Gastroenterology and Hepatology From Bed to Bench.
2024 **RIGLD**, Research Institute for Gastroenterology and Liver Diseases

REVIEW ARTICLE

p-ISSN: 2008-2258 e-ISSN: 2008-4234

Biguanides and glucagon like peptide 1 receptor agonists in the amelioration of post liver transplant weight gain; a scoping review of the mechanism of action, safety and efficacy

Benjamin M Mac Curtain[1], Luke O'Brien[1], Omar El Sherif[2], Aidan Mc Cormack[2], Emer Carolan[3], John D Ryan[3], Donal O'Shea[4], Tom K Gallagher[1,2]

[1]Hepatopancreatobiliary Group, St Vincent's University Hospital, Dublin 4, Ireland
[2]National Liver Transplant Unit, St Vincent's University Hospital, Dublin 4, Ireland
[3]Department of Hepatology, Beaumont Hospital, Dublin 9, Ireland
[4]Department of Endocrinology, St Vincent's University Hospital, Dublin 4, Ireland

ABSTRACT

Weight gain post-liver transplant can lead to adverse patient outcomes in the post-transplant period. Pharmacotherapy and other measures can be utilised to reduce the burden and occurrence of weight gain in this population. We explored the mechanism of action, safety, and efficacy of these medications, specifically GLP-1 receptor agonists and metformin, focusing on liver transplant patients.
This scoping review was conducted in line with the scoping review structure as outlined by the PRISMA guidelines. Metformin and GLP-1 receptor agonists have been observed to be safe and effective in liver transplant patients. Experimental models have found liver-centric weight loss mechanisms in this drug cohort. There is a paucity of evidence about the use of antihyperglycemics in a post-transplant population for weight loss purposes. However, some small studies have shown strong safety and efficacy data. The evidence in relation to using these medications in patients with metabolic syndrome for weight loss warrants further study in a transplant population.

Keywords: Liver transplant, Body weight, Non-alcoholic steatohepatitis (NASH).

(Please cite as: **Mac Curtain BM, O'Brien L, El Sherif O, Mc Cormick A, Carolan E, Ryan J, O'Shea D, Gallagher TK. Biguanides and glucagon like peptide 1 receptor agonists in the amelioration of post liver transplant weight gain; a scoping review of the mechanism of action, safety and efficacy. Gastroenterol Hepatol Bed Bench 2024;17(1):17-27. https://doi.org/10.22037/ghfbb.v17i1.2899).**

Introduction

Excess weight gain after LT (liver transplant) is common, and may significantly affect graft and patient outcomes (1-4). It is estimated around 24% and 31% of patients post-LT are obese at 1 and 3 years, respectively (2). The prevalence of MS (metabolic syndrome) in this cohort has been reported as 59.2% after 3 years, progressing to 86.36% at 7 years. Age, weight, increased systolic blood pressure, and serum glucose levels have been reported as independent risk factors for MS development post-LT (5). LT recipients have been observed to gain the most weight when compared to transplant recipients of other organs, with an average of 4.8 kg gained when followed up 6 months to 3 years post-transplant (6). Obesity post LT at one year has been shown to increase the risk of death 2 fold (7).

NASH (nonalcoholic steatohepatitis) is a severe form of NAFLD (nonalcoholic fatty liver disease) characterised by hepatocyte damage which can progress to cirrhosis and HCC (hepatocellular carcinoma), the latter being the primary cause of NASH-related mortality (8). The incidence of NASH is increasing more than any other aetiology; it is projected to become the leading cause of LT worldwide within the next 10-20 years (4, 9-12). Recurrence of NASH can occur post LT and has been commonly observed (11, 13-15). While weight gain post-LT may be

Received: 19 October 2023 *Accepted*: 02 December 2023
Reprint or Correspondence: **Benjamin Mac Curtain,** *St Vincent's University Hospital, Dublin 4, Ireland.*
E-mail: benjaminmaccurtain@rcsi.com
ORCID ID: 0000-0003-4534-2795

associated with adverse outcomes, it is paradoxical that new-onset obesity post-LT (BMI > 30) has been shown to improve overall and graft survival in patients (16). The authors who put forward these results postulated that their patient cohort likely included malnourished patients who gained weight appropriately post-LT. Also, in their weight loss subgroup, there was a higher prevalence of hepatitis C infection and HCC, amongst other malignancies. They also note that with further follow up, their observed benefit of weight gain post-LT may decrease due to the long-term effects of MS. Baseline metabolic co-morbidities and worsening metabolic profile post-LT are the principal drivers of NASH recurrence, which have been seen to reoccur in 41.2% of patients in one study (15). This may increase cardiovascular mortality in the long term after LT (17-20). These patients constitute a high-risk group where therapeutic interventions should be optimised (21, 22).

Metformin, a biguanide, is an oral anti-hyperglycaemic agent, considered first-line therapy in T2DM (23-25). Metformin predominantly acts on the liver, suppressing hepatic gluconeogenesis and reducing circulating blood glucose levels through AMPK activation. Other independent pathways have been linked with metformin's ability to lower glucose levels (24), while also acting on the GI tract, affecting the microbiome and increasing glucose update in the intestine (26). Additional advantages are low cost, favourable safety profile, and weight loss/neutrality (27). A body of evidence illustrates metformin's capacity to induce weight loss in patients, which is the primary interest of this scoping review (28). Metformin (off-label) is successful in reducing anti-psychotic-induced weight gain as well as weight gain in paediatric genetic disorders of obesity (29, 30). It has also been shown to lead to weight loss in NASH patients and is possibly mediated by appetite suppression and increased insulin sensitivity. One meta-analysis reported that metformin, improved liver function and BMI in NAFLD while slightly reducing BMI in NASH patients. However, it did not lead to a histological improvement in the NASH cohort (31). Further meta-analyses have shown metformin's ability to enhance weight loss in NASH / NAFLD (32). Metformin has also been linked to reduced odds of developing HCC (33).

GLP-1 agonists are another class of drugs used in the treatment of T2DM. Liraglutide is also recommended by NICE for the treatment of obesity when fulfilling other criteria (34, 35). Liraglutide and Semaglutide are licensed in the EU for weight loss (36, 37). They have been shown to induce weight loss and improve patient lipid parameters (38). GLP-1 agonists induce insulin secretion and inhibit glucagon secretion while also acting on the pancreatic beta cells and the GI tract, slowing gastric emptying. Similar to metformin, GLP-1 agonists reduce glucose levels and can aid in weight reduction (39). In terms of weight loss, GLP-1 agonists are understood to enhance central satiety and delay gastric emptying to promote a weight reduction (40). GLP-1 receptor agonists have been observed to have an anti-lipogenic effect on hepatocytes, independent of weight loss (41).

The efficacy of liraglutide has shown promising results in a phase 2 study in NASH, with the resolution of histopathological liver biopsies in 39% of patients compared with 9% in the placebo group (42). Semaglutide is one GLP-1 agonist that has been shown to produce weight loss in patients through reduced appetite (43, 44). It has also shown to be a promising treatment for NASH in a large phase 2 randomised controlled trial (45). Similarly, dulaglutide, another GLP-1 agonist, has shown to reduce liver fat content and GGT levels in NAFLD patients (46). The main side effects of GLP-1 agonists are GI-related, with approximately 5% of patients reporting these symptoms as intolerable in trial settings (47).

Methods

This section has been authored with the guidelines Arksey and O Malley set in mind. We have also adopted the recommendations of Levec et al. and included a 6 stage methods model for this scoping review (48, 49). This paper, as a whole, has also been constructed using the PRISMA guidelines available (50).

Study rationale

The basis for this study was to examine if metformin and GLP-1 agonists can be used to reduce weight gain post-transplant. These drugs have a good safety profile, are financially accessible, well studied, and have been demonstrated to contribute to patient weight loss. The reduction of weight post-LT may positively impact graft and patient survival and reduce cardiovascular outcomes.

Study objectives

This scoping review aims to identify, categorise and summarise the available knowledge regarding the mechanisms of action of metformin and GLP-1 agonists for the prevention of weight gain post-LT. Potential safety concerns relating to this patient cohort will be examined. We also will examine the theoretical boundaries about how and if metformin and GLP-1 agonists may result in weight loss from a liver perspective.

Identifying research question

To investigate whether metformin and GLP-1 receptor agonists could be effective for the pharmacological management of weight gain post LT.

To investigate whether using metformin and GLP-1 agonists in post LT patients is safe.

To investigate potential liver-based mechanisms of action by which metformin and GLP-1 agonists may induce weight loss in patients.

Identifying relevant studies

PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials were searched up to 28/4/2023; the search is listed as a supplement. Finally, the reference list of selected articles was examined, and any papers of relevance were also included. 2 independent reviewers were used to carry out the searches, and a 3rd independent reviewer reviewed any discrepancies for inclusion.

Selecting studies

Inclusion Criteria:

Studies examining the mechanism of action of metformin and GLP-1 receptor agonists about weight loss and liver physiology,

Studies evaluating the safety efficacy of metformin or GLP-1 receptor agonists in patients post-LT,

Studies evaluating the weight loss efficacy of metformin or GLP-1 receptor agonists in patients post-LT.

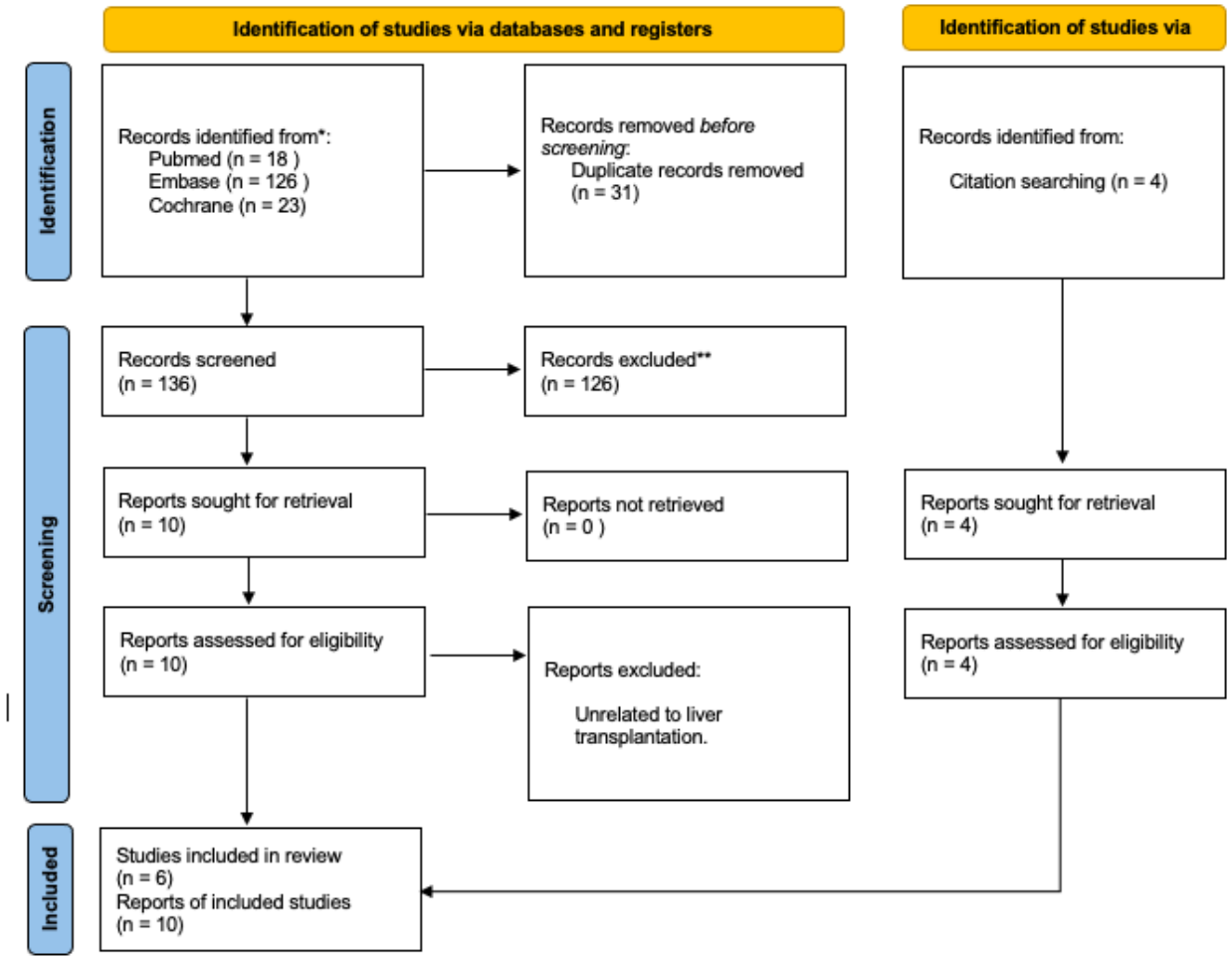

Figure 1. PRISMA chart for studies relating to mechanism of action

Exclusion criteria:
Non-English language
Case reports
Non -liver based mechanisms of action
Non-LT safety and efficacy studies.

Duplicates were screened for Using Rayyan and subsequently deleted (51). As outlined in the PRISMA flow chart, studies were first screened for inclusion/exclusion by both reviewers based on title and abstract. The full texts of the included studies were then screened by all reviewers for final inclusion/exclusion in the scoping review.

Charting the data

The included studies are presented in table format below using the following demographics: Title, Authors, Study design, Sample Cohort, Country, Drug, Mechanism of Action / Safety & Efficacy.

Collating, summarising and reporting results

A summary of the search results is presented in the PRISMA flow chart, listed in Figures 1 and 2. The demographics mentioned above in the Charting the data section will be presented in tabular format. The results and implications for clinical practice will be discussed further narratively in the discussion and conclusion section.

Results

Mechanisms of action – Metformin

The potential mechanisms of action of metformin and GLP-1 receptor agonists in weight reduction post-LT are displayed in Table 1. Genetic downregulation in the liver was observed as a mechanism of action in weight loss (52). Weight loss has also been described as being independent of SIR1 pathways (53). Schommers et al. propose metformin's ability to induce weight loss stem from constructing a futile ATP cycle and using the produced lactate for gluconeogenesis in the liver, as further described in Table 1 (54).

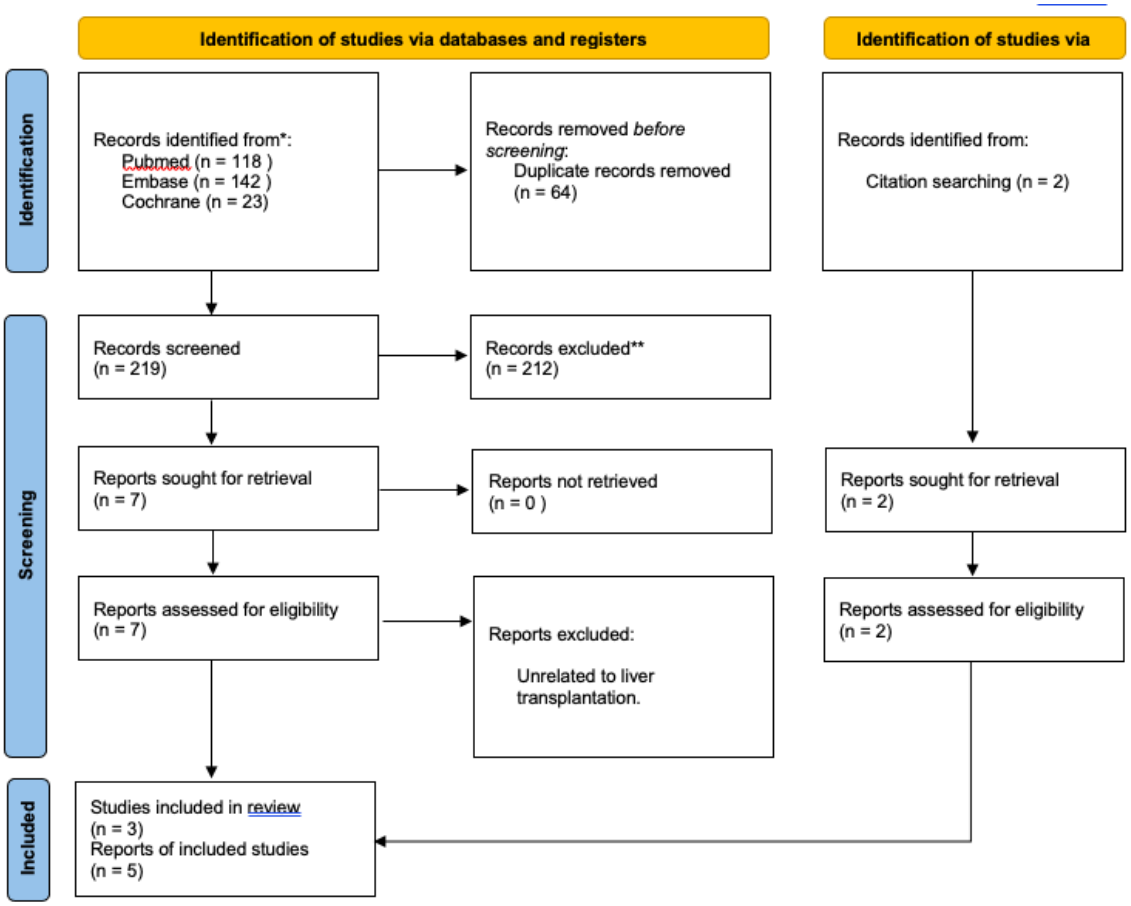

Figure 2. PRISMA chart for studies relating to safety and efficacy

Tokubuchi et al. discuss the fat oxidation pathways altered by metformin. Their study verified the weight loss effect in humans. Then it used rat models to postulate the mechanisms of action of how this change may have come about, such as enhancement of anaerobic glycolysis, accelerated fatty oxidation, and reduction in fat, independent of appetite (55). Contrary to previous studies we have included, it has been put forward that additional energy expenditure is not the cause of weight loss with metformin but rather a decrease in appetite mediated by growth differentiation factor 15 (GDF15) induction (56). Moreover, GDF15 has recently been shown to be a marker of disease severity in NASH patients, with increasing levels seen according to disease stage (57). Lin et al. reported the importance of TNFa reduction in lowering hepatic lipid accumulation when taking metformin (58). Metformin has been shown to decrease chemerin levels (which are usually elevated in obesity) in NASH. However, it is unknown if this leads to its therapeutic effect (59).

Mechanisms of action – GLP-1 receptor agonist

Ben-Shlomo et al. determined the pAMPK as the key mediator in decreasing lipogenic content in a mouse model (60). A reduction in hepatic lipogenic genes was also postulated as a potential mechanism of action of exenatide (61). While Yang et al observed liraglutide to induce weight loss in their mouse study. They also proposed the mechanism of action that HNF1α-dependent PCSK9 expression in HepG2 cells is suppressed as well as low-density lipoprotein receptors (62). Another study presented in Table 1 outlines how liraglutide's weight loss capabilities are seen secondary to its effect on hepatic glucose production and metabolism. They also describe its improvement in lipid levels and how this is likely due to signaling pathways involved in fatty acid degradation, oxidative phosphorylation, and cholesterol metabolism (63). These are, in addition, the known GLP-1 agonists effects discussed in the Introduction.

Safety in LT patients and weight loss efficacy – Metformin

Metformin has been safely used in a LT cohort, as displayed in Table 2. Side effects have been observed to be infrequent or of minor severity, and lactic acidosis is described as an extremely rare occurrence in this population. The most common side effect observed in one study was hypoglycaemia in 14% of patients, it is not stated in this study if this was due to polypharmacy (64). It has also been speculated that due to predominant renal clearance, it should be safe in a LT cohort (65). The use of metformin in LT patients with new or pre-existing T2DM, unless there is hepatic or renal insufficiency, is also endorsed by the American Association for the Study of Liver Diseases and the American Society of Transplantation (66). It has also been argued the use of metformin with reduced eGFR could have some therapeutic benefits, as lactic acidosis in this cohort is still rare (65); however, this use is against manufacturer's guidelines (67). Metformin's potential use as an anti-neoplastic agent is also proposed by some authors, demonstrating a reduction in HCC and all cause cancer related mortality (64, 68-70). Metformin with antimetabolites has been theoretically linked to possible increased GI side effects (68). Of note, there is a lack of evidence relating to metformin (and GLP-1 receptor agonist's) timing of use in the post-transplant period and how NODAT (new onset diabetes after transplant) effects affect this pharmacotherapy. This serves to emphasise the unmet clinical need for a trial in this area (71).

Safety in LT patients and weight loss efficacy – GLP-1 receptor agonists

GLP-1 receptor agonists are considered a safe and effective therapy in transplant patients, including liver, as shown in Table 2. There are few observed interactions with anti-rejection therapy. A significant weight reduction was observed in one small study including different solid organ transplant recipients (72). Three studies examined the use of GLP-1 agonists in a liver transplant population. While the sample sizes were rather small, these preliminary retrospective studies serve as proof of concept. Initial results show they are well tolerated, leading to statistically significant drops in BMI, with little safety concerns (73-75). Of note, the importance of renal function and immunosuppressant monitoring in this population should not be undervalued. These studies did not show any significant change in immunosuppressant levels; however, owing to their small sample size, renal and immunosuppressant levels should be closely monitored in a clinical setting.

Table 1. Possible Mechanisms of Actions for Metformin and GLP-1 receptor agonists

Authors	Title	Design	Sample Cohort	Mechanism of Action
GLP – 1 receptor agonists				
Ben-Shlomo et al (60)	Glucagon-like peptide-1 reduces hepatic lipogenesis via activation of AMP-activated protein kinase	Experimental	Mice	pAMPK is the key mediator through which GLP-1 signals to suppress lipogenesis in the liver through cAMP induction.
Yang SH et al (62)	Liraglutide downregulates hepatic LDL receptor and PCSK9 expression in HepG2 cells and db/db mice through a HNF-1a dependent mechanism	Experimental	Mice	Suppressed both PCSK9 and HNF1α expression in HepG2 cells in a time and concentration dependent manner.
Tølbøl KS et al (63)	Metabolic and hepatic effects of liraglutide, obeticholic acid and elafibranor in diet-induced obese mouse models of biopsy-confirmed nonalcoholic steatohepatitis	Experimental	Mice	Showed effects on hepatic gene transcriptional signatures associated to the canonical effects of GLP-1 receptor agonists on hepatic glucose metabolism and production. Total hepatic galectin-3 and Col1a1 levels were significantly lowered in both DIO-NASH and *ob/ob*-NASH mice.
Kalavalapalli et al (61)	Impact of exenatide on mitochondria lipid metabolism in mice with nonalcoholic steatohepatitis	Experimental	Mice	Exenatide lowered expression of hepatic lipogenic genes (*Srebp1C*, *Cd36*)
Metformin				
Kim et al (52)	Metformin Inhibits Nuclear Receptor TR4–Mediated Hepatic Stearoyl-CoA Desaturase 1 Gene Expression With Altered Insulin Sensitivity	Experimental	Mice	*TR4*-deficient mice have reduced fat-pad size, enhanced lipid oxidation, and insulin sensitivity as a result of reduced *SCD1* gene expression in liver.
Xu F et al (53)	The effects of metformin on improving obesity and hepatic steatosis are sirt1-independent	Experimental	Mice	the effects of Metformin on improving obesity and hepatic steatosis are independent of SIRT1
Schommers P et al (54)	Metformin causes a futile intestinal-hepatic cycle which increases energy expenditure and slows down development of a type 2 diabetes-like state	Experimental	Mice	Circulating levels of doubly labelled glucose-1,6-13C were twice as high in the presence of metformin after oral administration of glucose-1-13C. Breakdown of glucose-1-13C will yield one molecule of lactate-3-13C, which can be converted in the aldolase reaction into doubly-labelled glucose-1,6-13C, when by chance two labelled lactate-3-13C molecules are used for gluconeogenesis. Since more lactate-3-13C is generated in the intestinal wall in the presence of metformin and released into the portal vein, it is more likely that doubly labelled glucose-1,6-13C molecules are generated in the liver. Metformin has been shown to activate anaerobic glycolysis probably due to the efficient translocation into enterocytes mediated by the apical transporters PMAT (SLC29A4) and SERT (SLC6A4).
Tokubuchi I et al (55)	Beneficial effects of metformin on energy metabolism and visceral fat volume through a possible mechanism of fatty acid oxidation in human subjects and rats	Experimental	Human and Rat	Enhanced the phosphorylation of AMPK leading to the phosphorylation and suppression of ACC (acetyl-Co-A carboxylase), increased the levels of fat oxidation-related enzymes such as acyl-CoA synthase, CPT-1 and acyl-CoA dehydrogenase. Caused enhancement of PDK (Pyruvate dehydrogenase kinase), up-regulation of fat oxidation-related enzyme in the liver, UCP-1 in the brown adipose tissue and UCP-3 in the skeletal muscle.
An H et al (56)	The importance of the AMPK gamma 1 subunit in metformin suppression of liver glucose production	Experimental	Mice	Reduced apatite from increased GDF15 induced by metformin. AMPK αβγ heterotrimeric complex - depletion of γ1, but not γ2 or γ3, drastically reduced metformin activation of AMPK cystathionine-β-synthase (CBS) domain in the γ1 subunit in metformin action and found that deletion of either CBS1 or CBS4 negated metformin's effect on AMPKα phosphorylation at T172 and suppression of glucose production in hepatocytes.
Lin HZ et al (58)	Metformin reverses fatty liver disease in obese, leptin-deficient mice	Experimental	Mice	Inhibits hepatic expression of tumour necrosis factor (TNF) α and TNF-inducible factors that promote hepatic lipid accumulation and ATP depletion. Inhibits SREBP-1–DNA binding activity in ob/ob liver nuclear extracts and down-regulates FAS protein expression in ob/ob hepatocytes.

Discussion

Metformin and GLP-1 receptor agonists have shown clinical efficacy for weight loss, while their exact mechanism of action is unknown (76, 77). Previous reviews have touched on the potential positive role of GLP-1 receptor agonists in the post-LT setting (78). Studies suggested that these medications may be suitable for use in this LT cohort of patients from a safety point of view. Table 2 includes two retrospective observational studies in which 46 subjects post-LT were taking metformin (n = 43) or a GLP-1 receptor agonist (n = 3). Data from these studies suggests that the use of these anti-hyperglycaemic drugs in this patient cohort is safe, with only a small incidence of documented adverse drug reactions, including hypoglycaemia and lactic acidosis. Due to the risk of lactic acidosis, it is important to closely monitor eGFR levels in all patients taking metformin, especially in patients post liver transplant. Importantly, the studies we examined showed no evidence that metformin or GLP-1 receptor agonists alter the levels of immunosuppressive drugs.

Table 2. Safety and efficacy of Metformin / GLP-1 receptor agonists in a liver transplant cohort

Authors	Title	N	Design	Country	Safety / Efficacy (weight loss) outcomes
Metformin					
Choi, J. et al (64)	Use of metformin in liver transplant recipient with hepatocellular carcinoma	43 liver	Retrospective observational (Abstract)	South Korea	Hypoglycaemia - 14% of patients, 5 patients – discontinued due to renal impairment. Lactic acidosis did not occur. Disease free survival and overall patient survival rates at 1 and 2 year were 97.7, 94.7 % respectively. No weight data.
GLP 1 receptor agonist					
Krisl, J et al (72)	Long-acting glucagon-like peptide-1 (GLP-1) agonist therapy in post solid organ transplant patients	20 total, 3 liver	Retrospective observational (Abstract)	USA	12 month mean reduction in weight of 16 lbs +- 7.6 (not specified which transplant), no effect on immunosuppressive drugs, 2 patients - dose reduction for side effects, 3 patients - drug discontinuation (cost). There were no events of pancreatitis
Singh, P et al (73)	Largest single centre experience of dulaglutide for management of diabetes mellitus in solid organ transplant recipients.	63 total, 11 liver	Retrospective cohort	USA	12 month mean of paired difference for weight 4.01 Kgs (p value < 0.001) Well tolerated in post-transplant population. No severe hypoglycaemic events and <3% incidence of GI side effects. 3% patients- non-severe hypoglycaemic event .Other 3% patients - GI manifestations (nausea, vomiting, diarrhoea abdominal pain). No increase in the incidence of pancreatitis, gallstones or thyroid cancer. One patient - post-transplant lymphoproliferative disorder.
Thangevelu, T; et al (74)	A retrospective study of glucagon like peptide 1 receptor agonists for the management of diabetes after transplantation	19 total, 7 liver	Retrospective cohort	USA	1.86 Kg CI (−7.79, −1.93) 12 month weight reduction amongst all transplant cohorts (36% of which were liver). 5 patients – nausea, 3 patients – discontinued for GI side effects, 2 patients – discontinued for cost reasons No incidence of severe hypoglycaemia, pancreatitis or malignancy.
Sweiss et al (75) 2022	Single-centre Evaluation of Safety & Efficacy of Glucagon-Like Peptide-1 Receptor Agonists in Solid Organ Transplantation	118 total, 23 liver, 3 kidney-liver	Retrospective cohort	USA	12 month Loss of mean 0.2 kg (SD16) p<0.001, stroke (n=1), heart failure (n=3), 12 patients (10%) - nausea or vomiting, 4 patients (3.4%) - diarrhoea, 5 patients (4.2%) - pancreatitis, 9 patients (7.1%) - at least one hypoglycaemic event. 2 patients had confirmed discontinuation due to adverse effects. Three patients (2.5%) were readmitted during the evaluation period for rejection, 1 (1%) for graft dysfunction, and 1 (1%) for transaminitis. (outcomes not stratified on type of organ transplant, n=118 total)

Another potential benefit of using metformin in this patient cohort is that it has been linked to having a chemoprotective effect, which may decrease the risk of HCC secondary to NASH (79).

The second part of the study aimed to investigate potential mechanisms of action by which metformin and GLP-1 receptor agonists could cause weight loss in humans (Table 1). Due to the nature of experimental pharmacological studies, all studies we identified were undertaken using animal models of mice or rats. This was to suggest biological plausibility behind the observed weight loss associated with metformin and GLP-1 receptor agonists in human LT subjects. A previous review examined how metformin reduces appetite through the activity of hypothalamic AMPK. They also allude to a reduction in lipids production and fat deposition (80). Some of the suggested mechanisms of action include altering hepatocyte cell signaling pathways, expression of proteins/receptors, induction of autophagy, and redistribution of lipids. However, it is important to remember that these experimental studies were undertaken in animal models and not in human subjects, particularly patient's post-LT with risk factors for obesity, including immunosuppressive medications, steroids, donor & recipient BMI, and diet (81).

Limitations include these studies being retrospective and not randomised prospective controlled trials. Another major limitation of the safety and efficacy data presented is that the authors do not stratify results based on the type of transplant cohort. As such, we can postulate that these medications are safe and efficacious in LT patients as they account for a proportion of the patients in each of the studies presented. However, definite prospective studies are required to examine the use and effect of metformin and GLP-1 receptor agonists on weight loss post-LT.

The theoretical boundaries of the mechanisms of action for weight loss post-LT of both metformin and GLP-1 receptor agonists were reviewed. Also, the safety and efficacy of these medications in a LT cohort were assessed from retrospective studies. While high-level evidence supporting their use in the post-transplant setting is lacking, strong clinical evidence exists of benefit in patients with MS. Considering the evidence, prospective interventional studies are warranted to evaluate the role of anti-hyperglycaemic medications in LT recipients.

Conflict of interests

There is no conflict of interest for authors of this article.

References

1. Beckmann S, Denhaerynck K, Stampf S, Saigi-Morgui N, Binet I, Koller M, et al. New-onset obesity after liver transplantation—outcomes and risk factors: the Swiss Transplant Cohort Study. Transpl Int 2018;31:1254-67.

2. Richards J, Gunson B, Johnson J, Neuberger J. Weight gain and obesity after liver transplantation. Transpl Int 2005;18:461-6.

3. Jeong HW, Jung KW, Kim SO, Kwon HM, Moon YJ, Jun IG, et al. Early postoperative weight gain is associated with increased risk of graft failure in living donor liver transplant recipients. Sci Rep 2019;9:20096.

4. Lattanzi B, D'Ambrosio D, Tavano D, Pitoni D, Mennini G, Ginanni Corradini S, et al. Weight gain and De Novo metabolic disorders after liver transplantation. Nutrients 2019;11:3015.

5. Vida Perez L, Montero Alvarez JL, Poyato Gonzalez A, Briceño Delgado J, Costan Rodero G, Fraga Rivas E, et al. Prevalence and predictors of metabolic syndrome after liver transplantation. Transplant Proc 2016;48:2519-24.

6. Beckmann S, Nikolic N, Denhaerynck K, Binet I, Koller M, Boely E, et al. Evolution of body weight parameters up to 3 years after solid organ transplantation: The prospective Swiss Transplant Cohort Study. Clin Transplant 2017;31.

7. van Son J, Stam SP, Gomes-Neto AW, Osté MCJ, Blokzijl H, van den Berg AP, et al. Post-transplant obesity impacts long-term survival after liver transplantation. Metabolism 2020;106:154204.

8. Povsic M, Wong OY, Perry R, Bottomley J. A structured literature review of the epidemiology and disease burden of non-alcoholic steatohepatitis (NASH). Adv Ther 2019;36:1574-94.

9. Perumpail BJ, Khan MA, Yoo ER, Cholankeril G, Kim D, Ahmed A. Clinical epidemiology and disease burden of nonalcoholic fatty liver disease. World J Gastroenterol 2017;23:8263-76.

10. Golabi P, Bush H, Stepanova M, Locklear CT, Jacobson IM, Mishra A, et al. Liver transplantation (LT) for cryptogenic cirrhosis (CC) and nonalcoholic steatohepatitis (NASH) cirrhosis: data from the scientific registry of transplant recipients (SRTR): 1994 to 2016. Medicine 2018;97:11518.

11. Taneja S, Roy A. Nonalcoholic steatohepatitis recurrence after liver transplant. Transl Gastroenterol Hepatol 2020;5:24.

12. Zezos P, Renner EL. Liver transplantation and non-alcoholic fatty liver disease. World J Gastroenterol 2014;20:15532-8.

13. Contos MJ, Cales W, Sterling RK, Luketic VA, Shiffman ML, Mills AS, et al. Development of nonalcoholic fatty liver disease after orthotopic liver transplantation for cryptogenic cirrhosis. Liver Transpl 2001;7:363-73.

14. Malik SM, Devera ME, Fontes P, Shaikh O, Sasatomi E, Ahmad J. Recurrent disease following liver transplantation

for nonalcoholic steatohepatitis cirrhosis. Liver Transpl 2009;15:1843-51.

15. Bhati C, Idowu MO, Sanyal AJ, Rivera M, Driscoll C, Stravitz RT, et al. Long-term outcomes in patients undergoing liver transplantation for nonalcoholic steatohepatitis-related cirrhosis. Transplantation 2017;101:1867-74.

16. Martinez-Camacho A, Fortune BE, Gralla J, Bambha K. Early weight changes after liver transplantation significantly impact patient and graft survival. Eur J Gastroenterol Hepatol 2016;28:107-15.

17. Satapathy SK, Charlton MR. Posttransplant metabolic syndrome: new evidence of an epidemic and recommendations for management. Liver Transpl 2011;17:1-6.

18. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med 2018;24:908-22.

19. VanWagner LB, Holl JL, Montag S, Gregory D, Connolly S, Kosirog M, et al. Blood pressure control according to clinical practice guidelines is associated with decreased mortality and cardiovascular events among liver transplant recipients. Am J Transplant 2020;20:797-807.

20. Campbell PT, VanWagner LB. Mind the gap: statin underutilization and impact on mortality in liver transplant recipients. Liver Transpl 2019;25:1477-9.

21. Tan HL, Lim KB, Iyer SG, Chang SK, Madhavan K, Kow AW. Metabolic syndrome after a liver transplantation in an Asian population. HPB (Oxford) 2015;17:713-22.

22. Izzy M, VanWagner LB, Lee SS, Altieri M, Angirekula M, Watt KD. Understanding and managing cardiovascular outcomes in liver transplant recipients. Curr Opin Organ Transplant 2019;24:148-55.

23. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the american diabetes association (ADA) and the european association for the study of diabetes (EASD). Diabetes Care 2018;41:2669-701.

24. Fujita Y, Inagaki N. Metformin: new preparations and nonglycemic benefits. Curr Diab Rep 2017;17:5.

25. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). Eur Heart J 2019;41:255-323.

26. McCreight LJ, Bailey CJ, Pearson ER. Metformin and the gastrointestinal tract. Diabetologia 2016;59:426-35.

27. Sanchez-Rangel E, Inzucchi SE. Metformin: clinical use in type 2 diabetes. Diabetologia 2017;60:1586-93.

28. Yerevanian A, Soukas AA. Metformin: mechanisms in human obesity and weight loss. Curr Obes Rep 2019;8:156-64.

29. Hilado MA, Randhawa RS. A novel mutation in the proopiomelanocortin (POMC) gene of a Hispanic child: metformin treatment shows a beneficial impact on the body mass index. J Pediatr Endocrinol Metab 2018;31:815-9.

30. Wang M, Tong J-h, Zhu G, Liang G-m, Yan H-f, Wang X-z. Metformin for treatment of antipsychotic-induced weight gain: A randomized, placebo-controlled study. Schizophr Res 2012;138:54-7.

31. Li Y, Liu L, Wang B, Wang J, Chen D. Metformin in non-alcoholic fatty liver disease: A systematic review and meta-analysis. Biomed Rep 2013;1:57-64.

32. Musso G, Gambino R, Cassader M, Pagano G. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. Hepatology 2010;52:79-104.

33. Cunha V, Cotrim HP, Rocha R, Carvalho K, Lins-Kusterer L. Metformin in the prevention of hepatocellular carcinoma in diabetic patients: a systematic review. Ann Hepatol 2020;19:232-7.

34. NICE. National Institute for Health and Care Excellence, Liraglutide for managing overweight and obesity Technology appraisal guidance 2020.

35. NICE. National Institute for Health and Care Excellence, Type 2 diabetes in adults: management NICE guideline 2020.

36. Summary of Product Characteristics of Semaglutide (Wegovy) [Internet]. 2022. Available from: https://ec.europa.eu/health/documents/community-register/2022/20220106154093/anx_154093_en.pdf.

37. Summary of Product Characteristics - Liraglutide (Saxenda) [Internet]. 2021. Available from: https://www.ema.europa.eu/en/documents/product-information/saxenda-epar-product-information_en.pdf.

38. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. N Engl J Med 2015;373:11-22.

39. Aroda VR. A review of GLP-1 receptor agonists: Evolution and advancement, through the lens of randomised controlled trials. Diabetes Obes Metab 2018;20:22-33.

40. Shah M, Vella A. Effects of GLP-1 on appetite and weight. Rev Endocr Metab Dis 2014;15:181-7.

41. Armstrong MJ, Hull D, Guo K, Barton D, Hazlehurst JM, Gathercole LL, et al. Glucagon-like peptide 1 decreases lipotoxicity in non-alcoholic steatohepatitis. J Hepatol 2016;64:399-408.

42. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387:679-90.

43. Blundell J, Finlayson G, Axelsen M, Flint A, Gibbons C, Kvist T, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes Obes Metab 2017;19:1242-51.

44. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021;384:989-1002.

45. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 2020;384:1113-24.

46. Kuchay MS, Krishan S, Mishra SK, Choudhary NS, Singh MK, Wasir JS, et al. Effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD: randomised controlled trial (D-LIFT trial). Diabetologia 2020;63:2434-45.

47. Prasad-Reddy L, Isaacs D. A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond. Drugs Context 2015;4:212283.

48. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005;8:19-32.

49. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010;5:69.

50. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169:467-73.

51. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev 2016;5:210.

52. Kim E, Liu NC, Yu IC, Lin HY, Lee YF, Sparks JD, et al. Metformin inhibits nuclear receptor TR4-mediated hepatic stearoyl-CoA desaturase 1 gene expression with altered insulin sensitivity. Diabetes 2011;60:1493-503.

53. Xu F ZX, Liang H, Weng J. The effects of metformin on improving obesity and hepatic steatosis are sirt1-independent - Integrated Physiology/Obesity. Diabetes 2016;65:458-523.

54. Schommers P, Thurau A, Bultmann-Mellin I, Guschlbauer M, Klatt AR, Rozman J, et al. Metformin causes a futile intestinal-hepatic cycle which increases energy expenditure and slows down development of a type 2 diabetes-like state. Mol Metab 2017;6:737-47.

55. Tokubuchi I, Tajiri Y, Iwata S, Hara K, Wada N, Hashinaga T, et al. Beneficial effects of metformin on energy metabolism and visceral fat volume through a possible mechanism of fatty acid oxidation in human subjects and rats. PLoS One 2017;12:0171293.

56. An H, Wang Y, Qin C, Li M, Maheshwari A, He L. The importance of the AMPK gamma 1 subunit in metformin suppression of liver glucose production. Sci Rep 2020;10:10482.

57. Govaere O, Cockell S, Tiniakos D, Queen R, Younes R, Vacca M, et al. Transcriptomic profiling across the nonalcoholic fatty liver disease spectrum reveals gene signatures for steatohepatitis and fibrosis. Sci Transl Med 2020;12:eaba4448.

58. Lin HZ, Yang SQ, Chuckaree C, Kuhajda F, Ronnet G, Diehl AM. Metformin reverses fatty liver disease in obese, leptin-deficient mice. Nat Med 2000;6:998-1003.

59. Krautbauer S, Wanninger J, Eisinger K, Hader Y, Beck M, Kopp A, et al. Chemerin is highly expressed in hepatocytes and is induced in non-alcoholic steatohepatitis liver. Exp Mol Pathol 2013;95:199-205.

60. Ben-Shlomo S, Zvibel I, Shnell M, Shlomai A, Chepurko E, Halpern Z, et al. Glucagon-like peptide-1 reduces hepatic lipogenesis via activation of AMP-activated protein kinase. J Hepatol 2011;54:1214-23.

61. Kalavalapalli S, Bril F, Guingab J, Vergara A, Garrett TJ, Sunny NE, et al. Impact of exenatide on mitochondrial lipid metabolism in mice with nonalcoholic steatohepatitis. J Endocrinol 2019;241:293-305.

62. Yang SH, Xu RX, Cui CJ, Wang Y, Du Y, Chen ZG, et al. Liraglutide downregulates hepatic LDL receptor and PCSK9 expression in HepG2 cells and db/db mice through a HNF-1a dependent mechanism. Cardiovasc Diabetol. 2018;17:48.

63. Tølbøl KS, Kristiansen MN, Hansen HH, Veidal SS, Rigbolt KT, Gillum MP, et al. Metabolic and hepatic effects of liraglutide, obeticholic acid and elafibranor in diet-induced obese mouse models of biopsy-confirmed nonalcoholic steatohepatitis. World J Gastroenterol 2018;24:179-94.

64. Choi J, Lee K, Rhu J, Gil E, Na B, Oh D. Use of metformin in liver transplant recipient with hepatocellular carcinoma.: Abstract# C1967. Transplantation 2014;98:750.

65. Therasse A, Wallia A, Molitch ME. Management of post-transplant diabetes. Curr Diab Rep 2013;13:121-9.

66. Lucey MR, Terrault N, Ojo L, Hay JE, Neuberger J, Blumberg E, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl 2013;19:3-26.

67. Summary of Product Characteristics Glucophage (Metformin Hydrochloride) [Internet]. 2018. Available from: https://www.medicines.ie/medicines/glucophage-500mg-film-coated-tablets-32305/spc.

68. Sharif A. Should metformin be our antiglycemic agent of choice post-transplantation? Am J Transplant 2011;11:1376-81.

69. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. BMJ 2005;330:1304-5.

70. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care 2006;29:254-8.

71. Peláez-Jaramillo MJ, Cárdenas-Mojica AA, Gaete PV, Mendivil CO. Post-liver transplantation diabetes mellitus: a review of relevance and approach to treatment. Diabetes Ther 2018;9:521-43.

72. Krisl J, Gaber A, Sadhu A. Long-acting glucagon-like peptide-1 (GLP-1) agonist therapy in post solid organ transplant patients: Abstract# B913. Transplantation 2014;98:523-4.

73. Singh P, Pesavento TE, Washburn K, Walsh D, Meng S. Largest single-centre experience of dulaglutide for management of diabetes mellitus in solid organ transplant recipients. Diabetes Obes Metab 2019;21:1061-5.

74. Thangavelu T, Lyden E, Shivaswamy V. A retrospective study of glucagon-like peptide 1 receptor agonists for the management of diabetes after transplantation. Diabetes Ther 2020;11:987-94.

75. Sweiss H, Hall R, Zeilmann D, Escamilla J, Bhayana S, Patel R, et al. Single-center Evaluation of Safety & Efficacy

of Glucagon-Like Peptide-1 Receptor Agonists in Solid Organ Transplantation. Prog Transplant 2022;32:357-62.

76. Ryan D, Acosta A. GLP-1 receptor agonists: Nonglycemic clinical effects in weight loss and beyond. Obesity 2015;23:1119-29.

77. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. Diabetes Care 2012;35:731-7.

78. Cigrovski Berkovic M, Virovic-Jukic L, Bilic-Curcic I, Mrzljak A. Post-transplant diabetes mellitus and preexisting liver disease - a bidirectional relationship affecting treatment and management. World J Gastroenterol 2020;26:2740-57.

79. Grohmann M, Wiede F, Dodd GT, Gurzov EN, Ooi GJ, Butt T, et al. Obesity Drives STAT-1-Dependent NASH and STAT-3-Dependent HCC. Cell 2018;175:1289-306.

80. Malin SK, Kashyap SR. Effects of metformin on weight loss: potential mechanisms. Curr Opin Endocrinol Diabetes Obes 2014;21:323-9.

81. Everhart JE, Lombardero M, Lake JR, Wiesner RH, Zetterman RK, Hoofnagle JH. Weight change and obesity after liver transplantation: incidence and risk factors. Liver Transpl Surg 1998;4:285-96.