific intracellular pathways are common to obesity, T2DM, and other inflammatory conditions.

The additional recognition of direct anti-inflammatory actions of both classes of drug has been followed by a series of investigations to understand the mechanisms that underpin these actions, opening new indications for the use of their outside of T2DM and obesity, as outlined in this review. There is extensive evidence to support the repurposing of GLP-1RAs and SGLT2 inhibitors in a range of obesity-related comorbidities, which are often driven by chronic inflammation. Given the ever-growing burden of obesity [2] and the economic appeal (both financially and temporally) of drug repurposing [149], investigating the protective properties of GLP-1RA and SGLT2 inhibitors in other inflammatory settings, such as cardio-, renal-, neuro-, hepatic-inflammatory conditions and 'inflamm-aging', has become a burgeoning area of research. Understanding the molecular mechanisms that drive the immunomodulatory properties of GLP-1RA and SGLT2 inhibition is critical to harness their potential for repurposing, especially beyond obesity. With the rapidly increasing portfolio of GLP-1RAs and their expanding use in the management of obesity, their anti-inflammatory properties are clearer than ever; however, we lack a full understanding of the major molecular pathways mediating these effects. Similarly, although ongoing research continues to uncover the mechanisms underpinning the cardio- and renoprotective effects of SGLT2 inhibition, the dominant mechanisms through which highly selective inhibitors mediate their effect remain unknown.

Furthering our understanding of the predominant molecular mechanisms governing these immunomodulatory effects, particularly resolving class-wide versus drug-specific effects, would allow more targeted use in obesity-related inflammatory disease. The major unknown that the community needs to address is whether the anti-inflammatory effects of these drugs extend beyond weight loss and improved glycaemic control. In addition, several other important questions remain (see Outstanding questions). Growing *in vitro* and animal model data support a direct immunomodulatory effect, and clinical trials in patients without obesity will be required, but there is a strong potential for the repurposing of these drugs for a range of inflammatory conditions.

Outstanding questions

Can we separate the anti-inflammatory effects of GLP-1RAs and SGLT2 inhibitors from improvements in systemic metabolism?

Do the direct effects of GLP-1RAs and SGLT2 inhibitors on immune cells extend beyond macrophages and T cells?

What are the molecular underpinnings of the immune effects? Are they signalling mediated, cellular metabolism mediated, or both?

Are the anti-inflammatory responses tissue specific?

At the doses used therapeutically, will the tissue concentrations of SGLT2 inhibitors be sufficient to elicit anti-inflammatory responses?

Are the immune cell effects, especially with GLP-1 therapies, receptor mediated?

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Declarations of interest

The authors declare no conflicts of interest.

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