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Effects of glucagon-like peptide 1 receptor agonists on comorbidities in older patients with diabetes mellitus

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Abstract: Elderly patients with diabetes are at high risk of polypharmacy because of multiple coexisting diseases and syndromes. Polypharmacy increases the risk of drug–drug and drug–disease interactions in these patients, who may already have age-related sensory and cognitive deficits; such deficits may delay timely communication of early symptoms of adverse drug events. Several glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been approved for diabetes: liraglutide, exenatide, lixisenatide, dulagluatide, semaglutide, and albiglutide. Some are also approved for treatment of obesity. The current review of literature along with clinical case discussion provides evidence supporting GLP-1 RAs as diabetes medications for polypharmacy reduction in older diabetes patients because of their multiple pleiotropic effects on comorbidities (e.g. hyperlipidemia, hypertension, and fatty liver) and syndromes (e.g. osteoporosis and sleep apnea) that commonly co-occur with diabetes. Using one medication (in this case, GLP-1 RAs) to address multiple conditions may help reduce costs, medication burden, adverse drug events, and medication nonadherence.

Keywords: Diabetes mellitus, Glucagon-like peptide-1 receptor agonists, Geriatric, Comorbidities, polypharmacy, Osteoporosis, Parkinson's disease, Non-alcoholic fatty liver disease, Sleep apnea, Alzheimer's

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Key points

- Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have multiple pleiotropic effects that can help reduce polypharmacy in older diabetes patients with co-occurring chronic diseases (e.g. fatty liver disease and hypertension) and syndromes (such as sleep apnea and Parkinson's disease).
- GLP-1 RAs in older patients with diabetes may manifest salutary effects in systems other than the endocrine system.
- The multisystemic effects of GLP-1 RAs warrant more rigorous studies to harness their positive effects while minimizing the risk of negative effects.

Introduction

Medications for type 2 diabetes with low risk of hypoglycemia are especially important in the setting of multiple coexisting chronic diseases (multimorbidity) and advanced age. The risks of hypoglycemia and adverse drug events (ADEs) are amplified in the older adults by myriad diabetic complications: chronic kidney disease affecting drug clearance, stroke and peripheral neuropathy affecting manual dexterity, physical ability and cognition, and diabetic retinopathy affecting proper dosing of insulin.[1,2] Higher rates of complications and mortality are associated with both longer duration of disease and greater age, as well as coexistence of multiple chronic diseases.[3] When diabetes coexist with multiple chronic diseases such as Alzheimer's and Parkinson's disease in an older adults, the risk of serious hypoglycemia is further heightened by exposure to multiple medications (polypharmacy), age-related change in drug metabolism and sensory function, and suboptimal adherence to diet and medications. Hypoglycemic events place older adults with diabetes at greater risk for falls, fractures, depression, cardiac arrhythmias and other cardiac events, dementia, and

reduced quality of life.[4,5] One strategy to reduce hypoglycemic events, polypharmacy, ADEs, cost, and treatment nonadherence in older diabetic patients is to use one medication, such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs), to address multiple conditions and chronic diseases that are commonly associated with diabetes.

Why is it important to favor a strategy of treating many conditions with one therapeutic agent? Many older adults with diabetes present with concomitant multiple conditions and chronic diseases that complicate their treatment, with use of multiple medications with potential for ADEs and burdensome lifestyle changes. A 2011 study found that about two-thirds of Medicare beneficiaries had two or more chronic conditions, including diabetes.[6] In addition to the known cardiovascular complications of diabetes (including coronary artery, peripheral artery, and cerebrovascular diseases), diabetes has been associated with nonalcoholic fatty liver disease (NAFLD),[7] cognitive impairment and dementia,[5] mood disorders, and pain.[8] Older adults in general are at higher risk for sleep apnea[9,10] and bone loss and fractures.[11] This review presents evidence and illustrative cases on the effects of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on diabetes-associated comorbidities (e.g. NAFLD and hypertension) and geriatric syndromes (e.g. Parkinson's and sleep apnea) beyond the endocrine system. GLP-1 RAs may allow clinicians, especially geriatricians and primary care physicians, caring for clinically complex diabetes patients, to address multiple symptoms and conditions with one medication—GLP1RAs. Such a 'one-stop shop' approach can lead to reduction of medication burden, adverse drug events, hypoglycemic episodes, medication costs, and treatment nonadherence.

The mechanism of action of GLP-1 RAs in diabetes has been well documented in both human and animal studies.[12–14] Briefly, the gastrointestinal tract releases GLP-1 when food is ingested. GLP-1 receptor agonists stimulate GLP-1 receptors expressed on pancreatic islet beta cells, but also those expressed in cells in multiple systems, thus potentially explaining the other beneficial effects of GLP-1 RAs,[12,13] as discussed below and presented in Table 1.[14–54] The use of GLP-1 RAs is associated primarily with dose-related gastrointestinal side effects (nausea, diarrhea, vomiting), and is not indicated in patients at risk for pancreatitis or kidney disease.[55] Despite these contraindications, a recent meta-analysis ($n=4330$) found GLP-1 receptor agonists superior to alternative incretin-based therapy, dipeptidyl peptidase-4 (DPP-4) inhibitors, in reducing hemoglobin A1c (HbA1c).[56]

Methodology of evidence review

The primary aim of the current review was to characterize the secondary effects of GLP-1 RAs that may be relevant to clinically complex older adults with diabetes and multimorbidity, in whom polypharmacy is a concern.[57,58] In September 2017, a PubMed search was conducted for relevant terms, including glucagon-like peptide-1 receptor agonists, exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, and semaglutide, and suspected secondary effects (e.g. exenatide + cardiovascular); a search of cited and related articles was done in PubMed and Google Scholar. Sources were examined until no new human studies were found. The relevance of each reference was discussed until consensus was obtained. Animal studies were included when human studies were missing. Expert opinion was included when deemed relevant by the authors. A summary of results (Table 1) was developed using previous guides.[54,57] Drugs were evaluated based on the effect on a secondary system (i.e. blood lipids, hypertension, liver, brain, etc.) and effects refined as indicated. Levels of Evidence for Therapy/Prevention/Etiology/Harm: 1a, Systematic reviews (with homogeneity) of randomized controlled trials (RCTs); 1b: Individual RCTs (with narrow confidence interval); 1c: All-or-none RCTs; 2a: Systematic reviews (with homogeneity) of cohort studies; 2b: Individual cohort study or low quality RCTs (e.g. <80% follow-up); 2c: 'Outcomes' Research; ecological studies; 3a: Systematic review (with homogeneity) of case-control studies; 3b: Individual case-control study; 4: Case-series (and poor quality cohort and case-control studies); and 5: Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.[54]

Secondary effects and mechanism of action of GLP-1RAs on comorbidities: evidence from clinical and basic science research

Effects on the cardiovascular system

The effect of GLP-1 receptor agonists on triglyceride, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels has been evaluated in multiple studies.

Table 1. Level of evidence for secondary effects of GLP-1 RAs.

First author (year)	Evidence type	Sample size	Relevant findings	Limitations	Level of evidence*	Clinicaltrials.gov number
Cardiovascular						
Sun (2015)[14]	Systematic review and meta-analysis	35 trials with 13 treatments (n = 14,340)	GLP-1 RAs were associated with modest reductions in LDL-C, total cholesterol, and triglycerides but no significant improvement in HDL-C	Further evidence needed to indicate cardiovascular outcomes	1a	
Robinson (2013)[15]	Systematic review and meta-analysis	32 trials at least 12 weeks long	Liraglutide or exenatide reduced SBP −1.79 mmHg (95%CI: −2.94, −0.64) versus placebo and −2.39 mmHg (95%CI: −3.35, −1.42) versus active control; DBP reductions were not statistically significant	Shares some studies with Sun (2015)[14]	1a	
Sun (2015)[16]	Systematic review and meta-analysis	60 trials; (n = 22,890 for SBP; n = 18,795 for DBP)	Bayesian network meta-analysis indicated that exenatide, liraglutide, and albiglutide were ranked as most beneficial among 14 treatments in terms of effect on SBP and DBP		1a	
Marso (2016)[17]	LEADER clinical trial	9340 with established CVD or risk factors	Over a median duration of 3.8 years, liraglutide significantly reduced death from CV causes, nonfatal MI, nonfatal stroke (HR 0.87, 95% CI 0.78–0.97)		1b	NCT 01179048
Marso (2016)[18]	SUSTAIN-6 clinical trial	3297 with established CVD, CHF or CKD	Over a median duration of 2.1 years, semaglutide significantly reduced death from CV causes, nonfatal MI, nonfatal stroke (HR 0.74, 95% CI 0.58–0.95)		1b	NCT 01720446
Simó (2015)[19]	RCT of exenatide vs glimepiride	1029	Over 36 months, those who took metformin plus exenatide (n = 515) had improved HDL and triglycerides. Significantly fewer needed additional hypertensive (20.4 vs 26.4 %; p = 0.026) or lipid-lowering medication (8.4 vs 12.8 %; p = 0.025)	Open-label trial; those not maintaining glycemic control dropped out	1b	NCT 00359762
Armstrong (2016)[20]	Double-blind, randomized, placebo-controlled trial	18 patients	Liraglutide reduced cholesterol-LDL (−0.7 vs. +0.05mmol/l; $p < 0.01$), ALT (-54 vs. −4.0IU/l; $p < 0.01$) and serum leptin, adiponectin, and CCL-2 (all $p < 0.05$)	Small sample size	1b	NCT 01237119

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Table 1. (Continued)

First author (year)	Evidence type	Sample size	Relevant findings	Limitations	Level of evidence*	Clinicaltrials.gov number
Blackman (2016)[21]	Double-blind RCT	359 nondiabetic obese patients with OSA	Patients took either 3.0 mg liraglutide ($n = 180$) or placebo ($n = 179$). Liraglutide reduced SBP compared with placebo but no significant effect on DBP	2.23% of subjects dropped out during trial	1b	
Zhao (2013)[22]	Review of preclinical and five clinical studies	234 patients with MI, heart failure or CAD	Patients improved (LVEF scores or other measures of coronary strength) after hospital infusion of GLP-1 or long-term infusion	Small sample size (studies of 10, 12, 20, 20 and 172 patients)	2a	
Katout (2014)[23]	Systematic meta-analysis and meta regression study of 33 trials	12,469	12–56 weeks of GLP-1 therapy was associated with a weighted mean difference (WMD) in SBP of −2.22 mmHg (95CI: −2.97 to −1.47); and WMD in DBP of −0.47 (95%CI: −1.20 to −0.25) using a random effect model. Meta-analysis showed a SBP reduction of −1.56 mmHg (95%CI: − 2.78, −1.35)		2a	
Tanaka (2011)[24]	Review		Exenatide reduced mean SBP by −3.8 mmHg and DBP −2.3 mmHg vs placebo. Liraglutide also reduced mean SBP (−5.7 mmHg) and DBP (−3.7 mmHg) in obese patients over a 3-week period. Pooled data from 6 trials showed antihypertensive effects of exenatide lasted for 6 months. An open labelled study showed exenatide reduced SBP and DBP for up to 3.5 years vs lifestyle modification alone	Some reviewed studies were open labelled	2a	
Liu (2012)[25]	Rat and human experiment	10 human renal artery specimens	In 10 human renal artery specimens from normotensive and hypertensive patients, EX-4 resulted in nitric oxide production SHR aortic endothelial cells and improved endothelial function in renal arteries from hypertensive patients	Effects of sitagliptin on resistant arteries were not studied	5	
Liver						

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Table 1. (Continued)

First author (year)	Evidence type	Sample size	Relevant findings	Limitations	Level of evidence*	Clinicaltrials.gov number
Carbone (2015)[26]	Meta-analysis using random effects model	136 with NAFLD and T2DM	Treatment with GLP-1 agonists or DPP-4 inhibitors (24-48 weeks) significantly decreased serum ALT, a marker for liver inflammation. Studies with imaging showed decreased steatosis, inflammation, and fibrosis	Potential confounding in 36 of 136 participants (19.4%) who also took metformin; lack of controls or tissue samples	1a	
Armstrong (2016)[20]	Double-blind, randomised, placebo-controlled trial	18 patients	Liraglutide increased hepatic insulin sensitivity (−9.36 vs. −2.54% vs low-dose insulin; $p < 0.05$); decreased hepatic de novo lipogenesis in vivo (−1.26 vs. +1.30%; $p < 0.05$); and decreased lipogenesis in primary human hepatocytes (24.6% vs. untreated controls; $p < 0.01$)		1b	NCT 01237119
Klonoff (2008)[27]	Placebo controlled trial	217 patients	Patients (151 with 3.5 years exenatide) with elevated serum ALT at baseline ($n = 116$) had reduced ALT (−10.4 ± 1.5 IU/L; $p < 0.0001$) and 41% achieved normal ALT		1b	
Brain						
Parkinson's disease						
Aviles-Olmos (2014)[28]	Single blind trial	44 'moderate' PD patients (20 treated, 24 controls)	At 12 months post-treatment, exenatide treated patients scored 5.6 points higher in MDS-UPDRS motor scale ($p = 0.002$) and 5.3 points higher on the Mattis DRS-2 ($p = 0.006$). Previously lowered LED doses were increased by 24 months	3 patients (1 in treatment group, 2 controls) required DBS during the post-treatment period; analysis was adjusted for these patients. Timed tasks, depression, sleep scores and QOL scores not statistically different	1b	

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Table 1. (Continued)

First author (year)	Evidence type	Sample size	Relevant findings	Limitations	Level of evidence*	Clinicaltrials.gov number
Aviles-Olmos (2013)[29]	Single blind trial	45 'moderate' PD patients	Treated patients improved 2.7 points in MDS-UPDRS at 12 months; untreated patients declined 2.2 points ($p = 0.037$). Differences persisted to 14 months	Treated patients were slightly older and had slightly shorter disease course than controls. Should be considered 'proof of concept' because of sample size; LED reduced in 5 treated patients due to increase in LID	1b	NCT 01174810
Athauda (2017)[30, 31]	Phase 2 double blind placebo control trial	60 'mid-stage' PD patients	Significant improvements in severity of PD motor symptoms persisted after 48 weeks of treatment and 12-week wash-out period	Secondary outcome measures did not reach significance. Cautions to consider the results 'proof of concept' rather than 'proof of efficacy'	1b	
Woert and Mueller (1971)[32]	Clinical study	24 PD patients treated with levodopa	Impaired insulin response and abnormal GTT found in PD patients treated with levodopa that could not be accounted for by age, diet or disease state		3b	
Athauda and Foltynie (2017)[33]	Invited review			Need to determine long term safety and efficacy in terms of motor skills; determine mechanism of GLP-1 agonists to determine whether it treats the disease or symptoms	5	
Li (2016)[34]	Review article		Incretins (GLP-1 and GIP) have shown positive results in clinical trials. Similar compounds have been tested in preclinical studies (GIP agonists, DPP-4 inhibitors, OXM, dual GLP-1/GIP receptor agonists, and triple GLP-1/GIP/glucagon receptor agonists	Neurodegenerative diseases = AD, PD, HD, ALS.	5	
Alzheimer's Disease						

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Table 1. (Continued)

First author (year)	Evidence type	Sample size	Relevant findings	Limitations	Level of evidence*	Clinicaltrials.gov number
Li (2014)[35]	Review and meta-analysis	Cross-sectional and longitudinal studies	7 of 10 major epidemiological studies ($n = 2998$ stroke patients) reported that those with T2DM have a 2–3 times higher risk of post-stroke dementia	None studied relationship of prediabetes and risk of dementia; different values may exist between studies of T2DM, vascular dementia, AD	1a	
Geji (2016)[36]	Placebo-controlled double-blinded study	38	GLP-1 RAs prevented the decline of brain glucose consumption but had no effect on fibrillary amyloid accumulation or cognition.	Small sample size; 6 month study	1b	NCT 01469351
Craft (2012)[37]	randomized, double-blind, placebo-controlled clinical pilot trial	104 with MCI (64) or mild-to-moderate AD (40)	After 4 months' treatment, memory improvements in treated group persisted for a further 2 months		1b	
Lerche (2008)[38]	Randomized double-blinded placebo-controlled crossover study	10 healthy men	The cerebral metabolic rate of glucose was reduced by 12–18% with GLP-1 infusion but the difference was not significant. GLP-1 reduces BBB transport of glucose in general in the brain and helps to maintain cerebral glucose balance using PET scan and may also have neuroprotective effects linked to both peripheral and cerebral glucose metabolism	Small sample size	1b	
Watson (2005)[39]	Placebo-controlled, double-blind, parallel-group pilot study	30 subjects with mild AD or amnestic MCI	Subjects were randomized to a 6-month course of rosiglitazone (4 mg daily; $n = 20$) or placebo ($n = 10$). Memory and attention approved at 6 months in treated subjects		1b	
Bae and Song (2017)[40]	Review		Argues for use of GLP-1 RAs against 'type 3 diabetes' (AD)		5	

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Table 1. (Continued)

First author (year)	Evidence type	Sample size	Relevant findings	Limitations	Level of evidence*	Clinicaltrials.gov number
Bak (2011)[41]	Expert opinion		Convincing amount of evidence has shown a beneficial effect of GLP-1 RA treatment on cognitive function	Expert opinion	5	
Depression/mood disorders						
Mansur (2017)[42]	Open label trial of liraglujtide (4-week pilot)	19 with MDD or BD	The TMTB (trail making test B) executive function increased significantly from baseline to week 4, as did the DSST (executive function, speed of processing, attention) and RAVLT (learning memory/acquisition)	Small sample size; open-label design; lack of placebo group or other hypothetical agents; short duration of the study; low statistical power	2b	
Grant (2011)[43]	Matched groups on exenatide or insulin for poorly controlled T2DM	71 patients with exenatide, 67 with insulin	Scores of treatment satisfaction, well-being and depression improved for those on exenatide, but not those on insulin ($p < 0.05$)		2b	
Sleep apnea						
Amin (2015)[44]	Individual RCT	27 (18 treated, 9 controls)	Overall AHI for treated group decreased from 50 ± 32 to 38 ± 30 events/hour ($p = 0.002$). In 2.7% of the treated group, AHI declined by 44%, but 30% showed no response to treatment. Controls had no change in AHI	Small sample size, short duration	1b	
Blackman (2016)[21]	Double-blind RCT	359 nondiabetic obese patients with OSA	Patients took 3.0 mg liraglutide ($n = 180$) or placebo ($n = 179$). Most reduction in mean AHI occurred in first 12 weeks. At 32 weeks, AHI decreased significantly in the liraglutide group vs placebo (12.2 ± 1.8 versus 6.1 ± 2 events /hour). Liraglutide reduced SBP vs with placebo but no significant effect on DBP	2.23% of subjects dropped out during trial	1b	
Matsumoto (2016)[45]	Individual cohort study	96 OSA patients	In patients with varying levels of OSA (43 had 3 months' CPAP), fasting GLP-1 was significantly higher in those with severe OSA ($n = 30$), and was positively correlated with AHI	Small sample size; all patients Asian; no control for CPAP group	2b	

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Table 1. (Continued)

First author (year)	Evidence type	Sample size	Relevant findings	Limitations	Level of evidence*	Clinicaltrials.gov number
Reutrakul (2017)[46]	Cross sectional study	71	Increasing OSA severity was associated with lower GLP1 response to glucose challenge after adjusting for sex, BMI and glycemic status	Small sample size, cross-sectional study	4	
Bone						
Su (2015)[47]	Meta-analysis of 16 RCTs	11,206 patients	Liraglutide was associated with a significantly lower risk of incident bone fractures (MH-OR = 0.38, 95% CI 0.17–0.87), but exenatide treatment was associated with a doubled risk (MH-OR = 2.09, 95% CI 1.03–4.21)		1a	
Mabilleau (2014)[48]	7 RCTs	4255 patients in 7 RCTs	Pooled MH-OR for GLP-1 receptor agonists was 0.75 (95% CI 0.28–2.02, $p = 0.569$) in trials versus DPP-4	Studies with a follow up <52 weeks had higher MH-OR, but difference was not significant	1a	NCT 00935532
Li (2015)[49]	Parallel, randomized, placebo-controlled trial	62 patients newly diagnosed with T2DM	24-week treatment with exenatide, insulin or pioglitazone improved glucose control, but had no impact on bone turnover markers or BMD		1b	
Iepsen (2015)[50]	RCT	37 healthy obese women on weight loss diet	Total BMC loss was four times greater in the control group vs the liraglutide group; the latter also had 16% greater bone formation after weight loss and at 52-week follow up		1b	NCT 02094183
Driessen (2015)[51]	Population-based cohort study	216,816	GLP-1 RA use not associated with a decreased risk of bone fracture vs. users of other antihyperglycemic drugs		2b	
Driessen (2015)[52]	Case control study	229,114 cases (with fracture), 229,114 controls	Current GLP-1 RA use was not associated with a decreased risk of fracture [adjusted (adj.) OR 1.16; 95%CI 0.83–1.63]. Osteoporotic fracture risk was also not associated with current GLP-1 RA use (adj. OR 0.78; 95%CI 0.44–1.39)	Average GLP-1 RA use was short (36 weeks), perhaps limiting ability to detect association	4	

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Table 1. (Continued)

First author (year)	Evidence type	Sample size	Relevant findings	Limitations	Level of evidence*	Clinicaltrials.gov number
Skin						
Faurschou (2014)[53]	Case report	1 59-year old male	Moderate and stable plaque psoriasis of 15-year duration improved immediately and at 3 months with liraglutide titrated to 1.8 mg over 5 weeks		4	
Hogan (2011)[54]	Case series ($n = 2$)	2 male patients 48 and 49 years	6 weeks of liraglutide significantly reduced PASI scores from 13.2 to 10.8 and from 4.8 to 3.8.		4	

AHI, apnea hypopnea index; ALS, amyotrophic lateral sclerosis; ALT, alanine transaminase; aMCI, amnestic mild cognitive impairment; ARIT, apomorphine induced rotation test; BBB, blood brain barrier; BD bipolar disorder; BMC, bone mineral content; BMD, bone mineral density; CAD, coronary artery disease; CHF, congestive heart failure; CI (confidence interval); CKD, chronic kidney disease; CPAP, continuous positive airway pressure therapy; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; DBS, Deep Brain Stimulation; DPP-4, dipeptidyl peptidase-4; EX-4, extendin 4; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HD, Huntington's disease, HR, hazard ratio; LED, Levodopa equivalent dose; LID, L-dopa-induced dyskinesia; LVEF, left ventricular ejection fraction; Mattis DRS-2, Mattis Dementia Rating scale; MDD, major depressive disorder; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; MH-OR, Mantel-Haenszel odds ratio; MI, myocardial infarction; NAFLD; Nonalcoholic fatty liver disease; OXM, oxyntomodulin; PASI, Psoriasis Area and Severity Index; PD, Parkinson's Disease; QOL, quality of life; RA, receptor agonist; RCT, randomized controlled trial; SBP, systolic blood pressure; WMD, weighted mean difference.
*Levels of Evidence for Therapy/Prevention/Etiology/Harm:[54]
1a:Systematic reviews (with homogeneity) of RCTs.
1b:Individual RCTs (with narrow confidence interval).
1c:All or none RCTs.
2a:Systematic reviews (with homogeneity) of cohort studies.
2b:Individual cohort study or low quality RCTs (e.g. <80% follow-up).
2c:'Outcomes' Research; ecological studies.
3a:Systematic review (with homogeneity) of case-control studies.
3b:Individual case-control study.
4:Case-series (and poor quality cohort and case-control studies).
5:Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.

In the meta-analysis by Sun and colleagues, 35 trials were analyzed for the effects of exenatide, liraglutide, or taspoglutide on lipid profile.[14] GLP-1 agonist therapy was associated with modest decreases in LDL-C, triglycerides, and total cholesterol, but no significant effect on HDL-C. Compared with placebo, the GLP-1 agonist group demonstrated a reduction in LDL-C from −0.08 mmol/L to −0.16 mmol/L.[14] Exenatide, liraglutide, and taspoglutide treatment led to a decrease in total cholesterol, while liraglutide and taspoglutide led to a reduction in triglyceride levels.[14] Other studies showed a reduction in one or more lipid levels with exenatide or liraglutide.[19,20]

Hypertension, found in 30–70% of those with type 2 diabetes, is a well-known risk factor for both cardiovascular and cerebrovascular disease.[24] The mechanisms for the antihypertensive effects of GLP-1 RAs include a reduction in the risk of left ventricular hypertrophy, an increase in sodium excretion and increased atrial natriuretic peptide (ANP) secretion, leading to reduced blood pressure (BP).[22] Indeed, GLP-1 receptor-deficit mice secreted no ANP when given GLP-1 RAs, indicating a putative BP-regulating pathway *via* a gut-heart GLP-1 receptor-dependent and ANP-dependent axis.[22] In humans, Zhao found strong evidence from clinical and preclinical studies that GLP-1 RA treatment can benefit patients with myocardial ischemia and heart failure.[22] Sun and colleagues, in a second systematic review and network meta-analysis of 26,654 patients, found exenatide to significantly reduce systolic blood pressure (SBP) compared with insulin (–4.86 mmHg 95%CI: −8.33, −1.40) or sulphonylurea (–3.00 mmHg 95% CI: −5.84,–1.35). In the same review, albiglutide reduced BP compared with placebo but not when compared with other treatments. Exenatide also reduced diastolic blood pressure (DBP) significantly (–0.9 mmHg 95%CI: −1.68, −0.11), as did sulphonylurea (–1.60 mmHg 95%CI: −2.86, −0.35). Dulaglutide produced no significant effect.[16] A similar meta-analysis of 32 trials found that liraglutide or exenatide reduced SBP −1.79 mmHg (95%CI: −2.94, −0.64) *versus* placebo and −2.39 mmHg (95%CI: −3.35, −1.42) *versus* active control; DBP reductions were not statistically significant.[15] Liraglutide also reduced mean SBP (–5.7 mmHg) and DBP (–3.7 mmHg) in obese patients over a 3-week period.[24]

Long-term studies indicate a sustained effect of GLP-1 RAs on BP. For example, in a systematic meta-analysis and meta-regression study of 33 trials covering 12–56 weeks ($n = 12{,}469$), Katout and colleagues found a weighted mean difference (WMD) in SBP reduction of −2.22 mmHg (95%CI: −2.97 to −1.47), and WMD in DBP reduction of −0.47 mmHg (95%CI: −1.20 to −0.25) in the GLP-1 RAs group *versus* control.[23] The greatest BP-lowering effect was found with exenatide, which reduced mean SBP by −3.8 mmHg at 5–10 mcg and DBP −2.3 mmHg at 10 mcg *versus* placebo. Data from six large trials showed that the antihypertensive effects of exenatide lasted 6 months, with greatest reduction in patients with SBP greater than 150 mmHg. In another open labeled study, exenatide treatment for up to 3.5 years reduced SBP and DBP in diabetic patients, in comparison with lifestyle modification alone.[24]

The effect of GLP-1 RAs on cardiovascular health has been studied in a number of large trials. Four trials of the cardiovascular effects of GLP-1 RAs in patients with diabetes and cardiovascular risk factors have been published: ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN-6 (semaglutide), and EXSCEL (exenatide extended release).[17,18,59,60] Of these, LEADER and SUSTAIN-6 showed significant reductions in the primary outcome and reduction in cardiovascular death. Liraglutide reduced the primary outcome (a combination of first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, including silent, or nonfatal stroke) 13% [hazard ratio (HR) 0.87, 95% CI 0.78, 0.97] and reduced cardiovascular death 22% over a median follow up of 3.8 years.[17] Semaglutide, over a median follow up of 2.1 years, reduced the same primary outcome 26% (HR 0.74, 95% CI 0.58, 0.95) but did not significantly affect cardiovascular death.[18] A meta-analysis of seven trials, including LEADER and SUSTAIN-6, concurs that liraglutide and semaglutide both offer protection from adverse cardiovascular events, but only liraglutide reduced cardiovascular mortality.[61] One review recommended that GLP-1 RAs could replace metformin as a first-line therapy in those with type 2 diabetes with high cardiovascular risk factors or those who are intolerant to metformin.[62] The PIONEER 6 trial, to determine the cardiovascular safety of semaglutide in type 2 diabetes patients with high cardiovascular risk, is currently

ongoing and has enrolled 3183 patients in 21 countries (NCT02692716).[63]

Effects in the liver

NAFLD is common in patients with type 2 diabetes.[7] Indeed, a 2015 systematic review in JAMA estimates 66% of adults over 50 who are overweight and have diabetes are also likely to have the NAFLD subtype, nonalcoholic steatohepatitis with advanced fibrosis.[64] NAFLD and diabetes together worsen hepatic function and hasten development of diabetes complications.[7] Mechanistic evidence from several animal studies indicate that treatment of diabetes with GLP-1 RAs affects hepatic function both directly and indirectly. Treatment of mice with exenatide for 60 days significantly decreased hepatic lipid content.[65] In mice fed a high fat/fructose diet, the liraglutide group demonstrated a significant reduction in hepatic lipid accumulation as well as significant improvements in insulin sensitivity and glucose tolerance, lower serum triglyceride and cholesterol levels.[66]

Multiple clinical trials and meta-analyses show improved hepatic function in NAFLD as measured by transaminase levels, biopsy, and images. In studies of patients with both type 2 diabetes and NAFLD (diagnosed by imaging or biopsy), GLP-1 receptor agonists (liraglutide and/or exenatide) and a DPP-4 inhibitor (sitagliptin) lowered serum alanine aminotransferase (ALT) levels by a mean of 14.1 IU/L. Other studies of GLP-1 RAs using ultrasound or proton magnetic resonance spectroscopy assessment of fat content or liver biopsy showed a 42% median relative reduction in intrahepatocellular lipid in imaging, and significant histological improvement in the biopsy group.[26] Other RCTs found similar positive results: an average reduction of ALT of −54 IU/L in the liraglutide group versus −4.0 IU/L in the placebo group, with $p < 0.01$ and a significant decrease in de novo lipogenesis in the liraglutide group (−1.26% *versus* +1.30%; $p < 0.05$);[31] and a mean ALT reduction over 3 years in 217 diabetes patients values, with mean ALT change of −10.4 +/– 1.5 IU/L; ($p < 0.0001$) in a 3-year clinical trial of exenatide therapy.[27]

Effects in the brain

GLP-1 receptors are present in many areas of the brain, including neurons, glia, and astrocytes. Studies show an abundance of GLP-1 receptors in the central nervous system (CNS), especially in areas of the brain critical for memory, learning, and locomotion.[67–69] These include the pyramidal neurons of the hippocampus and the cerebral cortex. In addition, activated glial cells express GLP-1 receptors under stress, suggesting a potential role for GLP-1 RAs in modulating the inflammatory response.[67–70] Han and colleagues found that GLP-1 RAs and GLP-1 receptors are produced by the hippocampus, first as a post-translational product of preglucagon, acting as a growth factor in the brain.[71] GLP-1 is neurotrophic *via* its protection of neurons against glutamate-mediated apoptosis and oxidative injury. Indeed, both mice and rats overexpressing hippocampal GLP-1 receptors experienced substantial neurotic growth, learned faster, and had better memory.[70–80] In addition, administration of liraglutide significantly protected against amyloid beta 25–35-induced reduction in spatial cognition in rats.[71–74] Similar anti-amyloid effects were demonstrated with lixisenatide.[72]

Parkinson's disease. The evidence from basic science research, mostly in animal models,[80,82–85] led to human studies and clinical trials of GLP-1 RAs,[28–32] especially since GLP-1 agonists/analogs have been shown to cross the blood-brain-barrier (BBB) and stimulate the GLP-1 receptor in the brain.[37,81] Lerche and colleagues found that GLP-1 RAs modulate transport of glucose through the BBB and help maintain cerebral glucose balance, as shown by PET scans. This function may have neuroprotective effects via peripheral and cerebral glucose metabolic pathways that may benefit Parkinson's Disease (PD) patients.[37] A 12-month trial of exenatide in 44 'moderate' PD patients (20 treated, 24 controls) found that the treated patients improved by 2.7 points in Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores, while untreated patients declined 2.2 points ($p = 0.037$); these differences lasted for 14 months.[29] In an open-labelled RCT of 45 patients with PD, a mean improvement of 1.8 points in the Mattis dementia rating scale, was observed at 24 months in patients treated with exenatide, compared with a mean deterioration of 3.5 in the control group.[28] Similarly, in a single center, double-blind, randomized placebo-controlled 60-week trial with 62 participants,[30] the exenatide group had MDS-UPDRS scores 3.5 points lower than the placebo group. This improvement in severity of PD motor systems persisted for 48 weeks of treatment and through

the 2-week wash-out period.[20] These results are considered 'proof of concept' rather than 'proof of efficacy,' and larger and longer RCT studies are needed to confirm these findings.[86]

Alzheimer's disease. Impairment of short-term or long-term memory and learning is a key symptom of Alzheimer's disease (AD), the cause of 60–80% of all cases of dementia in older adults.[87,88] Thus, there is an urgent need for more effective medications to treat AD and other neurodegenerative diseases.[89,90] GLP-1 RAs in particular have shown promise as therapy for AD and other causes of dementia.[87,89,90] The hallmark of AD is the accumulation of amyloid plaques in the hippocampus and cerebral cortex,[72,88] and the effects of GLP-1 RAs on reducing amyloid load and neuroinflammation are documented.[78,79] Type 2 diabetes and AD share several clinical and pathologic characteristics, including the role of insulin signaling in neuroprotection, neuronal stem cell activation, and general cell growth.[39,90] GLP-1 RAs help normalize insulin signaling,[91] and GLP-1 receptors are located widely throughout the brain.[92–94]

In a 26-week, placebo-controlled double-blinded intervention ($n = 38$) in AD patients with long-standing diabetes, the use of liraglutide prevented the expected decline of cerebral metabolic rate for glucose uptake (using FDG-PET) in the parieto-temporal frontal and posterior cingulate cortices.[35] Clinical studies on GLP-1 RAs provide evidence of promising neuroprotective, and even regenerative, properties that may be utilized in patients with AD or PD.[28–32,35–38] Given further clinical evidence, they have the potential to be the therapeutic agent of choice for diabetic patients with AD.[28,40,89,90] For example, in clinical trials, exenatide-treated patients showed a clear improvement in cognitive score, suggesting a beneficial effect on cognition and memory; this benefit was still visible 1 year after the trials.[28] Optimism for the benefit of GLP-1 RAs in AD has recently been dampened, however. A recent Cochrane review found no relationship between the use of diabetes medications and cognitive decline during a follow-up period of 40–60 months,[95] and a recent review of clinical treatment of diabetes in the elderly argues for a holistic approach that incorporates caregiver input, screening for geriatric syndromes, functional medicine, and periodic re-evaluation of targets and strategies.[96]

Depression/mood disorders. Mood disorders (major depressive and anxiety disorders) are common coexisting chronic diseases in diabetic patients, which increase morbidity, disability, and mortality in these patients.[8] GLP-1 receptor agonists have been found to affect areas of the brain associated with emotional regulation.[97] In a meta-analysis, McIntyre and colleagues found improvement in mood and cognition with GLP-1 RAs, regardless of psychiatric diagnoses.[98] More recently, Billings and colleagues found that those taking weekly GLP1-RAs (exenatide, dulaglutide, or semaglutide) had greater health-related quality of life (i.e. improved treatment satisfaction and willingness to continue treatment) over those taking daily GLP-1 RAs; weekly semaglutide was associated with the greatest treatment satisfaction.[99] The cognitive effects of GLP-1 RAs are especially important in patients with diabetes and psychiatric comorbidities, given the high prevalence of cognitive impairment and antipsychotic related metabolic syndrome in this population.[100] In a case-controlled study of diabetic patients ($n = 138$), Grant and colleagues found that exenatide-treated patients had significantly reduced Hospital Anxiety and Depression Scale (HADS) scores at 6 months when compared with the insulin-treated group, indicating greater treatment satisfaction and higher wellbeing.[42] Another open labelled trial with 19 patients showed a significant increase from baseline to week 4 in scores for the Trail Making Test B (executive function), in Digit Symbol Substitution Test (DSST; executive function, speed of processing, attention) and in the Rey Auditory Verbal Learning Test (RAVLT; learning memory)/acquisition), in response to liraglutide, especially in patients with comorbid bipolar disorder (BD) or major depressive disorder (MDD) and cognitive impairment.[41]

The mechanisms for the above findings have not been well described but initial studies provide some insight. Sharma and colleagues found that liraglutide reversed the behavioral depression and metabolic abnormalities (weight gain, increased blood lipids) associated with long-term atypical antipsychotic treatment in rats.[100] In another experimental rat model, Anderberg and colleagues found that liraglutide reversed the antipsychotic-induced metabolic abnormalities in rats, and that chronic injections of exenatide were neither anxiogenic nor anxiolytic, but caused a reduction in depression-like behavior.[97] The

presence of GLP-1 receptor in the dorsal raphe (DR), a major area of serotonergic neurons, suggests a potential role for GLP-1 RAs in emotional processing and mood regulation. Activation of the DR-GLP-1 receptor alone is sufficient to increase anxiety-like behavior − an effect similar to findings in the initial use of selective serotonin reuptake inhibitors.[97] In summary, use of GLP-1 RAs in older multimorbid diabetes patients with depression and bipolar and other psychiatric disorders may help improve mood and cognition, while reducing the metabolic side effects of antipsychotics such as obesity, hyperlipidemia, and hypertension.[100]

However, those with nondementia psychoses are likely to be unaffected, or any effect is not clinically relevant. A recent study from Denmark found no cognitive improvement from exenatide in obese patients with clinically stable schizophrenia who were also receiving antipsychotic treatment. The authors noted, however, that 3 months may not have been enough time for cognitive effects to manifest. These subjects were primarily young and middle-aged adults, and none were over 65 years (exenatide group: $n=23$, age 37.1 ± 10.6, range 19–65 years; placebo group: $n=22$, age 34.5 ± 10.1, range 19–56 years).[101]

Pain. Pain syndromes of multifactorial etiologies are highly prevalent, but potentially treatable, causes of excess disability in diabetes patients.[8] GLP-1 RAs may be useful in pain management. Gong and colleagues, in a rat model experiment, found GLP-1 receptors expressed in spinal microglia and upregulated after peripheral nerve injury.[102] When GLP-1 RAs stimulate spinal microglia GLP-1 receptors, beta-endorphins are released and pain diminishes. Exenatide and GLP-1 have been associated with a decrease in pain hypersensitivity *via* its antinocioceptive effect, an effect mediated by activation of GLP-1 receptors. This effect can be blocked by naloxone, suggesting a modulatory effect on opioidergic pathways.[102,103]

Sleep apnea. Obstructive sleep apnea (OSA) symptoms include snoring, apneas during sleep, and excessive daytime somnolence.[9,10] Untreated, OSA has been linked to hypertension, stroke, congestive heart failure, type 2 diabetes, and depression. OSA is common in mid and later life especially in older obese men.[9,10] In an RCT of 30 OSA subjects, Amin and colleagues found that the overall apnea-hypopnea index (AHI) for patients treated with liraglutide decreased from 50+ or −32 to 38+ or −30 ($p=0.002$). In 70% of the treated group, AHI declined by 44% or 20+ or −12 events per hour, while 30% showed no response to treatment. AHI was 32.6+ or −21 *versus* 33.2+ or −21 at follow up. Body mass index (BMI) did not change from baseline in either group.[43] In another double blinded RCT ($n=359$), Blackman and colleagues found that the greatest reduction in AHI occurred in the first 12 weeks of treatment and minimally thereafter. In the liraglutide group, AHI was significantly reduced after 32 weeks compared with placebo, independent of age, baseline BMI or OSA severity. Fewer subjects in the liraglutide group met the criteria for OSA diagnosis after treatment.[21] A cross-sectional study by Reutrakyl and colleagues ($n=70$) found that increasing OSA was associated with a lower GLP-1 response to a glucose challenge after adjusting for sex, BMI, and glycemic status.[45] In an individual cohort study, Matsumoto and colleagues ($n=96$) found higher fasting GLP-1 levels in a severe OSA group, and concluded that this was a compensatory mechanism to increase insulin levels to prevent the development of diabetes, since hypoxia leads to pancreatic damage.[44] The benefit of GLP-1 RAs may therefore increase as the severity of OSA increases.

Effects in bone

Evidence, mostly from basic science research (largely in rodents and *in vitro* studies), supports the salutary effects of GLP-1 RAs on bone mass and strength reported in human studies; however, the effect on fracture prevention is less clear. Overall, research shows the presence of GLP-1 receptors in bone tissue, especially in osteoblasts, osteocytes, and osteoclasts.[104–109] The thyroid parafollicular cells, known as C-cells, make a peptide hormone called calcitonin that controls calcium homeostasis. A rise in serum calcium levels stimulates calcitonin secretion from C-cells, which, in turn, inhibits osteoclast-induced bone resorption. The C-cells express GLP-1 receptors; C-cell activation suppresses bone-resorption activity and osteoclast proliferation.[104–106] The localization of GLP-1 receptors in bone and C-cells has led to various mechanistic studies explaining the antiresorptive and bone-building effects of GLP-1 RAs. These mechanisms include an increase in the activity of osteoblast in response to GLP1R

agonist; an increase in the activity of C-cells, which leads to increased levels of calcitonin – a potent inhibitor of osteoclast-induced bone resorption; and improvement in collagen synthesis, bone blood supply, and bone architecture.[106–109]

Reports of the effect of GLP-1 agonist on bone integrity in humans are mixed, ranging from no difference between GLP-1 agonist and other antidiabetic medications,[48,50] to significant reduction in fractures with liraglutide and a higher rate of fractures with exenatide.[46] The meta-analysis by Mabileau and colleagues analyzed the fracture rate of seven RCTs, and found that GLP-1 receptor agonists (specifically, exenatide in three studies, liraglutide in four) did not significantly reduce incidents of bone fracture in comparison with other antidiabetic medications.[47] Another meta-analysis by Su and colleagues of 16 RCTs using GLP-1 agonists showed that patients receiving liraglutide had a significantly decreased risk of bone fracture, whereas those receiving exenatide had an increased risk of bone fracture.[46] The bone-protective effect of liraglutide was further supported by Iepsen and colleagues in their RCT of 17 obese women randomized to liraglutide or placebo; liraglutide increased bone formation by 16% and prevented the bone loss associated with weight loss.[49] A more recent Bayesean network meta-analysis of many of the same studies found that exenatide was the safest GLP-1 RA to prescribe to reduce fracture risk, followed by dulaglutide, then liraglutide, albiglutide, lixisenatide, and finally semaglutide.[110] Other controlled trials and cohort studies have also shown no significant difference between the GLP-1 agonist group and the control group using other anti-glycemic drugs.[50,51] However, these studies failed to separate out the effect of different GLP-1 agonist medications (liraglutide *versus* exenatide *versus* others). Some of the inconsistency between trials may reflect differences among patients in dose and duration of GLP-1 RAs, type and number of coprescribed medications, severity of diabetes, adherence to diabetes medications, and comorbidity burden. Additional studies are needed to clarify the effect of different GLP-1 receptor agonists on bone formation.

Effects on skin

The evidence for GLP-1 RAs on skin diseases is still very preliminary, with antioxidant, anti-inflammatory, and neuromodulatory mechanisms likely responsible for the effects. In a case report by Faurschou and colleagues, psoriasis was found to clear after liraglutide was prescribed for the patient's type 2 diabetes.[52] In another case, the patient was taken off liraglutide and psoriasis returned; two subsequent patients showed lower Psoriasis Area and Severity Index (PASI) scores with treatment.[53] In all four cases, PASI scores lowered immediately. Another report showed plaque clearance with sitagliptin.[111] Glycemic control was not associated with plaque clearance, suggesting another mechanism, perhaps anti-inflammatory or the operation of T-cells.[52,53,112]

Contraindications

Important clinically relevant adverse effects (nausea, vomiting, and diarrhea) warrant mention.[113–116] These adverse effects are extensions of the pharmacological effects of the GLP-1 RAs, especially when they are started at higher doses in frail elders with dementia and multiple coexisting morbidities. Indeed, the side effects of nausea (about 50%, mostly mild and transient) and vomiting (about 10%) were the reasons most commonly reported for discontinuing GLP-1 RAs, which occurs in about 5% of patients. Rarely, the gastrointestinal side effects can lead to dehydration and acute kidney injury.[55] The severity of gastrointestinal side effects depends on both the dose of the GLP-1 RAs and the coprescribed drug, such as metformin. Lowering the dose, using long-acting GLP-1 RAs, and avoiding pro-diarrhea/emetic drugs (e.g. metformin or high-dose cholinesterase inhibitors) can reduce the incidence of side effects.[116]

In a systematic analysis of 32 clinical trials with GLP-1 RAs, Bettge and colleagues found a significant relationship between the risk of nausea and diarrhea and the dose of long-acting GLP-1 RAs; however, this relationship was not significant for vomiting. They also found that concomitant use of metformin significantly increased the odds of nausea ($p = 0.04$) and vomiting ($p = 0.0009$).[116] Among all GLP-1 RAs, lixisenatide treatment resulted in the least nausea and vomiting, and semaglutide the most, while all long-acting GLP-1 RAs had lower rates of nausea and vomiting, but higher rate of diarrhea, than short-acting ones.[116–118] Minor side effects, such as injection site reactions, headache, and nasopharyngitis, rarely led to drug discontinuation and were usually transient. Because of the

pancreatic and thyroid tissue effects of GLP-1 RAs, reports of adverse effects from animal studies and database analyses have raised concerns about the potential for increased risk pancreatitis, pancreatic cancer, and thyroid cancer in GLP-1 RA users, but no cause and effect associations have been seen in any of these studies.[113–116] Most recently, once-weekly semaglutide has been associated with an increased risk of diabetic retinopathy complications.[119] Nevertheless, patients on GLP-1 RAs should be monitored for these side effects if the clinical scenario fits. Although GLP-1 RAs do not cause hypoglycemia, all clinicians should reduce or discontinue concomitant sulphonylurea or insulin to avoid hypoglycemia.

Illustrative cases

Case #1

A 76-year-old woman was seen regularly by her primary care physician (PCP) for type 2 diabetes, hypertension, hypertriglyceridemia, and vascular dementia/AD. The duration of her conditions were unclear except that she had been on antihypertensive, antilipid and antidiabetes medications for at least 6 years. Her medications included donepezil 10 mg daily, hydrochlorothiazide 25 mg daily, lisinopril 20 mg daily, sitagliptin 100 mg daily, metformin 1000 mg twice daily, pravastatin 10 mg daily, gemfibrozil 600 mg twice daily, omega-3-fatty acid 2000 mg twice daily, aspirin 81 mg daily, and insulin glargine 50–55 units subcutaneous injection daily. Diabetes remained uncontrolled, with HbA1c levels at 12–13 and BMI at 29 kg/m^2. Because of prior episodes of recurrent hypoglycemia in the setting of dementia [Mini-Mental State Examination (MMSE) = 25/30], the patient's caregiver and clinician agreed to a noninsulin approach for glycemic control. Thus, the patient was started on weekly injections of 2 mg exenatide, changed 5 months later to daily 1.2 mg liraglutide injections. Eight months thereafter, hypoglycemia episodes abated, HbA1c levels fell to 5.3%, BMI to 23 kg/m^2, triglycerides from 849 mg/dl to 250 mg/dl, total cholesterol from 202 mg/dl to 111 mg/dl, thyroid stimulating hormone (TSH) from 1.65 mIU/l to 0.80 mIU/l (normal range 0.45–4.70 mIU/l), and SBPs averaged in the 100s mmHg. Because of the aforementioned numbers, indicating tight control of blood pressure, diabetes, and lipids, all medications were stopped except vitamin D3 and aspirin. The patient's family stopped donepezil because of concerns about additional weight loss and low appetite. After 3 months of cessation, lisinopril, and liraglutide were restarted due to an increase in HbA1c levels to 8% and SBP into the 140s mmHg. MMSE done at the 1-year follow-up visit was 21. Because the patient had nausea on a full GLP-1 RA dose, the patient's caregiver decided on her own, against the physician's instruction for daily dosing, to reduce daily liraglutide to three times per week. The nausea abated. The HbA1c level was 7.3% at the 4-month follow up.

Case #2

A 73-year-old man was being followed by his PCP for type 2 diabetes, AD and vascular dementia, low energy, OSA on a continuous positive airway pressure (CPAP) machine, obesity (BMI 43 kg/m^2), uncontrolled hypertension (SBP in the 170s mmHg), benign prostatic hyperplasia, hypothyroidism, depression, hyperlipidemia, and seasonal allergic rhinitis. The patient had received a diagnosis of dementia 2 years prior to his first PCP visit. He had been on medications for the rest of his medical conditions for at least 5 years prior to his visit, but the patient and his spouse were unsure of the onset and duration of his conditions. The patient received a once-a-day dose of the following medications: amlodipine 5 mg, losartan 100 mg, hydrochlorothiazide 25 mg, levothyroxine 25 µg, sitagliptin 100 mg, bupropion SR 100 mg, finasteride 5 mg, rivastigmine patch 9.5 mg, simvastatin 20 mg, aspirin 81 mg, and venlafaxine 37.5 mg. Fexofenadine 60 mg was twice daily. Diabetes control was adequate for age, with multiple HbA1c results ranging between 7% and 8%. The patient's BMI remained at 43 kg/m^2 with worsening of his mood (Patient Health Questionnaire-2, PHQ-2), energy, and OSA. MMSE was 22. His Geriatric Depression Scale (GDS) score was zero, but his PHQ-2 screen positive for depression. His SBP remained in the 170s mmHg despite three drugs. His tests showed total cholesterol was 222 mg/dl, LDL was 147 mg/dl, and TSH was 4.28 mIU/l. After a discussion with the patient and his spouse about using GLP-1 RAs for diabetes and weight, the patient was started on subcutaneous exenatide 2 mg per week. His sitagliptin was stopped. Simvastatin was changed to pravastatin, which is hydrophilic and thus has lower cognitive side effects. His venlafaxine was increased to 75 mg daily to further help his depression as well as his mild anxiety symptoms. About 6 months thereafter, the patient's average

SBP remained in the 130s mmHg, his BMI remained around 39 kg/m^2, and his HbA1c levels ranged from 7% to 8%. His MMSE was 17, despite the family reporting an improvement in patient's conversational skills, attention, and memory for people names. His repeat blood tests showed LDL was 103 mg/dl, total cholesterol was 180 mg/dl, and TSH was1.91 mIU/l. Both his GDS and PHQ-2 depression screens were negative. The patient reported being more energetic, sleeping better, and feeling less depressed, prompting discontinuation of his bupropion (which, according to his spouse, worsened his sleep). The patient's family stopped fexofenadine because of abatement of the allergic rhinitis symptoms and concerns about the patient taking too many pills. Sitagliptin was stopped due to overlapping mechanism of action (incretin-based therapeutics) with GLP-1 RAs. The patient continued to tolerate the exenatide with no reports of nausea, vomiting, diarrhea, or abdominal pain (known side effects of exenatide). After up to 15 months of periodic follow-up, the patient remained nondepressed and free of gastrointestinal side effects.

The improvement in HbA1c, weight, lipid profile, and blood pressure in the cases described above (especially in our first patient) is consistent with recent findings from the SUSTAIN-5 Trial, a 30-week multicountry randomized double-blind, placebo-controlled trial of weekly semaglutide 0.5 or 1.0 mg among 397 diabetes patients on stable basal insulin dose.[120] However, unlike the subjects in the SUSTAIN-5 trial, basal insulin was discontinued in our elderly dementia patient, because of recurrent hypoglycemia episodes.

Clinical implications

A key approach from our clinical experience to reducing the risk of GLP-1 RA-related gastrointestinal side effects is by starting at a low dose (e.g. at 25% of recommended starting dose in frail elders) and by slow titration over months instead of weeks. Another approach is switching to a different GLP-1 RA, as was done for Case #1 above, as the minor pharmacokinetic and dynamic differences between GL-1 RAs may alter an individual patient's risk of adverse effects. The preponderance and variety of these GLP-1 RAs studies (both human and animal, and *in vitro*) would seem to indicate the need for larger, more rigorous, studies. In particular, more understanding is required of how genetic differences in drug metabolism and GLP-RA effects on renal functions among patients alter the secondary effects of GLP-1 RAs and the mechanisms behind these differences.[121–123] For example, recent evidence supports the renoprotective effect (*via* reduced proteinuria and increased natriuresis) of GLP-1RAs: a slowing of progression of diabetic kidney disease, and a better preservation of renal functions in diabetes patients with CKD.[122,123] Future studies are needed to understand the roles of genomics and metabolomics in determining the person-to-person differences in response to GLP-1RAs. Data from such studies and others have the potential to inform diabetes clinical practice guidelines vis-à-vis the use of GLP-1RAs.

One limitation of this review is that many of the studies lack the 'gold standard' rigor of RCTs. The number and variety of effects do, however, appear to indicate a trend. RCTs or database analysis of a large number of patients may be the next step before recommending prescribing changes.

Conclusion

GLP-1 RAs have multiple pleiotropic activities that may help reduce polypharmacy in elderly diabetes patients living with other serious comorbidities. The cases and evidence presented here support the potential for GLP-1 RAs to reduce the incidence or symptoms of those conditions (i.e. PD, osteoporosis, NAFLD, lipoprotein disorders, and hypertension), among other common comorbidities in older adults with diabetes. The effectiveness of GLP-1 RAs in patients with diabetes with impairments in systems other than the endocrine system – cardiovascular, liver, brain, bone, and skin – may reflect the multisystemic role of GLP-1 receptor functions. Inasmuch as the effects of GLP-1 RAs (both positive and negative) are multisystemic, they warrant more rigorous studies on how to harness the positive effects while minimizing the risk of negative effects. The usefulness of GLP-1 RAs in reducing polypharmacy and medication costs in patients with diabetes merits further study in a large randomized, controlled, clinically comparative trial.

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Ethical standards

The UTMB Institutional Review Board (IRB) has deemed this study exempt from IRB review.

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