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# Effect of weight reductions on estimated kidney function: Post-hoc analysis of two randomized trials

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ABSTRACT

*Aims:* Weight loss-induced serum creatinine reduction may increase creatinine-based estimated glomerular filtration rate (eGFR) producing incorrect estimates of kidney function. We investigated whether weight changes in the SCALE program with liraglutide 3.0 mg were associated with changes in serum creatinine.
*Methods:* Post hoc analysis of two 56-week, randomized, double-blind trials: SCALE Obesity and Prediabetes (n = 3731, without type 2 diabetes [T2D], randomized [2:1] to liraglutide 3.0 mg [n = 2487] or placebo [n = 1244]); SCALE Diabetes (n = 846 with T2D, randomized [2:1:1] to liraglutide 3.0 mg [n = 423], 1.8 mg [n = 211, excluded from this analysis] or placebo [n = 212]). NCT01272219/NCT01272232.
*Results:* In SCALE Obesity and Prediabetes, mean (± SD) weight loss (baseline to week 56) with liraglutide was 8.0 ± 6.7% (2.6 ± 6.9% with placebo); baseline creatinine with liraglutide was 76 ± 15 μmol/L and 74 ± 15 μmol/L after 56 weeks (similar across treatment groups). In SCALE Diabetes, weight loss with liraglutide was 5.9 ± 5.5% (2.0 ± 4.3% with placebo); baseline creatinine was 79 ± 19 μmol/L (77 ± 16 μmol/L, placebo) and 79 ± 20 μmol/L after 56 weeks (76 ± 15 μmol/L, placebo). No association between changes in weight and changes in serum creatinine was observed ($P \geq 0.05$, both trials, all tests).
*Conclusions:* Moderate gradual body weight reductions observed in the SCALE program were not associated with changes in serum creatinine.



## 1. Introduction

Accurate assessment of glomerular filtration rate (GFR) is important, both to evaluate the effect of weight loss or gain on kidney function, as well as to assess progression in nephropathy, decide drug dosing and patient counseling. However, methods for monitoring kidney function in the presence of moderate weight loss over time have not been validated.

Measuring kidney function using plasma clearance of an exogenous marker such as inulin is considered the 'gold standard' of

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GFR. However, this procedure is time-consuming and expensive, and hence not feasible as a routine measurement in clinical practice or in large randomized clinical trials. Clinicians therefore must rely on estimation of GFR, and equations based on serum creatinine are most commonly used (e.g. the 4-variable Modification of Diet in Renal Disease [MDRD][1] and Chronic Kidney Disease Epidemiology Collaboration[2,3]), as they are considered to be reliable and inexpensive. Skeletal muscle mass is the main determinant of creatinine generation/production with creatinine being the final catabolite of muscular energetic metabolism.[4] Hence, if body weight – and muscle mass in particular – changes over time, this would influence estimates of kidney function, if serum creatinine is also affected, without actual changes in measured GFR.

In a recent pooled analysis including 5100 patients, we demonstrated that a pharmaceutically induced weight loss of 1.9 kg on average was not associated with changes in serum creatinine.[5] However, in participants experiencing a fast and large weight loss following bariatric surgery, it has been well described that levels of serum creatinine decrease, resulting in increases in creatinine-based estimated GFR (eGFR); presumably explained by reductions in muscle mass.[6–8] Furthermore, these studies demonstrate a pronounced discrepancy between changes in eGFR and changes in measured GFR. The magnitude and rate of a weight loss associated with sufficient impact on muscle mass reduction to affect serum creatinine and thereby eGFR are currently unknown.

For the present study, we hypothesized that a weight loss of a magnitude observed in the Satiety and Clinical Adiposity — Liraglutide Evidence trials in individuals with and without diabetes (SCALE) program would lead to reductions in serum creatinine causing increases in eGFR (creatinine-based equations).

## 2. Materials and methods

### 2.1. Study design and participants

*Post-hoc* analysis of two 56-week, randomized, double-blind trials was performed: the SCALE Obesity and Prediabetes trial[9] and the SCALE Diabetes trial.[10]

The SCALE Obesity and Prediabetes trial included 3731 participants without type 2 diabetes (T2D) but with body mass index (BMI) ≥30 kg/m$^2$ or a BMI ≥27 kg/m$^2$ if they had treated or untreated dyslipidemia or hypertension. Participants were randomly assigned in a 2:1 ratio to receive once-daily subcutaneous injections of liraglutide at a dose of 3.0 mg (n = 2487) or placebo (n = 1244); both groups received counseling on lifestyle modification. Patients were stratified according to prediabetes status (American Diabetes Association 2010 criteria) at screening and according to BMI (≥30 vs. <30 kg/m$^2$).

The SCALE Diabetes trial included 846 adult participants with T2D and a BMI ≥27.0 kg/m$^2$, taking zero to three oral glucose-lowering agents with stable body weight, and $HbA_{1c}$ level 7.0% to 10.0%. Participants were randomly assigned (2:1:1) to receive once-daily subcutaneous liraglutide (3.0 mg; n = 423), liraglutide (1.8 mg; n = 211) or placebo (n = 212); all received counseling on lifestyle modification. For the present *post-hoc* analysis, only participants treated with liraglutide 3.0 mg or placebo were included; hence, in the SCALE Diabetes trial, a total of 211 subjects randomized to liraglutide 1.8 mg were excluded from the present investigation.

*Clinical trial registration:* ClinicalTrials.gov number: NCT01272219 and ClinicalTrials.gov number: NCT01272232.

### 2.2. Outcome measures

Changes from baseline in body weight and serum creatinine were assessed at week 28 and week 56.

### 2.3. Laboratory procedures

Serum creatinine was measured at a central laboratory using a rate-blanked and compensated-modified Jaffe method on the Roche BMD instrument (Roche Diagnostics Deutschland GmbH, Mannheim, Germany). Estimated GFR was calculated by the CKD-EPI equation from creatinine.[3]

### 2.4. Statistical analysis

Descriptive statistics are presented as averages and standard deviations are calculated using last observation carried forward at week 56 and through available cases at week 28. Scatterplots between changes in body weight and changes in serum creatinine were visually

**Table 1**
Baseline characteristics and outcome measures after 28 and 56 weeks of treatment.[a]

| Characteristic | SCALE Obesity and Prediabetes trial | | SCALE Diabetes trial | |
|---|---|---|---|---|
| | Liraglutide 3.0 mg | Placebo | Liraglutide 3.0 mg | Placebo |
| Patients, no. | 2487 | 1244 | 412[a] | 211 |
| Prediabetes, no. | 1528 | 757 | – | – |
| *Baseline* | | | | |
| Age, years | 45.2 (12.1) | 45.0 (12.0) | 55.5 (10.8) | 54.7 (9.8) |
| Female, % | 78.7 | 78.1 | 48.0 | 54.2 |
| $HbA_{1c}$, % | 5.6 (0.4) | 5.6 (0.5) | 7.9 (0.8) | 7.9 (0.8) |
| Weight, kg | 106.2 (21.2) | 106.2 (21.7) | 105.7 (21.9) | 106.5 (21.3) |
| Body mass index, kg/m$^2$ | 38.3 (6.4) | 38.3 (6.3) | 37.1 (6.5) | 37.4 (7.1) |
| Serum creatinine, μmol/l | 76 (15) | 76 (15) | 79 (19) | 77 (15) |
| eGFR, ml/min/1.73 m$^2$ | 90.2 (18.1) | 91.3 (18.1) | 87.5 (19.0) | 88.5 (15.4) |
| *Changes from baseline to week 28* | | | | |
| Body weight, kg | −8.6 (5.6) | −3.1 (5.6) | −6.3 (5.0) | −2.9 (4.0) |
| Serum creatinine, μmol/l | −2 | −1 | 0 | 0 |
| eGFR, ml/min/1.73 m$^2$ | 1.6 | 1.2 | -0.3 | 0.1 |
| *Changes from baseline to week 56* | | | | |
| Body weight, kg | −8.4 (7.3) | −2.8 (6.5) | −6.3 (6.0) | −2.2 (4.8) |
| Serum creatinine, μmol/l | −2 | −2 | 0 | −1 |
| eGFR, ml/min/1.73 m$^2$ | 2.1 | 1.8 | 0.3 | 0.4 |

Values are mean (SD) or %.
eGFR, estimated glomerular filtration rate.
Estimated GFR was calculated by the chronic kidney disease epidemiology collaboration (CKD-EPI) equation.
[a] In total, 423 patients were randomized to the liraglutide 3.0 mg group; however, serum creatinine measurements were only available for 412 and therefore only these patients were included in this current analysis.