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The influence of age and metformin treatment status on reported gastrointestinal side effects with liraglutide treatment in type 2 diabetes

K.Y. Thong [a,*], P. Sen Gupta [b], A.D. Blann [c], R.E.J. Ryder [b]

[a] School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia
[b] Diabetes Centre, City Hospital, Birmingham, England, United Kingdom
[c] University of Birmingham Centre for Cardiovascular Science, Department of Medicine, City Hospital, Birmingham, England, United Kingdom

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ABSTRACT

Aim: Treatment of type 2 diabetes with glucagon-like peptide-1 (GLP-1) receptor agonists may be limited by gastrointestinal side effects (GISE) in some patients. Risk factors for developing GISE are not known. We analysed patient characteristics that were associated with GISE among patients treated with the GLP-1 receptor agonist liraglutide.

Methods: Data was obtained from an audit database of liraglutide use based in clinical practice in the UK. Patients were grouped into those who did not report GISE, those who reported GISE but continued liraglutide and those who discontinued liraglutide due to GISE within 26 weeks of treatment. Baseline variables of age, diabetes duration, HbA_{1c}, weight, BMI, blood pressure, lipids, gender, ethnicity, alanine transaminotransferase, estimated glomerular filtration rate (eGFR) and diabetes treatment types were tested for possible associations with GISE outcome. Significant variables in univariate analyses were entered into ordinal logistic regression analyses.

Results: A total of 4442 patients were suitable for analysis. A total of 3905 (87.9%) did not report GISE, 297 (6.7%) and 240 (5.4%) had GISE and continued and discontinued treatment, respectively. Age, weight, eGFR, metformin status and insulin status were associated with GISE outcome in univariate analyses (P all <0.05). In the final regression model, age (adjusted OR 1.15 [95%CI 1.05,1.26], $P = 0.002$) and non-metformin use (adjusted OR 0.76 [95%CI 0.60,0.96], $P = 0.020$) were associated with worse GISE outcome.

Conclusion: Older age and non-metformin use were associated with more significant GISE leading to discontinuation of liraglutide treatment. The reasons for these findings are unclear and warrant further investigation.

* *Corresponding author at*: Department of Diabetes and Endocrinology, Rockingham General Hospital, Elanora Drive, Rockingham 6168, WA, Australia. Tel.: +61 8 95994697; fax: +61 8 95994737.
E-mail address: kythong@gmail.com (K.Y. Thong).

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1. Introduction

Glucagon-like peptide 1 (GLP-1) secretion by intestinal L cells leads to an increase in insulin secretion, suppression of glucagon secretion, slowing of gastric emptying and suppression of appetite. However, endogenous GLP-1 is rapidly degraded by the dipeptidyl peptidase-4 (DPP-4) enzyme. The use of GLP-1 receptor agonists which are resistant to such degradation or drugs inhibiting the DPP-4 enzyme, forms the pharmacological basis of incretin-based therapies in patients with type 2 diabetes [1].

Liraglutide, a once-daily injected GLP-1 receptor agonist helps improve glycaemia and reduce weight in patients with type 2 diabetes [2]. However, a disadvantage of the GLP-1 receptor agonist drug class including that of liraglutide is the occurrence of gastrointestinal side effects (GISE). Common symptoms include nausea, vomiting or diarrhoea [1]. Liraglutide has been shown to have less persistent GISE than exenatide twice daily, the first available GLP-1 receptor agonist [3]. The side effects of GLP-1 receptor agonists also tend to improve with longer duration of treatment, possibly due to the development of tachyphylaxis [4]. However, there remains to be patients who discontinue drug treatment due to severe or persistent symptoms; between four to five percent of patients treated with liraglutide 1.2 mg once daily discontinued liraglutide treatment due to GISE in the Liraglutide Effect and Action in Diabetes (LEAD) trials [5–7]. In the United Kingdom (UK), liraglutide 1.2 mg once daily is recommended for use by the National Institute for Health and Care Excellence (NICE) as a second or third line diabetes treatment after metformin and/or sulphonylurea in patients with body mass indices (BMI) greater than 35 kg/m^2 [8].

To date, there is a lack of large-scale data on the rates of GISE among patients treated with GLP-1 receptor agonists in real-life clinical practice. There is also little data on identifying patients who may be at risk. Using information from a nationwide audit database of liraglutide use in clinical practice, we investigated whether there were identifiable risk factors for developing GISE among patients treated with liraglutide.

2. Methods

2.1. Subjects

Data was obtained from the Association of British Clinical Diabetologists (ABCD) nationwide liraglutide audit database. ABCD had invited diabetes centres in hospitals and primary care across UK to submit anonymised data of patients treated with liraglutide in routine clinical practice during the period of 2009 to 2013. 117 diabetes centres enrolled and submitted varying degrees of data depending on date of participation, the frequency of patients' health visits and duration of liraglutide treatment that had taken place. Data entry and submission was performed using audit software provided by ABCD.

Data requested included patients' age, gender, ethnicity, pre- and post-liraglutide treatment information including diabetes treatments, glycated haemoglobin (HbA_{1c}), body weight, BMI, blood pressure, lipid parameters, alanine transaminotransferase (ALT) and creatinine, whenever these data were available. Contributors were also asked to report on occurrence of any GISE or other possible treatment related adverse events, as well as the main reason for liraglutide discontinuation if this occurred.

A total of 6238 patients had baseline data sent to ABCD. For this study, we excluded patients without at least one follow-up data submission ($n = 1296$) and those with less than 13 weeks data contribution or follow-up unless these patients were noted to have discontinued liraglutide ($n = 500$). Remaining 4422 patients were used for analyses.

2.2. Outcome and risk variables

Patients were classified into three GISE outcome groups: (a) patients without GISE, (b) patients reporting GISE but continued with liraglutide treatment and (c) patients who discontinued liraglutide due to GISE before 26 weeks (the three groups were coded 0, 1, and 2). We defined symptoms of GISE as those of nausea, diarrhoea, vomiting, crampy abdominal pain, constipation, belching, reflux, flatulence or similar related terms.

2.3. Statistical analyses

Univariate associations of all variables in the database were tested against GISE outcome using ANOVA, Kruskal–Wallis test and tabulated statistics depending on whether the variables were continuous and normally or non-normally distributed, or were categorical variables, respectively. Results shown for estimated glomerular filtration rates (eGFR) were those calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and data on eGFR was first analysed as a continuous variable. Sensitivity analyses were performed using eGFR derived by the Cockcroft-Gault equation adjusted for body surface area using the DuBois formula, and the Modification of Diet in Renal Disease (MDRD) equation. All eGFR equations used are shown in Appendix 1 [9,10]. eGFR was also analysed as a categorical variable based on chronic kidney disease (CKD) groups: CKD group 1 (eGFR $>$ 90 ml/min/1.73 m^2), CKD Group 2 (eGFR 60–89 ml/min/1.73 m^2) and CKD Group 3 (eGFR 30–59 ml/min/1.73 m^2). The associations between baseline diabetes treatments and GISE were also tested. In particular, the association between metformin use and GISE was tested due to clinical trials of liraglutide generally showing higher rates of GISE among patients on metformin compared with patients on sulphonylurea [5,7,11]. The association between insulin use and GISE was tested due to our previous finding of more frequent reports of GISE among insulin-treated patients as compared with non-insulin-treated patients when started on exenatide twice daily [12]. Variables with statistically significant association in univariate analyses ($P < 0.050$) were entered into an ordinal logistic regression analysis, with liraglutide dose (1.2 mg versus 1.8 mg), and prior exenatide use treated as covariates. Variables in logistic regression with the highest P value were sequentially removed until a final model with all variables with $P < 0.10$ was achieved. Due to findings of age being a significant risk factor for GISE in the final regression model, the results of rates of GISE according to decades of age are also

shown. Statistical analyses were performed using Minitab® Release 16 (Minitab Ltd, Coventry, UK).

3. Results

Baseline characteristics of the 4422 patient were, mean (±SD), age 56 ± 11 years, HbA_{1c} 9.4 ± 1.7% (79 ± 19 mmol/mol), weight 110.5 ± 22.5 kg and BMI 38.8 ± 7.2 kg/m^2. Median (inter-quartile range) diabetes duration was 9 [6–13] years. 41.2% of patients were on insulin at liraglutide initiation as opposed to the licensed prescribing indications for liraglutide.

A total of 537 (12.1%) patients reported GISE of which 297 (6.7%) continued liraglutide treatment while 240 (5.4%) discontinued liraglutide treatment due to GISE. The total number of patients discontinuing liraglutide within 26 weeks of treatment, including those who discontinued due to GISE, was 606 (13.6%).

Results of univariate analyses are shown in Tables 1 and 2. Variables significantly associated with GISE were older age, lower weight, poorer renal function, the use of insulin and non-use of metformin (*P* all <0.05).

The results of ordinal logistic regression analyses are shown in Table 3. In the final model of 4213 patients, a rise in one standard deviation of age which approximated an increase of 10 years of age (adjusted OR 1.15 [95%CI 1.05,1.27], *P* = 0.002) and non-metformin use (adjusted OR for metformin versus non metformin use 0.76 [95%CI 0.60,0.96], *P* = 0.020) were associated with GISE outcome. The proportions of patients reporting GISE according to decades of life are shown in Fig. 1.

Sensitivity analyses performed on eGFR derived by the Cockcroft-Gault and the MDRD equations showed similar findings to that when eGFR was derived by the CKD-EPI equation; the association of eGFR with GISE outcome in univariate analyses remained significant, and the association in multivariate analyses remained non-significant. Analysing eGFR according to CKD groups also did not alter our univariate or multivariate findings.

4. Discussion

Our analysis of the data from the ABCD liraglutide audit database hopes to bring renewed focus on the issue of drug tolerability of GLP-1 receptor agonists, rather than drug efficacy per se. To our knowledge, our analysis may be the first published attempt to characterise risk factors for developing GISE among patients treated with this class of treatment. There is now an expanding array of diabetes treatment options for type 2 diabetes beyond metformin, including sulphonylureas, thiazolidinediones, insulin, GLP-1 receptor agonists, DPP-4 inhibitors and more recently sodium glucose transporters 2 inhibitors [13]. Knowledge on potential risk factors for GISE may help guide clinicians in whether to select GLP-1 receptor agonists as an option for treatment escalation. However, the results of our study should be mainly treated as hypothesis-generating due to the susceptibility to biases of data in an audit, as well as the post hoc decision to analyse GISE data in such a manner.

Reported rates of nausea, vomiting or diarrhoea vary between GLP-1 receptor agonists but were generally lower for liraglutide or exenatide once weekly as compared with exenatide twice daily in head-to-head studies [3,14]. In the ABCD audit, the rates of all combined reported GISE with liraglutide 1.2 mg were low at 12.1%. Rates of liraglutide discontinuation due to GISE in the audit were 5.4% and were comparable with the rates of 4 to 5% in the LEAD trials [5–7].

Our results suggest that older age and non-metformin use are risk factors for GISE and drug discontinuation among

Table 1 – Baseline characteristics (continuous variables) and their association with the reporting of gastrointestinal side effects (GISE) and drug discontinuation due to GISE among patients treated with liraglutide.

	n	No	GISE status		*P* value
			Yes, did not discontinue	Yes, discontinued liraglutide	
Age (years)	4213	55 ± 11	55 ± 11	59 ± 12	<0.001
Diabetes duration (years)	3410	9 [6–13]	9 [6–14]	10 [6–14]	0.17
HbA1c (%; mmol/mol)	4153	9.4 ± 1.7; 79 ± 19	9.3 ± 1.6; 78 ± 18	9.4 ± 1.7; 79 ± 19	0.85
Weight (kg)	4262	110.7 ± 22.4	110.0 ± 24.0	106.7 ± 21.0	0.029
BMI (kg/m^2)	4173	38.9 ± 7.2	38.8 ± 7.4	38.2 ± 7.3	0.41
eGFR* (ml/min/1.73 m^2)	3474	83 ± 21	84 ± 21	77 ± 23	<0.001
ALT (U/L)	2727	28 [21–42]	30 [22–43]	29 [20–44]	0.47
TC (mmol/L)	3486	4.3 ± 1.2	4.2 ± 1.1	4.3 ± 1.0	0.68
HDL-C (mmol/L)	3073	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.80
TG (mmol/L)	2684	2.1 [1.5–2.9]	2.0[1.4,2.9]	2.2 [1.5,3.0]	0.58
SBP (mmHg)	3483	138 ± 18	139 ± 19	141 ± 19	0.15
DBP (mmHg)	3483	79 ± 11	79 ± 11	78 ± 11	0.37

Variables are shown as mean ± sd or median [inter-quartile range].
BMI; body mass index, eGFR; estimated glomerular filtration rate, ALT; alanine transaminotransferase, TC; total cholesterol, HDL-C; high density lipoprotein cholesterol, TG; triglyceride, SBP; systolic blood pressure, DBP; diastolic blood pressure.
* eGFR shown is calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Analyses using the Cockcroft-Gault equation adjusted by body surface area and Modified Diet for Renal Disease (MDRD) equation showed associations with significance of *P* = 0.001 and *P* = 0.009, respectively.

Table 2 – Baseline characteristics (categorical variables) and their association with the reporting of gastrointestinal side effects (GISE) and drug discontinuation due to GISE among patients treated with liraglutide.

	n	No	GISE status		*P* value
			Yes, did not discontinue	Yes, discontinued liraglutide	
Gender					
Male	4434	2076 (88.9)	144 (6.2)	116 (5.0)	0.13
Female		1823 (86.9)	152 (7.2)	123 (5.9)	
Ethnicity					
Caucasian	3673	2926 (88.1)	224 (6.8)	170 (5.1)	0.88
South-Asian		211 (87.9)	15 (6.3)	14 (5.8)	
Afro-Carribean		100 (88.5)	9 (8.0)	4 (3.5)	
CKD group*					
1	3452	1297 (89.5)	92 (6.3)	61 (4.2)	0.004
2		1296 (87.8)	88 (6.0)	92 (6.2)	
3		444 (84.4)	37 (7.0)	45 (8.6)	
Metformin use					
No	4442	739 (86.5)	49 (5.7)	66 (7.7)	0.003
Yes		3166 (88.2)	248 (6.9)	174 (4.9)	
Sulphonylurea use					
No	4442	2199 (87.7)	160 (6.4)	148 (5.9)	0.17
Yes		1706 (88.2)	137 (7.1)	92 (4.8)	
TZD use					
No	4442	3141 (87.8)	239 (6.7)	197 (5.5)	0.82
Yes		764 (88.3)	58 (6.7)	43 (5.0)	
Insulin use					
No	4442	2313 (88.6)	179 (6.9)	119 (4.6)	0.012
Yes		1592 (87.0)	118 (6.4)	121 (6.6)	

Variables are shown as *n* (%).
TZD; thiazolidinediones.
* CKD groups shown use eGFR calculated with the CKDEPI equation: CKD Group 1 eGFR >90 ml/min/1.73 m^2, CKD Group 2 eGFR 60–89 ml/min/1.73 m^2, CKD Group 3 eGFR 30–59 ml/min/1.73 m^2. Twenty-two patients with eGFR < 30 ml/min/1.73 m^2 were excluded due to small numbers in each GISE outcome category. Analyses using the Cockcroft Gault equation adjusted by body surface area and Modified Diet for Renal Disease (MDRD) equation showed associations with significance of $P < 0.001$ and $P = 0.031$, respectively.

patients treated with liraglutide. While eGFR was also significantly associated with GISE in univariate analysis, eGFR was highly collinear with age. Removing eGFR in the multivariate analysis resulted in the variable of age being significantly associated with GISE while eGFR itself did not achieve significance in any of our multivariate models. In increasing decades of life from age 30 years, there was a steady rise in reported rates of GISE (9.7% to 20.0%). Discordantly, there was also a high rate of reported GISE among patients age 20 to 29 years (15.6%) although the total number of patients were small in this group (64 patients). The reason for older age being a risk factor for more significant GISE is not clear. It is also possible that the higher rate of drug discontinuation in the elderly may signify a more precautionary approach to their management rather than them being more prone to developing severe GISE. Prescribing information for liraglutide suggests that no dose adjustment is required for patients older than 65 years, but highlighted the limited experience of the use of liraglutide among patients with age more than 75 years [15].

The findings of patients not on metformin reporting greater drug discontinuation due to GISE was initially a surprising finding. Clinical trials of liraglutide versus placebo or active comparator treatment have reported

Table 3 – Ordinal logistic regression analyses of variables associated with gastrointestinal side effects (GISE) or drug discontinuation due to GISE among patients treated with liraglutide.

	Model 1		Final model	
	Adjusted OR [95%CI]	*P* value	Adjusted OR [95%CI]	*P* value
Insulin use	1.26 [1.02, 1.55]	0.035	–	–
Metformin use	0.76 [0.59, 0.99]	0.043	0.76 [0.60,0.96]	0.020
Age	1.11 [0.99, 1.25]	0.083	1.15 [1.05,1.26]	0.002
Weight	0.96 [0.86, 1.06]	0.38	–	–
eGFR	0.98 [0.87, 1.10]	0.68	–	–

ORs represent a rise of 1-SD for continuous variable (age, weight, eGFR) and one category change of categorical variable (metformin use, insulin use). Results are sorted by *P* value. Model 1: all significant variables in univariate analyses; Final model: model after sequentially removing variables with the highest non-significant *P* value.

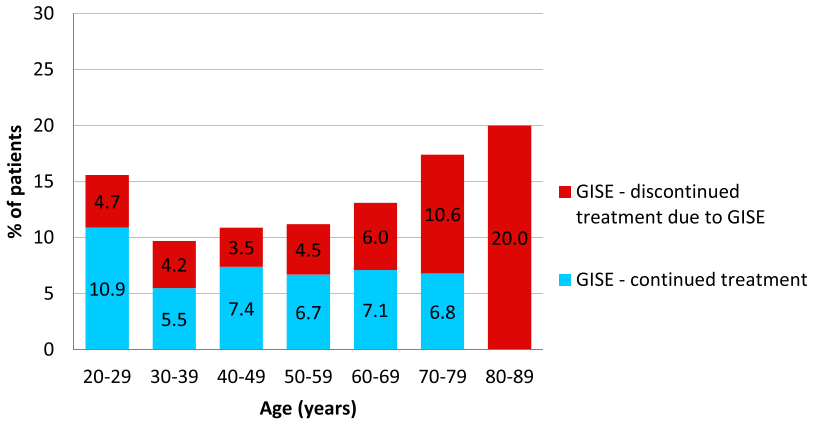

Fig. 1 – Rates of gastroinestinal side effects (GISE) among patients treated with liraglutide, results shown by decades of age. The interaction between age (decades) and GISE outcome was statistically significant ($P < 0.001$). Age 20–29 ($n = 64$), age 30–39 ($n = 236$), age 40–49 ($n = 862$), age 50–59 ($n = 1409$), aged 60–69 ($n = 1261$), age 70–79 ($n = 339$), age 80–89 ($n = 35$). Seven patients under 20 years of age were excluded for clarity.

generally higher rates of GISE when there was background treatment with metformin [5,7] as compared with a trial of liraglutide added to glimepiride without background metformin use [11]. However, in the latter trial, glimepiride treatment was used as part of a forced treatment-titration rather than due to metformin intolerance. In clinical practice, metformin is well-recognised as the first line diabetes treatment; patients in the audit not on metformin were possibly those who had encountered side effects to metformin earlier in their treatment algorithm. However, the audit did not capture data that could verify this, this hence being a limitation of this study. There is a plausible hypothesis that patients may share intolerance to both metformin and GLP-1 receptor agonists. The side effect profiles for both treatments are similar. Metformin has been shown to increase GLP-1 levels after an oral glucose load in obese subjects with or without diabetes, and the rise in GLP-1 may be a possible cause of the anorectic effects of metformin [16].

We have previously reported more frequent discontinuation of liraglutide in the audit among patients with mild and moderate renal impairment, a similar finding in the current univariate analysis [17]. However, when adjusted for other variables including age, renal function became non-significantly associated with GISE outcomes. A pharmacokinetic study testing the 0.75 mg dose of liraglutide showed no increase in drug exposure in patients with renal impairment [18]. The Prescribing Information for liraglutide have reported that liraglutide is metabolised endogenously much like large proteins rather than having a specific organ as a major route of elimination, and with no significant elimination through the faeces or urine [15]. Hence our finding that poorer renal function was not an independent risk factor for GISE with liraglutide treatment would be consistent with the pharmacokinetic studies above.

The strengths of our study include the fact that all available variables were tested and data was obtained from a large number of centres across UK. Weaknesses of the study include the potential for loss of follow-up or lack of data input among patients who discontinued liraglutide early due to GISE, as well as the potential for the audit not capturing data on other unknown determinants of GISE.

In conclusion, the results from our analyses would suggest caution in using liraglutide in older patients due to poorer drug tolerability. It may also be worthwhile investigating whether patients susceptible to GISE caused by metformin treatment are also at greater risk of developing GISE to GLP-1 receptor agonists.

Conflict of interest statement

KYT has received speaker fees and educational sponsorships from Novo Nordisk, manufacturer of liraglutide. PSG has received educational sponsorships from Novo Nordisk. REJR has received speaker fees, consultancy fees and educational sponsorships from Novo Nordisk. ADB has no conflicts of interest to declare.

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We thank all the nationwide contributors for submitting data on patients on liraglutide (listed in Appendix 2).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2015.04.009.

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