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The influence of pharmaceutically induced weight changes on estimates of renal function: A patient-level pooled analysis of seven randomised controlled trials of glucose lowering medication

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ABSTRACT

Background: Estimation of kidney function (eGFR) is essential in monitoring of patients with kidney disease. Estimates of kidney function based on serum creatinine are derived from cross-sectional studies. If body weight (BW) changes, this might affect creatinine and eGFR. The Cockcroft–Gault (CG) equation includes creatinine and BW, whereas the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations only include creatinine.

Methods: Data were pooled from the six LEAD (Liraglutide Effect and Action in Diabetes) trials and the LIRA-DPP4 trial. The trials were conducted in patients with type 2 diabetes and of 26 weeks duration.

We investigated changes in eGFR for patients treated with liraglutide, and for patients treated with glucose-lowering medications with less weight-reducing effects (insulin glargine, glimepiride, exenatide and rosiglitazone).

Results: We included 5100 patients (liraglutide n = 3173, comparator n = 1927). Mean (SD) CKD-EPI eGFR was 81.2 (20.6) ml/min/1.73 m^2 for liraglutide and 81.6 (20.3) ml/min/1.73 m^2 for comparator.

For liraglutide, BW changed −1.9 (95% CI (−2.0; −1.8)) kg, for comparator BW changed 0.2 (95% CI (0.03; 0.3)) kg. Using regression modelling, a 10% BW decrease yielded no change in creatinine, MDRD eGFR or CKD-EPI eGFR for both liraglutide and comparator, but was associated with a 10.2% (−11.3%; −9.1%) decrease in CG eGFR for liraglutide, and a 10.6% (−12.0%; −9.1%) decrease for comparator.

Conclusions: A liraglutide-induced weight reduction of 1.9 kg was not associated with change in creatinine. Accordingly, there was no change in weight-independent estimates of GFR, whereas weight-dependent estimates were changed. The MDRD and CKD-EPI equations can be used in patients experiencing pharmaceutically induced weight reductions.

1. Introduction

Estimation of glomerular filtration rate (eGFR) is essential in the diagnosis and monitoring of patients at risk of developing or with established kidney disease, and for correct dosage of drugs eliminated from the circulation by the kidneys. Estimation of GFR based on serum creatinine is most commonly used, since it has proven to be a reliable and inexpensive technique. The different eGFR equations based on serum creatinine are derived from cross-sectional studies. Skeletal muscle mass is the main determinant of creatinine generation/production with creatinine being the final catabolite of muscular energetic metabolism (Wyss & Kaddurah-Daouk, 2000). Hence, if body weight (BW) or body composition and in particular muscle mass change over time, and serum creatinine is also affected, this could influence estimates of renal function, without actual changes in true GFR. Whether these factors indeed influence eGFR depends on the applied equations, as for example the Cockcroft–Gault (CG) equation (Cockcroft & Gault, 1976) includes both creatinine and BW, whereas

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the 4-variable Modification of Diet in Renal Disease (MDRD) (Levey et al., 1999) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey, Stevens, Schmid, et al., 2009) equations only include creatinine and as a result would not be influenced by changes in BW alone.

The glucagon like peptide 1 (GLP-1) analogue liraglutide is a glucose-lowering agent, approved for management of type 2 diabetes in doses up to 1.8 mg once-daily. Furthermore, liraglutide treatment has been associated with sustained weight reductions in patients with type 2 diabetes of up to 3.4 kg (Bode, 2012).

Our pre-specified aim of the present study was to investigate changes in eGFR based on CG, MDRD and CKD-EPI in patients with type 2 diabetes treated with liraglutide, and in patients treated with other glucose-lowering medications with less or no weight-reducing effects (insulin glargine, glimepiride, exenatide, rosiglitazone), with the assumption that true renal function is not affected by these agents Our study hypothesis was that the weight reduction associated with liraglutide treatment would decrease muscle mass and creatinine leading to different changes in eGFR depending on the applied equation.

2. Methods

Data for this patient-level pooled analysis were pooled from the LEAD (Liraglutide Effect and Action in Diabetes) clinical trials (Buse, Rosenstock, Sesti, et al., 2009; Garber, Henry, Ratner, et al., 2009; Marre, Shaw, Brandle, et al., 2009; Nauck, Frid, Hermansen, et al., 2009; Russell-Jones, Vaag, Schmitz, et al., 2009; Zinman, Gerich, Buse, et al., 2009) and from the LIRA-DPP4 trial (Pratley, Nauck, Bailey, et al., 2012), all investigating liraglutide for the treatment of type 2 diabetes. The LEAD programme consisted of six phase 3, multicentre, parallel-group, placebo and active-controlled trials and the LIRA-DPP4 trial was a multicentre, active-controlled, parallel-group trial. This allows comparison of estimates of renal function in patients on weight stable or weight reducing glucose lowering agents not assumed to affect renal function.

A total of 5100 patients with type 2 diabetes were included in this patient-level pooled analysis. 192 patients did not have serum creatinine measurements at baseline. Consistent with standards for drug development at the time, patients with elevated serum creatinine levels were excluded from the individual trials as follows: monotherapy study (Garber et al., 2009) (≥1.7 mg/dL) and combination therapy studies (Buse et al., 2009; Marre et al., 2009; Nauck et al., 2009; Russell-Jones et al., 2009; Zinman et al., 2009) (males ≥1.4–1.5 mg/dL; females ≥1.3 mg/dL), whilst a CG eGFR below 50 mL/min was used as exclusion criterion in the LIRA-DPP4 trial (Pratley et al., 2012).

Three dosages of liraglutide, 0.6 mg daily, 1.2 mg daily and 1.8 mg daily, were compared with active comparator or placebo for efficacy and safety assessments. The active comparators were insulin glargine (Russell-Jones et al., 2009), glimepiride (sulfonylurea) (Garber et al., 2009), exenatide (GLP-1 receptor agonist) (Buse et al., 2009), rosiglitazone (glitazone) (Marre et al., 2009) and sitagliptin (DPP-4 inhibitor) (Pratley et al., 2012). In the LEAD studies including a placebo arm, placebo-treated patients also received background oral antidiabetic drug therapy. Glycaemic control, mean body weight, and systolic blood pressure were analysed to determine efficacy of liraglutide. Serum creatinine levels were compared between treatment arms for safety and tolerability assessment.

2.1. Estimation of GFR

For the CG eGFR the following equation was used:Cockcroft–Gault CrCl = (140 − age) * (weight in kg) * (0.85 if female)/(72 * Cr) (Cockcroft & Gault, 1976).

For the MDRD eGFR the following equation was used:MDRD eGFR = $175 \times (S_{Cr})^{-1.154} * (age)^{-0.203} * (0.742$ if female) (Levey et al., 1999).

For the CKD-EPI eGFR the following equations were used (Levey et al., 2009):

Sex	Serum Creatinine, S_{cr} (mg/dL)	Equation (age in years for ≥ 18)
Female	≤ 0.7	$GFR = 144 \times (S_{cr}/0.7)^{-0.329} \times (0.993)^{Age}$
Female	> 0.7	$GFR = 144 \times (S_{cr}/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤ 0.9	$GFR = 141 \times (S_{cr}/0.9)^{-0.411} \times (0.993)^{Age}$
Male	> 0.9	$GFR = 141 \times (S_{cr}/0.9)^{-1.209} \times (0.993)^{Age}$

2.2. Statistical analyses

All analyses used the full analysis population defined as patients exposed to at least one dose of trial product. Missing data were imputed using last observation carried forward. Comparisons of mean at baseline with mean at end of trial were done using paired t-test. The association between change in body weight on the endpoints creatinine, CG eGFR, MDRD eGFR, and CKD-EPI eGFR was investigated using separate lognormal linear regression models for liraglutide and comparator. Each trial was modelled separately and then the pool was analysed using both a fixed effect and a random effect approach. In the fixed effects model the effect of body weight is assumed to be the same for all trials, whereas in the random effect model the effect is assumed to follow a distribution. Specifically, the log transformed relative change in the endpoint was modelled using country and previous treatment as fixed factors and the log transformed endpoint at baseline, the log transformed body weight at baseline, and the log transformed relative change from baseline in body weight as covariates. For the pooled model the fixed effects approach also included trial whereas the random effects approach also included the random effect of log transformed relative change in body weight by trial. All analyses were programmed and executed by the study statistician and were independently validated.

3. Results

This patient-level pooled analysis included 3173 patients treated with liraglutide (1.2 or 1.8 mg/d) and 1927 patients treated with comparators. Baseline characteristics for the two groups are shown in Table 1. Patients were 52.7% male in the liraglutide treated group and 54.7% in the comparator group with a mean age (SD) of 55.7 (10) years and 56.0 (10) years, respectively. Median diabetes duration in the liraglutide group was 6.4 (range 0.1–40.3) years and 6.5 (0.2–43.5) years for the comparator group. Mean (SD) baseline weight was 87.5 (18.9) kg and 89.6 (18.8) kg, serum creatinine was 0.85 (0.21) mg/dl and 0.85 (0.21) mg/dl, whilst CKD-EPI eGFR was 81.2 (20.6) ml/min/1.73 m^2 and 81.6 (20.3) ml/min/1.73 m^2, in the liraglutide group and comparator group respectively.

During 26 weeks of treatment, for liraglutide BW changed −1.9 kg (95% CI (−2.0 to −1.8), $p < 0.0001$) and for comparator BW changed 0.2 kg (95% CI (0.03–0.3), $p = 0.017$).

3.1. Serum creatinine

Creatinine was unchanged in the liraglutide group (0.003 mg/dL (95% CI −0.005 to 0.01, $p = 0.44$)) and increased by 0.01 mg/dL (95%

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