Glucagon-like peptide-1 analogues in monogenic syndromic obesity

Ali, Sadaf; Baig, Shanat; Wanninayake, Subadra; da Silva Xavier, Gabriela; Dawson, Charlotte; Paisey, Richard; Geberhiwot, Tarekegn

DOI:
10.1111/dom.15398

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Ali, S, Baig, S, Wanninayake, S, da Silva Xavier, G, Dawson, C, Paisey, R & Geberhiwot, T 2023, 'Glucagon-like peptide-1 analogues in monogenic syndromic obesity: Real-world data from a large cohort of Alström syndrome patients', *Diabetes, obesity & metabolism*, pp. 1-8. https://doi.org/10.1111/dom.15398

Received: 3 October 2023 | Revised: 10 November 2023 | Accepted: 20 November 2023

DOI: 10.1111/dom.15398

ORIGINAL ARTICLE

WILEY

Glucagon-like peptide-1 analogues in monogenic syndromic obesity: Real-world data from a large cohort of Alström syndrome patients

Sadaf Ali MRCP[1,2] | Shanat Baig PhD[1,2] | Subadra Wanninayake MD[1] | Gabriela da Silva Xavier PhD[2] | Charlotte Dawson PhD[1] | Richard Paisey MRCP[3] | Tarekegn Geberhiwot PhD[1,2]

[1]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

[2]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK

[3]Torbay and South Devon NHS Foundation Trust, Torquay, Torbay, UK

Correspondence
Tarekegn Geberhiwot, PhD, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.
Email: tarekegn.geberhiwot@uhb.nhs.uk

Funding information
Big Lottery Fund grant, Grant/Award Number: RGT/1/010332749

Abstract

Aim: To examine the real-world efficacy of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in monogenic obesity in patients with Alström syndrome (ALMS).

Methods: We screened 72 UK adult patients with ALMS and offered treatment to 34 patients meeting one of the following criteria: body mass index of 25 kg/m^2 or higher, insulin resistance, suboptimal glycaemic control on antihyperglycaemic medications or non-alcoholic fatty liver disease.

Results: In total, 30 patients, with a mean age of 31 ± 11 years and a male to-female ratio of 2:1, completed 6 months of treatment with GLP-1 RAs either in the form of semaglutide or exenatide. On average, treatment with GLP-1 RAs reduced body weight by 5.4 ± 1.7 (95% confidence interval [CI] 3.6-7) kg and HbA1c by 12 ± 3.3 (95% CI 8.7-15.3) mmol/mol, equating to 6% weight loss ($P < .01$) and 1.1% absolute reduction in HbA1c ($P < .01$). Significant improvements were also observed in serum total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and alanine aminotransferase. The improvement of metabolic variables in our cohort of monogenic syndromic obesity was comparable with data for polygenic obesity, irrespective of weight loss.

Conclusions: Data from our centre highlight the non-inferiority of GLP-1 RAs in monogenic syndromic obesity to the available GLP-1 RA-use data in polygenic obesity, therefore, these agents can be considered as a treatment option in patients with ALMS, as well as other forms of monogenic obesity.

KEYWORDS
Alström, GLP-1 receptor agonists, insulin resistance, monogenic syndrome, obesity, type 2 diabetes

1 | INTRODUCTION

Obesity is a global pandemic, with an estimated 650 million adults affected worldwide.[1] It is a complex multisystem disorder leading to type 2 diabetes (T2D), dyslipidaemia and hypertension with associated increased cardiovascular morbidity and reduced life expectancy.[2,3]

Obesity is considered a polygenic disease, with environmental factors playing a key role.[4] However, in recent years, an increasing number of genetically determined obesity disorders have been identified, which contribute up to 5% of global obesity.[5] One form of monogenic obesity is Alström syndrome (ALMS), which is caused by mutations in the *ALMS1* gene and is characterized by childhood obesity, extreme insulin resistance (IR), T2D, accelerated non-alcoholic fatty liver disease (NAFLD) and premature cardiovascular events.[6,7] ALMS is rare with an estimated disease prevalence of 1:1 000 000 live births. Approximately 80%-90% of patients with ALMS develop early onset obesity between 18 months and 4 years of age that progresses to hyperinsulinaemia and T2D in 80% of those older than 16 years.[8,9] There is no disease-modifying therapy, and survival beyond the age of 50 years is rare.[10]

Glucagon-like-peptide 1 receptor agonist (GLP-1 RA) is a gut-derived incretin-based hormone mainly produced by enteroendocrine L cells in the distal intestine, alpha cells in the pancreas, and the central nervous system.[11] GLP-1 RAs have been widely used in the treatment of T2D.[12] Among multiple mechanisms of improving T2D, they stimulate insulin release from the pancreas in response to a glucose challenge and inhibit glucagon secretion, thereby improving glycaemic control.[13] In addition, they have been shown to be effective for weight loss[14] and improvement in insulin sensitivity, independent of their effects on beta cell function.[15] Recently, results of weekly semaglutide in obese people without diabetes for 68 weeks were striking, with clinically significant and sustained weight loss of 15 kg.[16]

The precise mechanisms by which GLP-1 RAs cause weight loss are still unclear, but current evidence suggests that a combination of effects on the gastrointestinal system and the brain may contribute to overall weight loss.[17] Emerging evidence of the efficacy of GLP-1 RAs in weight reduction and the improvement of metabolic variables in hypothalamic causes of obesity suggests that they may have a role in the regulation of hypothalamic centres of satiety and appetite regulation.[18] Recent data suggest that melanocortin-4 receptor, which is an important regulator of energy homeostatic pathways in the hypothalamus, resides in the primary cilium of hypothalamic neurons.[19] Because the *ALMS1* protein is localized in the primary cilium and is involved in microtubule organization, particularly in the formation of cilia, which are an important regulator of energy homeostatic pathways in the hypothalamus,[20–22] we postulated that GLP-1 RAs may be a treatment option for monogenic obesity in patients with ALMS. Here, we report the UK clinical experience of using GLP-1 RA treatment in 30 adult patients with ALMS.

2 | MATERIALS AND METHODS

2.1 | Patients and study setting

All adult patients with a clinically and genetically confirmed diagnosis of ALMS were screened for starting incretin-based therapy as a part of standard clinical care. The UK adult Alström Syndrome National Service is one of the largest centres in the world; it was previously based at Torbay Hospital and then later moved to the University Hospitals of Birmingham. The study was conducted at both Torbay Hospital and the University Hospitals of Birmingham. Patients who met at least one of the following criteria were offered treatment: body mass index (BMI; ≥ 25 kg/m^2), IR, suboptimal glycaemic control on antihyperglycaemic medications (AHAs) or NAFLD. We excluded patients under the age of 18 years, BMI less than 25 kg/m^2 and no evidence of IR, known active malignancy, end-stage renal failure or severe pulmonary and/or cardiovascular disease. Incretin-based therapy was administered alongside education on diet and lifestyle by a qualified specialist dietician in inherited metabolic diseases as part of their standard care, and data were gathered retrospectively. Of 34 patients who were offered treatment, 30 completed 6 months of treatment. Patients were followed up at 4-week intervals to report any adverse effects. Once the dose was titrated to the maximum maintenance dose, the follow-up intervals were reduced to 8-weekly and then 3-monthly. Treatment adherence was checked at all follow-up appointments and was reported to be optimal in all 30 patients who completed 24 weeks of treatment.

This study was approved by the National Research Ethics committee and all patients provided informed consent to participate (REC Reference 22/WM/0035).

2.2 | Clinical and biochemical assessment

Demographic and clinical variables were measured at baseline and 24 weeks following GLP-1 RA initiation. The clinical data were extracted from electronic patient health records held on secure systems at University Hospitals Birmingham NHS Foundation Trust and Torbay Hospital. These variables included age, sex and ethnicity, as well as co-morbidities (i.e. T2D, hypertension, NAFLD and liver fibrosis). Weight was measured using the same digital weighing scale at all study visits, height was measured using a stadiometer and BMI was calculated as weight in kg/height in m^2. Blood samples were taken for the measurement of HbA1c, insulin, C-peptide, lipids, enhanced liver fibrosis score, renal and liver function. IR was measured using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) with the formula [fasting insulin (μU/L) × fasting glucose (mmol/L)]/22.5. Insulin sensitivity was measured using the quantitative insulin sensitivity check index (QUICKI) with the formula 1/[log insulin (μU/mL) + log glucose (mg/dL)].

A medication list of all the patients was reviewed for the use of AHAs and adjusted as required for GLP-1 RA initiation. Self-reported

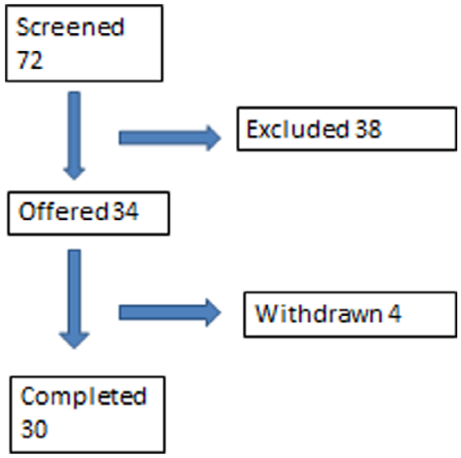

FIGURE 1 Study cohort flow diagram.

TABLE 1 Baseline characteristics of patients with Alström syndrome treated with GLP-1 RAs for syndromic obesity.

Characteristics ($n = 30$)	Mean ± SD
Age (y)	31 ± 11 (28)
Male, *n* (%)	19 (63)
Ethnicity, *n* (%)	British White 20 (67)
	British Asian 10 (33)
GLP-1, *n* (%)	Exenatide 9 (30)
	Semaglutide 21 (70)
Insulin (pmol/L)	4006 ± 1095
HOMA-IR	344 ± 1029
QUICKI	0.229 ± 0.03
Diabetes, *n* (%)	23 (77)
HTN, *n* (%)	21 (70)
NAFLD, *n* (%)	30 (100)
Other AHAs, *n* (%)	Metformin 30 (100%)
	SGLT-2i 8 (27%)
	Insulin 8 (27%)
	SU 2 (7%)
	Pioglitazones 3 (10%)

Abbreviations: AHAs, antihyperglycaemic agents; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HTN, hypertension; NAFLD, non-alcoholic fatty liver disease; QUICKI, quantitative insulin-sensitivity check index; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; SU, sulphonylurea.

medication adverse effects were recorded at each follow-up. Satiety was assessed by means of the visual analogue scale (VAS), a previously validated questionnaire.[23,24] To account for visual and hearing impairment in patients with ALMS, a modified version of the VAS was used based on answering four satiety-related questions adapted from Cazzo et al.[25] The main outcome measures in the observed group were changes in weight and HbA1c from baseline at 6 months with GLP-1 RA treatment.

2.3 | Statistical analysis

Descriptive statistics was used to summarize baseline characteristics and percentage changes in weight, HbA1c and metabolic variables following 24 weeks of GLP-1 RA treatment. Normality was assessed visually on histogram and using the Shapiro–Wilk test. Data are presented as mean ± standard deviation when normally distributed or otherwise median with interquartile range. Categorical variables are reported as numbers and percentages. All results were analysed using a two-sided 95% confidence interval. Using a paired *t*-test, statistical significance was set at *P* of .05 or less. Statistical analyses were performed using SPSS statistical software (version 24).

3 | RESULTS

3.1 | Study participants

All participants with ALMS had disease-causing pathogenic mutations (Table S1) and met the clinical diagnostic criteria. In total, 72 patients with ALMS were screened, 38 of whom were excluded because of end-stage pulmonary, cardiac or liver disease, malignancy, or end-stage renal failure requiring dialysis (Figure 1).

The baseline characteristics of our cohort are presented in Table 1. The mean age was 31 ± 11 years, and mean BMI was 34 ± 5 kg/m^2. Approximately 63% of the participants were male, 67% were White and 77% had T2D.

All patients had NAFLD, hyperinsulinaemia with a mean insulin concentration of 4006 ± 1095 pmol/L (normal reference range 18-173 pmol/L), HOMA-IR of 344 ± 1029 and QUICKI of 0.299 ± 0.03, reflecting extreme IR in ALMS.

All patients were on AHAs and GLP-1 RAs were used as an add-on treatment. Twenty one of 30 patients (70%) were on semaglutide and the remainder were on exenatide (immediate release). Exenatide subcutaneous (SC) injection was initiated at a dose of 5 micrograms (mcg) twice a day with an uptitration to 10 mcg 4 weeks later. For patients on semaglutide, 14 of 21 (67%) were on once-daily oral (PO) formulation and the reminder (33%) were on once-weekly SC formulation at standard doses (14 mg once-daily for PO and 1 mg once-weekly for SC preparation).

All patients were on AHAs, with the most common being metformin (100%), followed by sodium-glucose co-transporter-2(SGLT-2) inhibitors (27%), insulin (27%), sulphonylureas (7%) and pioglitazone (10%).

3.2 | Weight, HbA1c and, metabolic variables

Changes observed in weight, HbA1c and other metabolic variables at 6 months following GLP-1 RA initiation are summarized in Table 2. Study participants achieved an average weight loss of 5.4 ± 1.7 (95% confidence interval [CI] 3.6-7) kg with a 6% mean weight change from baseline ($P < .01$). Figure 2 shows the proportion of patients with percentage weight loss. In total, 87% of participants (26 of 30) lost

TABLE 2 Changes in weight, HbA1c and metabolic variables over 6 months of treatment with GLP-1 RAs.

Variables measured	Baseline (mean ± SD)	6 months (mean ± SD)	Mean absolute change	Mean % change	*P* value
Weight (kg)[a]	87.7 ± 15	82.3 ± 14.4	5.4	6	< .01
BMI (kg/m^2)[b]	33.5 ± 5.2	31.6 ± 5.2	2	6	< .01
Systolic BP (mmHg)	125 ± 17	118 ± 14	8	6	.03
Diastolic BP (mmHg)	75 ± 8.7	76 ± 8.6	0.1	0	.96
Glucose (mmol/L)[b]	9.8 ± 5	8 ± 4.6	1.8	19	.08
HbA1c (mmol/mol)[a]	68.5 ± 19.6	56.5 ± 17.9	12	18	< .01
C-peptide (pmol/l)[c]	3203 ± 2068	3618 ± 1827	415	13	.28
TG (mmol/L)[b]	3.3 ± 1.9	2.5 ± 1.1	0.8	24	.01
TC (mmol/L)[b]	4.5 ± 1.3	3.8 ± 0.9	0.7	15	.03
LDL-C (mmol/L)[d]	2.3 ± 0.6	1.9 ± 0.7	0.4	18	.03
HDL-C (mmol/L)[b]	0.9 ± 0.2	1 ± 0.3	−0.1	8	.02
ALT (IU/L)[b] (median, IQR)	65, 104-33	53,87–30	12	18	.04
AST (IU/L)[e]	42 ± 25	33 ± 19	9	21	.08
ELF score[f]	9.8 ± 0.6	9.7 ± 0.7	0.1	1	.34
Urea (mmol/L)[b]	7.5 ± 3.9	7 ± 3.5	0.4	6	.22
Creatinine (μmol/L)[b] (Median, IQR)	89 125-69	93 141–74	4.0	4	.12
eGFR (mL/min)[b]	74.2 ± 21.3	73.9 ± 23.1	0.3	0.4	.81

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; ELF, enhanced liver fibrosis; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TC, total cholesterol; TG, triglycerides.
[a]$n = 30$.
[b]$n = 21/30$.
[c]$n = 17$.
[d]$n = 10$.
[e]$n = 18$.
[f]$n = 8$.

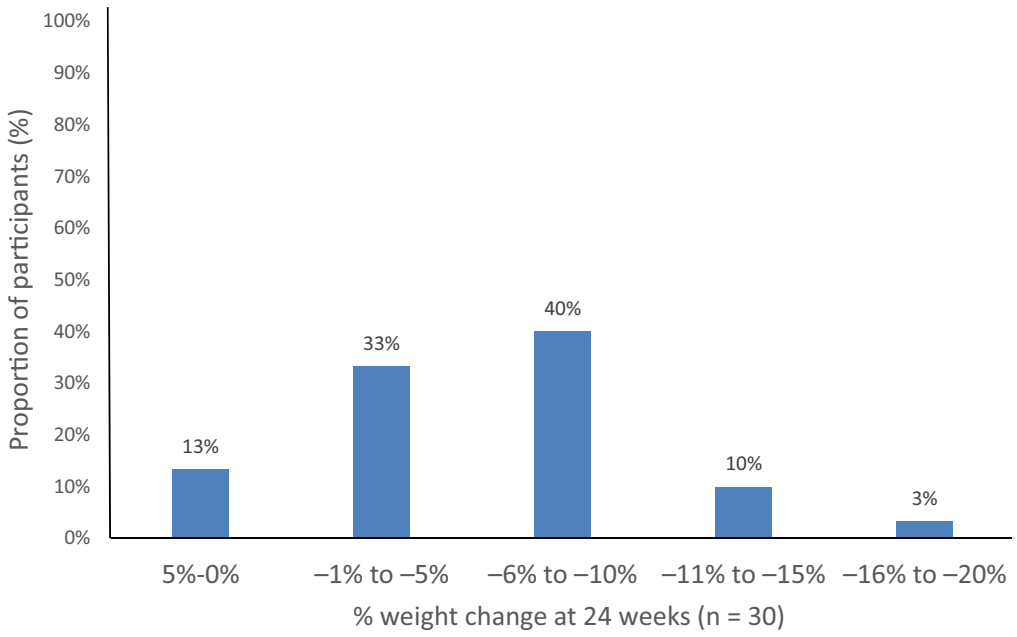

FIGURE 2 Observed percentage weight change from baseline following 24 weeks of treatment with GLP-1 RAs. GLP-1 RA, glucagon-like peptide-1 receptor agonist.

weight following 6 months of treatment with GLP-1 RAs, of which 62% (16 of 26) lost 5% or more body weight.

As shown in Table 2, HbA1c decreased by 12 ± 3.3 (95% CI 8.7-15.3) mmol/mol with an absolute reduction of 1.1% from baseline ($P < .01$). Similarly, statistically significant changes were observed in systolic blood pressure ($P \leq .03$) and other metabolic variables, including triglycerides (TG) ($P \leq .01$), total cholesterol (TC) ($P \leq .03$), low-density lipoprotein cholesterol (LDL-C) ($P \leq .03$) and, alanine aminotransferase (ALT) ($P \leq .04$).

Modest increases in C-peptide levels were observed post-treatment, with a mean change of 415 ± 739 (95% CI −324 - 1150) pmol/L following 24 weeks of treatment with GLP-1 RAs.

Satiety assessment was carried out by VAS scoring based on answering four questions. As shown in Table S2, post-treatment we observed changes in participant responses to all four domains of VAS scoring ($P < 0.01$), indicating satiety post-treatment.

Commonly reported side effects were transient and self-limiting nausea, abdominal discomfort and diarrhoea during the dose titration period in nine out of 21 patients.

4 | DISCUSSION

To the best of our knowledge, this is the first and largest reported real-world study of the efficacy of GLP-1 RAs for the treatment of monogenic obesity. In this observational study, we examined the role of GLP-1 RAs in weight reduction and metabolic profile improvement in a cohort of patients with ALMS, a type of monogenic obesity. We present evidence that the GLP-1 RAs exenatide and semaglutide not only effectively treat monogenic obesity, but also ameliorate the metabolic derangements seen as disease complications.

GLP-1 RAs have emerged as a promising option for the treatment of obesity and its attendant complications such as diabetes, NAFLD and dyslipidaemia.[26] Whether it confers the same metabolic benefits in monogenic obesity is unknown. It has been challenging to find treatment options for monogenic obesity syndrome given the rarity of conditions and difficulties in identifying targeted gene therapies. Previous evidence of treating monogenic syndromic obesity with GLP-1 RAs has come primarily from isolated case reports and limited case series, with a lack of clinical trials and large cohort data.[18,27–30]

We and others have shown that obesity in ALMS is associated with extreme IR and that it is disproportionate to body weight.[31,32] IR in ALMS precedes T2D with an unclear age of onset, but there is evidence to suggest it may be as early as 18 months of age.[7,32] We have also shown that relative adipose tissue failure plays an important role in IR.[31] Observational reports in ALMS have strongly suggested that diet and lifestyle can reduce obesity and T2D prevalence, in particular the contrasting outcomes in Canadian and Italian adolescents.[7,32]

In our own clinics, there have been striking examples of both short-term control of severe diabetes with exercise and longer term remission of diabetes, dyslipidaemia, hypertension and non-alcoholic steatohepatitis.[33] However, similar to the treatment of obesity in the general population, many patients with ALMS are unable to undertake lifestyle changes over the long term because of dual sensorineural deficits of the syndrome.[6] Bariatric surgery is of proven long-term benefit, although data are limited on its efficacy in syndromic obesity because of the low number of cases and limited follow-up times.[34,35] Hence, there is a need for a pharmacological intervention to help tackle obesity and difficult-to-control T2D in monogenic obesity syndrome of ALMS. Pharmacological intervention with semaglutide has been shown to be a promising treatment option for patients living with obesity and T2D.[36]

In our observational study of 30 adult patients with ALMS, GLP-1 RAs were shown to be effective for weight loss. More than one-half of patients (62%) lost clinically meaningful weight (≥ 5%) within 6 months of treatment. Clinical trials on various GLP-1 RAs in patients with T2D administered at standard doses have reported an average weight loss of ∼2-7 kg.[12,36,37] Recently, one of the largest published studies of real-world efficacy of these agents in ∼2400 patients with obesity and T2D showed a mean weight loss of 1.1% to 2.2% from week 8 to week 72, where one-third of patients lost at least 5% of their body weight.[38] Our observational cohort showed an average weight loss of 5.4 ± 1.7 (95% CI 3.6-7) kg, with more than one-half of participants (62%) losing 5% or more of their body weight at week 24. This is superior to weight loss observed in the real-world study of efficacy of these agents in T2D,[38] given the short duration of treatment in our cohort (24 vs. 72 weeks). On subgroup analysis between the groups administered semaglutide and exenatide (Table S3), average weight loss was comparable at −5.2 ± 4.4 and − 5.79 ± 5.38 kg, respectively. In the exenatide group, this is more significant than an average weight loss of ∼1-3 kg observed with daily administration of exenatide in patients with T2D.[12,39]

Now the question arises what causes the weight loss in ALMS. There are anecdotal reports of hyperphagia leading to childhood obesity in ALMS.[40,41] In a murine model of ALMS, hyperphagia was observed to precede the development of obesity and T2D.[42] There is extensive evidence to suggest that reduced food intake promotes weight loss with GLP-1 RAs[43,44] and hence its attendant complications such as IR.[45,46] In our cohort of patients, we used hunger and the satiety VAS to quantify satiety.[47] Significant improvement was observed in VAS score post-treatment (Table S2). All our patients on semaglutide (21/30) reported early satiety, reduced oral and caloric intake pertaining to weight-loss effects of GLP-1 analogues.

The available evidence supports the role of endogenous GLP-1 signalling within both the hypothalamus and brainstem for physiological control of appetite and food intake.[48] This has been supported by murine data showing increased food intake and body weight by administration of a glucagon-like-peptide-1-receptor-antagonists over 7 days in mice with diet-induced obesity.[49] With some evidence suggesting the role of the *ALMS1* gene in the regulation of food intake and hypothalamic origin as a possible cause of hyperphagia,[8,42] it is plausible that the enhanced weight-loss effects of GLP-1 RAs in ALMS can be attributed to its synergistic effects on the gut, as well as centrally and peripherally located receptors to cause satiety.

Significant reductions in HbA1c were also seen alongside weight loss with an HbA1c reduction of 12 ± 3.3 (95% CI 8.7-15.3) mmol/mol,1.1% Diabetes Control and Complications trial (DCCT) from

baseline, which was statistically highly significant ($P < .0001$). The SUSTAIN trials have shown semaglutide to be consistently efficacious across the continuum of diabetes care in a broad spectrum of patient subgroups with T2D, with an average HbA1c reduction of 1.5% from baseline across the SUSTAIN 1-5 trials.[50–54] Our real-world observation of a cohort with difficult to control T2D showed HbA1c reductions of 1.1%, highlighting non-inferiority to the available GLP-1 RA-use data across clinical trials. This small reduction in HbA1c compared with the SUSTAIN trials may be attributable to the numerous potent concomitant antidiabetic medication combinations that patients with ALMS in the current study were receiving when a GLP-1 RA was added to their treatment regime.

Although the number of patients on treatment with semaglutide ($n = 21$) and exenatide ($n = 9$) was variable, the HbA1c-lowering effects of both these agents were comparable, with HbA1c reductions of 12 ± 9.5 mmol/mol and 15 ± 8 mmol/mol in the semaglutide and exenatide groups, with no statistically significant superiority of one to another. The SUSTAIN and PIONEER trials, assessing the efficacy of SC and PO formulation of semaglutide for HbA1c reduction at doses of 1 mg once weekly for SC and 14 mg once daily for PO, reported an average HbA1c reduction of 1.5% - 1.8% for SC formulation and 1% - 1.4% for PO formulation during 30 - 56 weeks of treatment in patients with T2D.[55] Thus, our cohort of ALMS patients showed non-inferiority in HbA1c improvement with 24 weeks of treatment in the semaglutide treatment group.

The exact reason for such significant reductions in HbA1c with GLP-1 RAs in ALMS is not clear. Although GLP-1 RAs are known to have beneficial effects on pancreatic beta cell function, potentially contributing to appropriate insulin secretion, patients with ALMS exhibit severe IR (Table 1), which would preclude insulin action to lower blood glucose. We did not detect a significant difference in C-peptide levels between baseline and at 6 months of treatment (Table 2), indicating that this is probably not the main reason for the improvement in HbA1c. Clinical experience and our published data suggest that IR is more severe in ALMS and yet their metabolic profile change is exquisitely sensitive to caloric intake.[33] It has previously been shown that GLP-1 RAs can improve insulin sensitivity, independently of their effects on beta cell function in patients with type 1 diabetes.[15] Similarly, the GLP-1 RA response in ameliorating extreme IR and improving insulin sensitivity with weight loss in ALMS is profound, as depicted by our data. Furthermore, our unpublished data suggest that ALMS may have higher glucagon levels, an angle we intend to explore further as GLP-1 RAs have been shown to suppress the secretion of glucagon from pancreatic alpha cells, thereby decreasing hepatic glucose output.[56]

Treatment with GLP-1 RAs also led to a reduction in the atherogenic lipid levels in our observational cohort (Table 2). Dyslipidaemia is a major risk factor for cardiovascular disease. ALMS showed modest reductions in TG, TC and LDL-C and an improvement in high-density lipoprotein cholesterol (HDL-C) following 6 months of treatment with GLP-1 RAs that was statistically significant ($P < .05$). This correlates with findings reported in clinical trials with the use of this class of agents in T2D.[57]

The main strength of the study is the comparatively large cohort of ALMS patients with accurate genetic disease characterization. Adherence to, and tolerance of treatment was excellent. The study limitations include its short duration, the lack of a control arm and being based on a single monogenic obese cohort.

In conclusion, GLP-1 RAs are effective for weight loss, glycaemic control and the improvement of metabolic variables such as TG, TC, LDL-C and HDL-C in a large cohort of patients with ALMS, which is a monogenic form of obesity. The data we present indicate overall improvement of metabolic health with this class of agents in ALMS, which are comparable with data from polygenic obesity. Hence, in ALMS with no disease-modifying treatment and focus of care mainly on supportive care, GLP-1 RAs represent a possible treatment option for weight loss and difficult-to-control diabetes. Because disease manifestations with metabolic complications start at a young age, carefully designed studies are required to assess the effects of these medications in a paediatric age group with ALMS.

AUTHOR CONTRIBUTIONS

TG and RP conceived the study. SA, RP and TG initiated the treatment, followed up patients and collected the data. SA, SW and SB analysed the data. SA drafted the manuscript. All authors reviewed the data and approved the final draft of the manuscript.

ACKNOWLEDGEMENTS

We would like to thank patients with Alström syndrome, their families and ASUK for assisting with this study. This study was partly funded by the University Hospitals Birmingham NHS Foundation Trust and Big Lottery Fund grant RGT/1/010332749 to RP.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15398.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

ORCID

Sadaf Ali https://orcid.org/0000-0001-6768-5495
Tarekegn Geberhiwot https://orcid.org/0000-0002-3629-2338

REFERENCES

1. Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. *Metabolism*. 2022;133:155217.
2. IDF_Atlas_10th_Edition_2021.pdf [Internet]. [cited 2023 May 19]. Available from: https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf

3. Kivimäki M, Strandberg T, Pentti J, et al. Body-mass index and risk of obesity-related complex multimorbidity: an observational multicohort study. *Lancet Diabetes Endocrinol*. 2022;10(4):253-263.
4. Loos RJF, Yeo GSH. The genetics of obesity: from discovery to biology. *Nat Rev Genet*. 2022;23(2):120-133.
5. Kleinendorst L, Massink MPG, Cooiman MI, et al. Genetic obesity: next-generation sequencing results of 1230 patients with obesity. *J Med Genet*. 2018;55(9):578-586.
6. Tahani N, Maffei P, Dollfus H, et al. Consensus clinical management guidelines for Alström syndrome. *Orphanet J Rare Dis*. 2020;15(1):253.
7. Mokashi A, Cummings EA. Presentation and course of diabetes in children and adolescents with Alstrom syndrome. *Pediatr Diabetes*. 2011;12(3pt2):270-275.
8. Marshall JD, Bronson RT, Collin GB, et al. New Alström syndrome phenotypes based on the evaluation of 182 cases. *Arch Intern Med*. 2005;165(6):675-683.
9. Minton J a L, Owen KR, Ricketts CJ, et al. Syndromic obesity and diabetes: changes in body composition with age and mutation analysis of ALMS1 in 12 United Kingdom kindreds with Alstrom syndrome. *J Clin Endocrinol Metab*. 2006;91(8):3110-3116.
10. Choudhury AR, Munonye I, Sanu KP, Islam N, Gadaga C. A review of Alström syndrome: a rare monogenic ciliopathy. *Intractable Rare Dis Res*. 2021;10(4):257-262.
11. de Graaf C, Donnelly D, Wootten D, et al. Glucagon-like peptide-1 and its class B G protein-coupled receptors: a long march to therapeutic successes. *Pharmacol Rev*. 2016;68(4):954-1013.
12. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes – state-of-the-art. *Mol Metab*. 2020;46:101102.
13. Gupta V. Glucagon-like peptide-1 analogues: an overview. *Indian J Endocrinol Metab*. 2013;17(3):413-421.
14. Jensterle M, Rizzo M, Haluzík M, Janež A. Efficacy of GLP-1 RA approved for weight management in patients with or without diabetes: a narrative review. *Adv Ther*. 2022;39(6):2452-2467.
15. Rother KI, Spain LM, Wesley RA, et al. Effects of exenatide alone and in combination with daclizumab on β-cell function in long-standing type 1 diabetes. *Diabetes Care*. 2009;32(12):2251-2257.
16. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989-1002.
17. Shah M, Vella A. Effects of GLP-1 on appetite and weight. *Rev Endocr Metab Disord*. 2014;15(3):181-187.
18. Zoicas F, Droste M, Mayr B, Buchfelder M, Schöfl C. GLP-1 analogues as a new treatment option for hypothalamic obesity in adults: report of nine cases. *Eur J Endocrinol*. 2013;168(5):699-706.
19. Siljee JE, Wang Y, Bernard AA, et al. Subcellular localization of MC4R with ADCY3 at neuronal primary cilia underlies a common pathway for genetic predisposition to obesity. *Nat Genet*. 2018;50(2):180-185.
20. Hearn T. ALMS1 and Alström syndrome: a recessive form of metabolic, neurosensory and cardiac deficits. *J Mol Med*. 2019;97(1):1-17.
21. Andersen JS, Wilkinson CJ, Mayor T, Mortensen P, Nigg EA, Mann M. Proteomic characterization of the human centrosome by protein correlation profiling. *Nature*. 2003;426(6966):570-574.
22. Hearn T, Spalluto C, Phillips VJ, et al. Subcellular localization of ALMS1 supports involvement of centrosome and basal body dysfunction in the pathogenesis of obesity, insulin resistance, and type 2 diabetes. *Diabetes*. 2005;54(5):1581-1587.
23. Flint A, Raben A, Blundell JE, Astrup A. Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. *Int J Obes Relat Metab Disord*. 2000;24(1):38-48.
24. De Graaf C. The validity of appetite ratings. *Appetite*. 1993;21(2):156-160.
25. Cazzo E, Pareja JC, Chaim EA, Coy CSR, Magro DO. Glucagon-like peptides 1 and 2 are involved in satiety modulation after modified biliopancreatic diversion: results of a pilot study. *Obes Surg*. 2018;28(2):506-512.
26. Wang JY, Wang QW, Yang XY, et al. GLP−1 receptor agonists for the treatment of obesity: role as a promising approach. *Front Endocrinol (Lausanne)*. 2023;14:1085799.
27. Iepsen EW, Zhang J, Thomsen HS, et al. Patients with obesity caused by melanocortin-4 receptor mutations can Be treated with a glucagon-like peptide-1 receptor agonist. *Cell Metab*. 2018;28(1):23-32.e3.
28. Iepsen EW, Have CT, Veedfald S, et al. GLP-1 receptor agonist treatment in morbid obesity and type 2 diabetes due to pathogenic homozygous melanocortin-4 receptor mutation: a case report. *Cell Rep Med*. 2020;1(1):100006.
29. Welling MS, de Groot CJ, Kleinendorst L, et al. Effects of glucagon-like peptide-1 analogue treatment in genetic obesity: a case series. *Clin Obes*. 2021;11(6):e12481.
30. Paisey R, Bower L, Rosindale S, Lawrence C. Successful treatment of obesity and diabetes with incretin analogue over four years in an adult with Prader–Willi syndrome. *Pract Diabetes*. 2011;28(7):306-307.
31. Geberhiwot T, Baig S, Obringer C, et al. Relative adipose tissue failure in Alström syndrome drives obesity-induced insulin resistance. *Diabetes*. 2021;70(2):364-376.
32. Bettini V, Maffei P, Pagano C, et al. The progression from obesity to type 2 diabetes in Alström syndrome. *Pediatr Diabetes*. 2012;13(1):59-67.
33. Paisey RB, Geberhiwot T, Waterson M, et al. Modification of severe insulin resistant diabetes in response to lifestyle changes in Alström syndrome. *Eur J Med Genet*. 2014;57(2–3):71-75.
34. Vos N, Oussaada SM, Cooiman MI, et al. Bariatric surgery for monogenic non-syndromic and syndromic obesity disorders. *Curr Diab Rep*. 2020;20(9):44.
35. Poitou C, Puder L, Dubern B, et al. Long-term outcomes of bariatric surgery in patients with bi-allelic mutations in the POMC, LEPR, and MC4R genes. *Surg Obes Relat Dis*. 2021;17(8):1449-1456.
36. Ahrén B, Atkin SL, Charpentier G, et al. Semaglutide induces weight loss in subjects with type 2 diabetes regardless of baseline BMI or gastrointestinal adverse events in the SUSTAIN 1 to 5 trials. *Diabetes Obes Metab*. 2018;20(9):2210-2219.
37. Lingvay I, Hansen T, Macura S, et al. Superior weight loss with once-weekly semaglutide versus other glucagon-like peptide-1 receptor agonists is independent of gastrointestinal adverse events. *BMJ Open Diabetes Res Care*. 2020;8(2):e001706.
38. White GE, Shu I, Rometo D, Arnold J, Korytkowski M, Luo J. Real-world weight-loss effectiveness of glucagon-like peptide-1 agonists among patients with type 2 diabetes: a retrospective cohort study. *Obes (Silver Spring)*. 2023;31(2):537-544.
39. Hinnen D. Glucagon-like peptide 1 receptor agonists for type 2 diabetes. *Diabetes Spectr*. 2017;30(3):202-210.
40. Lee NC, Marshall JD, Collin GB, et al. Caloric restriction in Alström syndrome prevents hyperinsulinemia. *Am J Med Genet A*. 2009;149A(4):666-668.
41. Paisey RB, Steeds R, Barrett T, Williams D, Geberhiwot T, Gunay-Aygun M. Alström Syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. *GeneReviews® [Internet]*. University of Washington, Seattle; 2003.
42. Arsov T, Silva DG, O'Bryan MK, et al. Fat aussie—a new Alström syndrome mouse showing a critical role for ALMS1 in obesity, diabetes, and spermatogenesis. *Mol Endocrinol (Baltim)*. 2006;20(7):1610-1622.
43. Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metab*. 2013;17(6):819-837.
44. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368(9548):1696-1705.

45. Viljanen APM, Iozzo P, Borra R, et al. Effect of weight loss on liver free fatty acid uptake and hepatic insulin resistance. *J Clin Endocrinol Metab*. 2009;94(1):50-55.
46. Vitola BE, Deivanayagam S, Stein RI, et al. Weight loss reduces liver fat and improves hepatic and skeletal muscle insulin sensitivity in obese adolescents. *Obesity*. 2009;17(9):1744-1748.
47. Lindeman A, Huang M, Dawkins E. Using the visual analog scale (VAS) to measure perceived hunger and satiety at various mealtimes and environments. *J Acad Nutr Diet*. 2016;116(9):A99.
48. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metab*. 2018;27(4):740-756.
49. Patterson JT, Ottaway N, Gelfanov VM, et al. A novel human-based receptor antagonist of sustained action reveals body weight control by endogenous GLP-1. *ACS Chem Biol*. 2011;6(2):135-145.
50. Sorli C, Harashima S i, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes Endocrinol*. 2017;5(4):251-260.
51. Ahrén B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol*. 2017;5(5):341-354.
52. Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly Semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label randomized clinical trial. *Diabetes Care*. 2018;41(2):258-266.
53. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol*. 2017;5(5):355-366.
54. Rodbard HW, Lingvay I, Reed J, et al. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized controlled trial. *J Clin Endocrinol Metab*. 2018;103(6):2291-2301.
55. Meier JJ. Efficacy of Semaglutide in a subcutaneous and an Oral formulation. *Front Endocrinol (Lausanne)*. 2021;12:645617.
56. Drucker DJ, Habener JF, Holst JJ. Discovery, characterization, and clinical development of the glucagon-like peptides. *J Clin Invest*. 2017;127(12):4217-4227.
57. Sun F, Wu S, Wang J, et al. Effect of glucagon-like peptide-1 receptor agonists on lipid profiles among type 2 diabetes: a systematic review and network meta-analysis. *Clin Ther*. 2015;37(1):225-241.e8.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ali S, Baig S, Wanninayake S, et al. Glucagon-like peptide-1 analogues in monogenic syndromic obesity: Real-world data from a large cohort of Alström syndrome patients. *Diabetes Obes Metab*. 2023;1-8. doi:10.1111/dom.15398