GLP2: an underestimated signal for improving glycaemic control and insulin sensitivity

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Abstract

Glucagon-like peptide 2 (GLP2) is a proglucagon-derived peptide produced by intestinal enteroendocrine L-cells and by a discrete population of neurons in the brainstem, which projects mainly to the hypothalamus. The main biological actions of GLP2 are related to the regulation of energy absorption and maintenance of mucosal morphology, function and integrity of the intestine; however, recent experimental data suggest that GLP2 exerts beneficial effects on glucose metabolism, especially in conditions related to increased uptake of energy, such as obesity, at least in the animal model. Indeed, mice lacking GLP2 receptor selectively in hypothalamic neurons that express proopiomelanocortin show impaired postprandial glucose tolerance and hepatic insulin resistance (by increased gluconeogenesis). Moreover, GLP2 acts as a beneficial factor for glucose metabolism in mice with high-fat diet-induced obesity. Thus, the aim of this review is to update and summarize current knowledge about the role of GLP2 in the control of glucose homeostasis and to discuss how this molecule could exert protective effects against the onset of related obesity type 2 diabetes.

Introduction

Glucagon-like peptide 2 (GLP2) is a 33 amino acid proglucagon-derived peptide produced by a subset of enteroendocrine cells (L-cells) residing within the epithelium of the small and large intestine (Yusta et al. 2000). GLP2 is also produced in a discrete population of neurons in the brainstem, which projects mainly to the hypothalamus, brain area that plays a key role in control of food intake (Vrang et al. 2007). Prohormone convertase 1/3 (PC1/3) processes proglucagon in the gastrointestinal tract and in the brain, resulting in glucagon-like peptide-1 (GLP1), GLP2, intervening peptide-2, oxyntomodulin and glicentin (Ugleholdt et al. 2004). The studies on proglucagon-derived peptides have supplied two classes of glucose-lowering agents, the dipeptidyl peptidase IV (DPP-IV) inhibitors and GLP1 receptor agonists, useful tools for the treatment of type 2 diabetes (T2D) (Drucker & Nauck 2006). However, the overwhelming interest attracted by GLP1 analogues as potent incretins has somewhat clouded the efforts to understand the importance of other proglucagon-derived peptides. In fact, unlike GLP1, initially, GLP2 was not reported to modulate insulin secretion or glucose homeostasis (Schmidt et al. 1985, Ørskov et al. 1988); however, recent experimental data suggest that GLP2 exerts beneficial effects on glucose metabolism, especially in conditions related to increased uptake of energy, such as obesity, at least in the animal model (Cani et al. 2009, Bahrami et al. 2010, Shi et al. 2013, Guan 2014, Baldassano et al. 2015).
Thus, the aim of this review is to update and summarize current knowledge about the role of GLP2 in the control of glucose homeostasis and to discuss how this molecule could exert protective effects against the onset of related obesity type 2 diabetes.

**Overview on GLP2**

GLP2 was first discovered as an intestinalotrophic factor in 1996 (Drucker et al. 1996); however, today it is considered a pleiotropic hormone with a wide range of effects, mainly in the gastrointestinal tract. The main biological actions of GLP2 are related to the regulation of energy absorption and maintenance of mucosal morphology, function and integrity of the intestine (Drucker & Yusta 2014 for an extensive review).

GLP2 is released in response to stimulation by luminal nutrients, such as glucose, fatty acids and dietary fibre (Brubaker 2006). GLP2 is cleaved to inactive GLP2 (3–33) by DPP-IV; consequently, the half-life of intravenous GLP2 is very short, about 7 min in healthy humans (Hartmann et al. 2000). Indeed, GLP2 (3–33) may act as a weak agonist at pharmacological concentrations (Shin et al. 2005); however, it is able to act as a competitive antagonist of the GLP2 receptor (GLP2R) in rodents (Thulesen et al. 2002, Shin et al. 2005, Baldassano et al. 2009, 2013). Then DPP-IV-resistant GLP2 analogues, such as [Gly]{\textsuperscript{2}}-GLP2 (teduglutide), exhibit greater bioactivity relative to native molecule, due to their longer circulating half-lives (Tavares et al. 2000, Baldassano & Amato 2014).


GLP2R is also expressed in the central nervous system (CNS), specifically in key regions of the brain for energy balance, including the hypothalamus, hippocampus and brainstem (Tang-Christensen et al. 2000, Lovshin et al. 2004, Guan et al. 2012). As a neurotransmitter, GLP2 may mediate preproglucagonergic (PPG) neuron-induced synaptic transmission linking the hypothalamus and the brainstem and may act as a satiation signal in the control of feeding behaviour (Tang-Christensen et al. 2000). In fact, intracerebroventricular administrations of GLP2 reduce food intake in rodents (Tang-Christensen et al. 2000, Lovshin et al. 2001). In addition, knockout mice with GLP2R deletion selectively in hypothalamic arcuate nucleus neurons expressing proopiomelanocortin (POMC) display hyperphagic behaviour and late-onset obesity (Guan et al. 2012). These observations support the hypothesis of a physiological role in the regulation of food intake and body weight (Guan et al. 2012). Up to date, studies in humans have not demonstrated a decrease in food intake after peripheral GLP2 administration (Schmidt et al. 2000, Sørensen et al. 2003), even if recent data have shown that intraperitoneal injections of GLP2 or [Gly]{\textsuperscript{2}}-GLP2 reduce food intake in mice, suggesting a role for GLP2 in the short-term regulation of the eating behaviour (Baldassano et al. 2012). This effect is related to a significant decrease in the rate of gastric emptying (Baldassano et al. 2012), and it is well known that gastric emptying is a critical process for the short-term control of food intake (Janssen et al. 2011, Rotondo et al. 2011a). Moreover, in mice, GLP2R deletion in POMC neurons accelerates the rate of gastric emptying accounting for the hyperphagic behaviour and supporting the hypothesis that CNS GLP2 is a key satiety signal for the physiological short-term control of feeding behaviour (Guan et al. 2012).
GLP2 and glycaemic control

Up to date, the GLP2 action on glucose homeostasis has been scarcely investigated, and the importance of GLP2R signalling is not clear yet (Guan 2014). GLP2R global deficiency is not critical for glucose homeostasis in normal or lean diabetic mice because it is not associated with changes in fasting glucose, glucose tolerance or plasma glucagon levels (Bahrami et al. 2010). Also the observation that the chronic treatment with GLP2 (3–33), a GLP2R antagonist used to reveal the physiological actions of GLP2 (Shin et al. 2005, Nelson et al. 2008, Iakoubov et al. 2009, Baldassano et al. 2013), does not affect glycaemic parameters, glucose tolerance, insulin sensitivity or pancreas weight and β-cell mass in mice, has led to rule out a role for the endogenous GLP2 in glucose homeostasis in normal conditions (Baldassano et al. 2015). In addition, changes in glucagon levels or glycaemia have not been reported following acute or chronic GLP2 or teduglutide administration in patients with short bowel syndrome (Drucker & Yusta 2014).

We know for a long time that GLP2 does not exhibit any insulin-releasing properties (Schmidt et al. 1985, Ørskov et al. 1988). On the contrary, i.v. infusion of the peptide has been demonstrated to increase glucagon secretion in healthy, non-obese human subjects both in physiological and pharmacological plasma concentration (Sørensen et al. 2003, Meier et al. 2006) or in diabetic patients (Christensen et al. 2010, Lund et al. 2011). GLP2R has been localized to α-cells in both human and rat islets by means of immunohistochemistry as well as real-time PCR (de Heer et al. 2007). In contrast, full-length Gip2r mRNA transcripts have not been detected in RNA from murine islets, and GLP2 does not increase plasma glucagon levels in mice (Yusta et al. 2000, Bahrami et al. 2010). The discrepancy could be attributed to different species; however, caution should be taken in ruling out a glucagonotrophic role of GLP2 in mice. In fact, recent researches have demonstrated that GLP2R is more widely expressed than it was estimated (Angelone et al. 2012, El-Jamal et al. 2014). Therefore, it is necessary to explore the presence and localization of GLP2R in the pancreatic islets using validated GLP2R antibody and the opportune positive and negative controls to yield to conclusive results. Anyway, the GLP2 glucagonotrophic properties could suggest that the endogenous or exogenous peptide exacerbates the hyperglycaemia conditions related to diabetes. Nevertheless, the glucagon hypersecretion induced by oral glucose, which is typical of patients with T2D (Knop et al. 2007), is not a consequence of exaggerated secretion or effect of GLP2 (Lund et al. 2011), and GLP2R global absence in genetically obese mice increases glucagon secretion and hyperglycaemia (Bahrami et al. 2010). Therefore, the importance of GLP2 in the control of glucagon secretion in different species and in diverse pathological conditions related to glucose impairment requires further elucidation.

New evidence obtained from GLP2R tissue-specific KO mice indicates that GLP2R in POMC neurons is essential for suppressing hepatic glucose production (Shi et al. 2013). Indeed, mice lacking GLP2R selectively in POMC neurons display impaired postprandial glucose tolerance and hepatic insulin resistance (by increased gluconeogenesis), suggesting a physiological significance of GLP2 neural action in glycaemic control. Moreover, intracerebroventricular infusion of GLP2 increases glucose tolerance and insulin sensitivity and suppresses basal hepatic glucose production through GLP2R activation in POMC neurons (Shi et al. 2013). Therefore, GLP2 has been proposed as a crucial neuroendocrine signal for glucose homeostasis (Guan 2014). It will be crucial to determine whether CNS GLP2R is a key contributor to glycaemic control and insulin sensitivity also in humans.

Moreover, GLP2 seems to act as a beneficial factor for glucose metabolism in obesity condition. Loss of GLP2R leads to increased glucagon secretion and α-cell mass, impaired intraperitoneal glucose tolerance and hyperglycaemia, reduced β-cell mass and decreased islet proliferation in genetic obese ob/ob;Glp2r−/− mice. Then, the authors have suggested that GLP2R is required for the adaptation of the endocrine pancreas to metabolic stress (Bahrami et al. 2010). In mice fed a high-fat diet (HFD), endogenous GLP2 acts as a protective factor against the dysregulation of glucose metabolism that occurs in HFD-fed mice because GLP2 (3–33) chronic treatment exacerbates glucose metabolism disorders (Baldassano et al. 2015). It is well known that in C57BL/6J mouse model, a chronic exposure to HFD induces obesity and a progressive deterioration of metabolic control, characterized by hyperglycaemia, hyperinsulinaemia and peripheral and central insulin resistance (Surwit et al. 1988, Ahrén et al. 1997, Lee et al. 1995, Nuzzo et al. 2015). Mice after 10 weeks on HFD have greater mass gain compared with standard diet-fed mice, show hyperglycaemia, an impaired glycaemic response following intraperitoneal glucose load, high plasma insulin level after glucose load, increased pancreas weight and β-cell expansion, but not insulin resistance. In HFD-fed mice, GLP2 (3–33) treatment for 4 weeks (from the sixth to the tenth week of diet) does not affect fasting glucose levels, but significantly improves hepatic glucose production, inducing a reduction in body weight gain.
glycaemia; however, it significantly increases glucose intolerance, enhances both fasting and glucose-induced insulin concentrations and reduces sensitivity to insulin. Therefore, the reduction of GLP2R signalling accelerates the process leading to insulin resistance in HFD-fed mice (Baldassano et al. 2015). On the contrary, long-term exposure to GLP2 stable analogue improves the obesity-related glucose dysmetabolism in a concentration-dependent manner (Baldassano et al. 2016a). In fact, HFD-fed mice treated with pharmacological doses of Gly2-GLP2 for 4 weeks show a significant increase in glucose tolerance and exogenous insulin sensitivity and reduction in glucose-stimulated plasma insulin levels in comparison with pair-aged HFD-untreated animals, suggesting that the peptide is able to delay the onset of insulin resistance (Baldassano et al. 2016a). Indeed, a previous study has described the failure of GLP2 to modify diabetes onset in non-obese diabetic mouse, a model of type 1 diabetes (T1D) (Hadjiyanni et al. 2009). Therefore, due to different aetiology of T1D compared with T2D, it could be proposed that the protective role is associated exclusively with obesity conditions. An association between insulin resistance and GLP2 secretion has been found in a pilot study on obese human subjects (Geloneze et al. 2013). Hypothesis has been advanced that GLP2-increased secretion could be the cause of insulin resistance as GLP2 increases absorption of nutrients, especially fatty acids, a key factor for insulin resistance (Delarue & Magnan 2007) or for its glucagonotrophic action in healthy or diabetic subjects (Christensen et al. 2010, Lund et al. 2011). Glucagon is counter-regulatory to insulin action, increasing glucose output and inhibiting glucose uptake in the liver, and it has been linked to insulin resistance in obese subjects with normal or impaired glucose tolerance (Ahrén 2006, Weiss et al. 2011). However, this appears unlikely because bariatric surgery, particularly Roux-en-Y gastric bypass (RYGB) (Saedi et al. 2013), which is the most effective therapy for obesity and T2D (Carlsson et al. 2012, Cummings 2012), increases blood GLP2 (by 200%) at postprandial status (Le Roux et al. 2010). Bariatric surgery normalizes blood glucose concentrations in the majority of T2D humans independent of weight loss (Mingrone et al. 2012, Schauer et al. 2012) and can induce diabetes remission up to 6 years (Cohen et al. 2012). It is likely that the enhancement of nutrient flux into the distal small intestine after bariatric surgery triggers a signal leading to an anti-diabetic effect that does not appear related to gastric inhibitory peptide (GIP) or GLP1 (Breen et al. 2013). In fact, changes in circulating GLP1 are not consistent between models of diabetes that received duodenal–jejunal bypass (Breen et al. 2012). Moreover, bariatric surgery still improves glucose tolerance in GLP1 receptor-deficient HFD-fed mice (Wilson-Pérez et al. 2013). Therefore, GLP2 could be responsible for glycaemic improvement after bariatric surgery and can be considered as a key signal to drive intestinal reprogramming of glucose metabolism (Saedi et al. 2013). In addition, animal studies have shown that GLP2 secretion from ileal tissue is decreased in diabetic conditions (Shan et al. 2013), and reduced numbers of L-cells have been detected in the intestinal tissue from HFD-fed mice compared with intestinal tissue from mice receiving a control diet (Kappe et al. 2014). Therefore, GLP2-decreased production might lead to T2D. Further studies are needed to clarify definitively whether and how GLP2 is involved in the improvement of glycaemic control after bariatric surgery.

We speculate that GLP2 may act as a protective factor against the deregulation of the glucose metabolism that occurs in obese conditions. Of note, in obese patients without T2D, GLP2 concentrations in plasma are higher (8500 pg/mL) (Valderas et al. 2014) than in healthy human subjects (851±230 pg/mL) (Brubaker et al. 1997b). These GLP2 plasma high levels can be interpreted as a beneficial factor against T2D development. Also HFD-fed obese mice show GLP2 plasma levels higher than those in lean animals (Baldassano et al. 2013) and increased gut gene and protein expression of GLP2R (Rotondo et al. 2011b, Baldassano et al. 2013). Although nothing is known about the expression in human individuals, the positive correlation between GLP2 plasma levels and GLP2R mRNA and protein abundance indicates that Glp2r expression is not negatively affected by increased plasma GLP2 concentrations and could be interpreted as an adaptive signal involved in the regulation of glucose metabolism in conditions of obesity. In fact, as endogenous GLP2 causes a trophic effect on the mucosa of the small intestine with increased absorptive surface in HFD-fed obese mice (Baldassano et al. 2013), the hormone could aim to preserve and improve the glucose metabolic disorders induced by HFD. Although down-regulation after exposure to the receptor ligand is a common phenomenon, diverse studies report that exogenous GLP2 or inhibition of DDPIV (which doubles GLP2 levels) augments GLP2R expression in ileum and jejunum (Koopmann et al. 2008, Sueyoshi et al. 2014).
Mechanistic insight

The mechanisms underlying the beneficial effect of GLP2 on glucose metabolism remain to be established.

About glucose homeostasis in healthy mice, an elegant, recent work has pointed out that GLP2 can surely act in the CNS. In fact, GLP2 is able to modulate the excitability of POMC neurons in GLP2R- and PI3K-dependent manner (Shi et al. 2013). Hypothesis has been advanced that GLP2 activates POMC neurons to release α-melanocyte-stimulating hormone. This hormone activates melanocortin receptor 4-positive cholinergic neurons of vagal dorsal motor nucleus that enhance hepatic vagal output to suppress hepatic glucose production (Guan 2014). Alternatively, GLP2 may activate neurons in the nucleus of the solitary tract via afferent vagal inputs to modulate glucose metabolism. In fact, GLP2 activates vagal afferent pathways where GLP2R is expressed (Nelson et al. 2007). Although GLP2-modulated neural circuitries have not been fully defined, it has been speculated that GLP2R activation on vagal afferents will influence the preproglucagonergic neurons in the brainstem nucleus of solitary tract with consequent release of GLP2-activating hypothalamic neurons and vagal outputs from dorsal motor nucleus to regulate control of feeding behaviour and glucose homeostasis (Guan 2014). Anyway, according to these hypotheses, the glycemic control by GLP2 involves fine-tuning vagal outputs. One problem is represented by the identification of the GLP2 source (endocrine L-cells or PPG neurons), responsible for the control of glucose metabolism. Of note, to date, to our knowledge, there is no report on the passage of GLP2 across the blood–brain barrier (BBB); however, peripheral hormone could act in the hypothalamic arcuate nucleus where BBB is semipermeable.

The molecular mechanisms and the tissue targets underlying the beneficial effect of GLP2 on glucose metabolism in obese/HFD-fed mice have not been established yet (Baldassano et al. 2015, 2016a), but different speculations may be made (Fig. 1).

Because no changes in body weight or in the daily food intake have been observed in GLP2 (3–33)- or Gly2–GLP2-treated mice in comparison with untreated animals, an indirect effect mediated by an anti-obesity action has been ruled out (Baldassano et al. 2015, 2016a). It is well known that reduced adiposity could contribute to the preservation of insulin sensitivity because the adipose tissue has a considerable influence on systemic glucose homeostasis through secretion of adipocytokines (McArle et al. 2013). Interestingly, Glp2r mRNA expression has been detected in mouse mesenteric adipose tissue (El-Jamal et al. 2014); however, its functional significance is still unknown. It is important to characterize whether GLP2 increases glucose incorporation in adipocytes when their response to insulin is impaired by obesity conditions. In fact, although there are conflicting reports regarding the alterations in the basal glucose uptake, most reports provide evidence that insulin-induced glucose incorporation is suppressed in the obese state (Talior et al. 2003, Sancho et al. 2006, Crowe et al. 2008), and as GLP2...
rapidly increases intestinal hexose absorption (Cheeseman 1997, Au et al. 2002), it is not unlikely to hypothesize that it contributes to clearance of plasma glucose through an action on adipocytes. In addition or alternatively, GLP2 might influence and modulate the quality and quantity of secreted adipokines and the inflammatory state of adipose tissue.

Another hypothetical target for GLP2 could be represented by pancreas. Indeed, a direct action on β-cell function is improbable because the Glp2r mRNA transcripts have not been detected in pancreatic islets, but only in mouse whole pancreas (Bahrami et al. 2010) or rat and human pancreatic α-cells (de Heer et al. 2007). Despite exogenous GLP2 increases glucagon secretion (Meier et al. 2006, de Heer et al. 2007), elimination of GLP2R signalling in genetically obese mice leads to increased glucagon secretion and α-cell mass, which has been interpreted as due to increased proinflammatory signals (Bahrami et al. 2010), for example interleukin-6, in turn, involved in α-cell mass expansion (Ellingsgaard et al. 2008). Unluckily, glucagon levels were not measured in HFD-fed mice after GLP2 (3–33) or Gly2-GLP2 chronic treatment. Of note, GLP2 and GLP2R expression might change following HFD, as reported in gut tissue (Rotondo et al. 2011b, Baldassano et al. 2013). Moreover, recent studies on glucose-dependent insulinotropic polypeptide (GIP) and GLP1 have pointed out that both hormones are synthesized and secreted from islet α-cells under conditions of cellular stress imposed by cytotoxic attack or increased insulin demand (Fujita et al. 2010, Donath & Burcekin 2013, Moffett et al. 2014). Increased expression of PC1/3 relative to PC2 in islet α-cells directs proglucagon processing away from glucagon towards GLP1 in these conditions (Wideman et al. 2007, Marchetti et al. 2012). As GLP1 and GLP2 are produced by the same convertase in equimolar amount (Janssen et al. 2013), it is likely to hypothesize that GLP2 pancreatic expression also changes in stress conditions, such as derangements of islet cell function associated with prolonged consumption of HFD. Therefore, before reaching any conclusions about a link between GLP2 and pancreas function, it is necessary to verify whether GLP2 and GLP2R expressions in pancreatic islets also change consistently with their beneficial role in glucose metabolism.

It is also possible that GLP2 acts directly on the liver to modulate hepatic function related to glucose or lipid metabolism. Mouse liver expresses GLP2R (El-Jamal et al. 2014); however, nothing is known about other species, including humans. Moreover, fatty liver is strongly associated with insulin resistance (Astrid & Jornayvaz 2013), and non-alcoholic hepatic steatosis has been reported in HFD-fed mice (de Meijer et al. 2010, Fraulob et al. 2010). Indeed, in HFD-fed mice, chronic treatment with GLP2 (3–33) aggravates dyslipidaemia and hepatic lipid accumulation. It increases plasma triglyceride, cholesterol, ALT and AST levels, intrahepatic lipid concentration, reduces HDL and exacerbates the liver steatosis, suggesting that endogenous GLP2 may exert defensive role against lipid imbalance in obesity condition (Baldassano et al. 2016b). However, chronic administration of Gly2-GLP2 for 4 weeks is not associated with remarkable improvements in dyslipidaemia-related circulating parameters, and it does not prevent liver fat accumulation and the presence of microvesicular steatosis, suggesting that the level of insulin sensitivity in peptide-treated mice is not related to an apparently less severe tissue fat infiltration. Therefore, the beneficial effects of GLP2 chronic treatment on insulin sensitivity do not seem to be a consequence of an improvement in lipid metabolism (Baldassano et al. 2016a).

Another potential account for explaining endogenous or exogenous GLP2-protective effects against insulin resistance is related to GLP2 ability to reduce gut permeability and consequently the leakage of bacterial endotoxins into the portal blood circulation (Benjamin et al. 2000). Endotoxemia and low-grade inflammation have been associated with insulin resistance (Hotamisligil 2006, Cani et al. 2007), and activation of inflammatory pathways has emerged as an imperative link between T2D and obesity (Hameed et al. 2015). It is well accepted that GLP2 is involved in modulation of intestinal permeability (Moran et al. 2012). In diabetic rats, plasma lipopolysaccharide, zonulin 1 expression, insulin level and insulin-resistant index are closely related to GLP2 levels (Shan et al. 2013). On the basis of these observations, the authors advanced the very suggestive hypothesis that impaired GLP2 in prediabetic subjects may predispose these patients to T2D by increasing intestinal permeability and endotoxemia-related inflammation. However, prospective studies in humans are needed. They found that glutamine-induced GLP2 secretion is decreased in rats with streptozotocin-induced experimental diabetes (Shan et al. 2013). Impaired GLP1 secretion is a characteristic of the prediabetic situation such as impaired glucose tolerance and gestational diabetic mellitus (Lim & Brubaker 2006) and likely also GLP2 secretion from the same L-cells is impaired. However, the fasting plasma GLP2 concentrations reported in humans with glucose dysmetabolism (Gjesing et al. 2011) or patients with T2D (Aaboe et al. 2010) are lesser than those in healthy human subjects (Brubaker...
et al. 1997b). Also obese mice exhibit an altered gut barrier (Brun et al. 2007), and increased endogenous production of GLP2 induced by prebiotic diet improves gut barrier function (Cani et al. 2009). In fact, the block of the GLP2R exacerbates inflammation, whereas therapy with GLP2 reduces systemic and hepatic inflammation in ob/ob mice (Cani et al. 2009). Therefore, it is conceivable that GLP2 by enhancing epithelial barrier function and limiting the activation of processes that drive inflammation (Moore et al. 2010) can delay and reduce the development of insulin resistance. However, this hypothesis needs to be verified.

**Conclusion and perspective**

New evidence underlines the importance of GLP2 in promoting the control and insulin sensitivity in animal model, particularly in conditions associated with obesity. Results from human studies so far remain inconsistent; therefore, future research should be addressed to clarify the role of GLP2 in preventing human insulin resistance and, in turn, the development of T2D. The potential mechanisms driving the beneficial effects of GLP2 receptor activation may be multiple and not fully elucidated. Greater attention should also be given to investigate on this hormone and its receptor as targets for treatment of obesity-associated diabetes in consideration of the chemical strategies for the design of multifunctional peptides.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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