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# Creatinine-Cystatin C eGFR Discordance During Incretin-Based Weight Loss: A Narrative Review of Current Evidence and Clinical Implications

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## Abstract

**Background:** Glucagon-like peptide-1 (GLP-1) receptor agonists and dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonists lead to significant and durable weight loss, associated with quantifiable levels of decrease in lean and skeletal muscle mass, decreased food intake, and decreased levels of systemic inflammation. This change in non-glomerular filtration rate (non-GFR) factors that affect each biomarker (creatinine by muscle mass and protein intake, and tubular secretion; cystatin C by adiposity, inflammation, and metabolic status) suggests that observed trajectories during weight loss related to incretin based drugs may be partially due to these changes, and not just the changes in estimated glomerular filtration rate (eGFR).

**Objective:** This review critically evaluates the physiological basis and limitations of various equations measuring cross-sectionally the eGFR from creatinine, cystatin C, or both, and summarizes 2020-2026 data from peer-reviewed evidence regarding the effect of weight loss induced by incretin-based therapy on eGFR and/or biomarkers.

**Results:** Findings of discordance vary and in some direct dual-marker studies, such as the SURPASS-4 post hoc analysis, the analysis of the kidney parameters in the SURMOUNT-1/2 randomized trials, and the SUMMIT and SMART randomized trials, no correlation between discordance and body-composition change was observed; conflicting or opposing discordance findings were reported in certain incretin-treated populations, such as the analysis of the kidney parameters in the SURMOUNT-2 randomized trial. The evidence from the bariatric surgery literature, and the sarcopenia/cachexia literature, is more consistent with that of muscle mass loss leading to slight overestimation of eGFR using creatinine as compared to eGFR using cystatin C, and as compared to measured GFR.

**Conclusion:** Current data do not show that either marker better tracks true kidney function during incretin-induced weight loss; where an accurate GFR matters, such as dosing of renally cleared drugs, combined-marker eGFR or measured GFR should be considered.

**Keywords:** Cystatin C, Creatinine, estimated glomerular filtration rate, GLP-1 receptor agonist, tirzepatide, semaglutide, chronic kidney disease, body composition, and sarcopenia.

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## 1. Introduction

Recently, incretin-directed pharmacotherapies, including glucagon-like peptide 1 (GLP-1) receptor agonists, including semaglutide and liraglutide, and the glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonist tirzepatide have provided substantial and durable weight loss-approximately 10% with semaglutide in the SELECT cardiovascular outcomes trial [1] and 15-21% with tirzepatide in SURMOUNT-1, approaching magnitudes seen with bariatric surgery [2]. This degree of weight loss is accompanied by substantial loss of fat mass and lean and skeletal mass, with ~25% of the weight loss resulting from lean mass loss, as in dual-energy X-ray absorptiometry (DXA) substudies of SURMOUNT-1 [2]. These weight losses are also linked to lower caloric intake, lower protein intake [3], and lower circulating levels of inflammatory markers such as C-reactive protein (CRP) and tumour necrosis factor-alpha (TNF-α), with more variable effects on interleukin-6 (IL-6) [4-7].

The same physiological factors, including muscle mass, dietary protein intake, and systemic inflammation, are associated with the two most commonly used biomarkers that estimate kidney function, specifically glomerular filtration rate (GFR): serum creatinine and serum cystatin

C. Over the past few years, clinicians and investigators have noted changes in estimated GFR (eGFR) with incretin-based weight-loss therapies, including apparent eGFR reductions soon after treatment initiation in some analyses and apparent eGFR improvements over longer follow-up periods in cardiovascular outcome and kidney outcome trials [8-10]. The non-GFR determinants of creatinine and cystatin C differ, and in principle, a change in body composition, diet, or inflammatory status could impact them differently and lead to either 'discordance' between the two measures, or between eGFR based on creatinine and that based on cystatin C, which may or may not reflect a change in glomerular filtration.

This review aims to critically appraise the differences between eGFR calculated from creatinine, from cystatin C, and from both markers combined; to summarise peer-reviewed articles published in the last six years (2020-2026) that describe changes in these biomarkers and/or eGFR during pharmacologic (incretin-based) weight loss; and to assess whether discordance reported in the literature reflects a change in GFR or a change in the non-GFR factors that affect each biomarker. The specific contribution of this review is to examine how the non-GFR determinants of creatinine and cystatin C relate to the dual-marker data currently available in the setting of incretin-based weight loss. The difference between direct evidence and evidence of the mechanism is highlighted throughout, and isolated shifts in biomarkers are not used as a substitute for improved or decreased renal function. The clinical relevance of eGFR staging in the context of chronic kidney disease (CKD), monitoring kidneys, understanding changes in eGFR, dosage of some medicines, and identifying patients who might benefit from combined-marker eGFR and/or measured GFR are then discussed.

## 2. Review

### 2.1 Physiological Basis of eGFR Equations With Limitations

### 2.2 Creatinine-Based eGFR

It is an endogenous product that is synthesized in the muscle and passes through the renal tubule, filtered, and actively secreted; the filtered product is serum creatinine. Its serum concentration therefore depends on GFR, muscle mass, dietary meat and protein intake, drugs that inhibit tubular secretion (e.g. trimethoprim and cimetidine), and assay interference [11]. Altered muscle mass has been a recent topic of review in GFR assessment settings, where it is stated that “standard assays of GFR based on creatinine show limitations in the context of sarcopenia due to reduced creatinine production, decreased GFR in the presence of sarcopenia, expanded volume of distribution, increased tubular secretion and increased assay interference” [11]. The race term was removed from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation in 2021 [12]. Creatinine-based equations may be less accurate in people with obesity or sarcopenia.

### 2.3 Cystatin C-Based eGFR

Cystatin C is a low-molecular-weight cysteine protease inhibitor that is freely filtered by the glomerulus, reabsorbed and catabolized by the proximal tubule rather than secreted, and is less strongly affected by protein intake and muscle mass than creatinine [13]. However, cystatin C is not without non-GFR factors, and a forthcoming review warns that thyroid disorders, corticosteroid therapy, inflammation, smoking, obesity, and malignancy may affect the level of this marker and should be interpreted accordingly [13]. A few of the findings on this list are in line with cross-sectional and cohort data. Cystatin C showed the highest correlation among the three different eGFR formulas, and higher FM was an independent risk factor for lower eGFR levels in a Swedish population [14]. Bioimpedance-measured visceral fat area was positively associated with serum cystatin C in patients with type 2 diabetes [15]. The young were also shown to have an increasing concentration of cystatin C that was related to body mass index (BMI), visceral fat, insulin, and high-sensitivity CRP (hs-CRP) in young women; in a separate regression model, eGFR based on cystatin C was independently predicted by hs-CRP, visceral fat, systolic blood pressure, and insulin [16]. A single case report illustrates a possible thyroid-cystatin C effect: in a patient with Sjögren's syndrome and hyperthyroidism, the discrepancy between cystatin C-based and creatinine-based eGFR narrowed after treatment of thyroid function; however, the patient also received corticosteroids and dehydration correction, so a mechanism cannot be established from this single case [17]. Together, these studies indicate that adiposity or inflammation or endocrine status play some role in affecting cystatin C, even if it is one that is not linked directly to GFR, and that it is not nearly as sensitive to changes in muscle mass.

### 2.4 Combined Creatinine-Cystatin C eGFR

Combining the two markers is expected to give a more accurate GFR estimate with less bias specific to either marker, because creatinine and cystatin C are affected by partially non-overlapping non-GFR factors (muscle mass/diet versus adiposity/inflammation/endocrine status). The National Kidney Foundation-American Society of Nephrology (NKF-ASN) Task Force made it clear that cystatin C is recommended for use in particular, and with filtration markers, as combining filtration markers is more accurate [12]. In a large multi-cohort US analysis (n=62,011), the race-free combined creatinine-cystatin C equation preserved the higher risk of kidney failure and death among Black participants at a given eGFR, whereas the race-free creatinine-only equation did not [18]. A subsequent KDIGO Controversies Conference on obesity and CKD references the inclusion in the Kidney Disease: Improving Global Outcomes (KDIGO) 2024 CKD guideline update of cystatin by itself or combined with creatinine for GFR estimation and CKD staging, stating that it is in need of further refinement, specifically in the context of obesity and altered body composition [19]; the 2026 review further mentions the incorporation of cystatin (alone or combined with creatinine) in GFR estimation and CKD staging from the KDIGO 2024 CKD guideline update, as this may be useful in individuals with altered body composition, such as during weight loss [20]. In fact, there is substantial variation in the staging of CKD with the use of different equations of choice; in one cohort, 44 of 435 patients (10.1%) were staged differently depending on whether one of three equations (creatinine, cystatin C, or combined) was used, and among the 16 of these 44

patients with clinically confirmed CKD, the GFR category differed between the creatinine-only and combined equations in 9 (56%), including four patients reclassified from G2 to G3a-G4 [21].

### 2.5 Measured GFR as the Reference Standard

The reference methods for the validation of all these estimating methods continue to be based on plasma clearance of either iohexol, iothalamate, or (less often) inulin or $^{51}$Cr-EDTA. Several studies conducted in 2020-2026 confirmed that none of the equations performed well throughout the extremes of body composition: In a single-centre study using iohexol-measured GFR, the non-indexed European Kidney Function Consortium (EKFC) equation underestimated GFR in participants with overweight (median bias −7.81 mL/min) and obesity (−4.57 mL/min); it was outperformed by the CKD-EPI 2021 equation and by machine-learning models in the same cohort [22]. Both sets of equations (using either creatinine or cystatin C for the assessment) showed “significant biases, high errors, and poor accuracy” when used to categorize the various stages of GFR, and misclassified patients relative to standard GFR categories in approximately half of the intensive care unit (ICU) cases studied, with creatinine-based (but not cystatin C-based) estimates drifting over the ICU stay in a pattern more attributable to sarcopenia than fluid balance [23]. These results highlight the principle (independent of incretin-specific results) that eGFR equations are least valid in the population with the greatest fluctuation or change in body composition - the physiology of incretin-induced weight loss.

## 3. Mechanistic Basis for Discordance During Incretin-Based Weight Loss

### 3.1 Lean and Skeletal Muscle Mass Loss

Loss of skeletal muscle reduces creatinine generation, which is known to cause creatinine-based eGFR to overestimate the true GFR. A large longitudinal study (PREVEND, n=8,076) revealed that as muscle mass decreased (measured by urinary creatinine excretion over 24 hours), the differences between eGFR using cystatin C and eGFR using creatinine became increasingly larger over 15 years of follow-up; at baseline, 15.2-18.5% of participants aged 60 and older with low muscle mass were already discordantly classified between the two equations [24]. In patients with cancer, sarcopenia (as defined by computed tomography [CT] scan) was independently associated with cystatin C-based eGFR more than 30% lower than creatinine-based eGFR (adjusted odds ratio [aOR] 1.90; 95% confidence interval [CI] 1.12-3.24) and more than 50% lower (aOR 2.34; 95% CI 1.21-4.51); high adiposity was also independently associated (aOR 2.01; 95% CI 1.15-3.52 and aOR 2.23; 95% CI 1.19-4.17), and discordance was rising with a progressive loss of skeletal muscle index [25]. Notably, DXA substudies show that incretin therapies with GLP-1 and dual action worsen loss of lean mass: in SURMOUNT-1, the lean mass loss after 72 weeks with tirzepatide was 10.9%[2] and in a smaller real-world cohort of adults with obesity and type 1 diabetes treated with liraglutide, semaglutide, or tirzepatide, lean mass loss at 12 months correlated with overall body weight reduction ($R^2$=0.36)[26]; the type 1 diabetes population limits generalizability to the non-diabetic or type 2 diabetes populations discussed elsewhere in this review. Some literature exists that addresses the more advanced field of bariatric surgery, showing that the creatinine-only equation overestimates measured GFR (mGFR) after substantial weight loss in bariatric surgery, while the combined creatinine-cystatin C equation is the least biased and most accurate of the available equations in this setting [27,28].

### 3.2 Dietary Intake

Reduced appetite and lower intake of energy and protein are core effects of incretin treatment [3]. However, it is well known that dietary protein or meat consumption influences serum creatinine levels, and this change is not due to GFR; therefore, it would be expected that a reduction in dietary protein or meat would lower the serum creatinine and thus "improve" the change in serum creatinine-driven GFR without any change in filtration. There is also indirect evidence, detailed in a systematic review and meta-analysis of 22 randomized controlled trials, that demonstrated a beneficial effect of high-protein diets on eGFR, not accompanied by any alterations in serum levels of creatinine alone [29], and one umbrella review of systematic reviews that revealed that low-protein and very-low-protein diets supplemented with ketoanalogue had a beneficial effect on proteinuria and blood urea nitrogen levels among populations with CKD [30]. We were not able to find through this search a study that directly measured the simultaneous change, both in dietary intake and in creatinine levels of the patients receiving incretins.

### 3.3 Inflammation

This effect of GLP-1 receptor agonists and to a lesser extent dual GIP/GLP-1 agonists on circulating CRP with some meta-analysis showing a similar effect on IL-6 and TNF-α is independent of glycaemic effects and supported by multiple systematic reviews and meta-analysis of randomized trials (2020-2026) [4-7]. Cystatin C is known to be influenced by the inflammatory status [13,19] which, in turn, might create a chain of events wherein inflammatory factor reduction after incretin use results in a decrease in cystatin C, but no significant reduction in GFR. However, there are no data yet that directly link body-composition or metabolic changes due to semaglutide specifically to proteinuria and to the change of eGFR, and even the SMART trial directly aimed at examining the correlation between body composition and the corresponding eGFR change, measured by either urinary cystatin C or serum creatinine, did not show any significant correlation (Spearman coefficients <0.23 for each one of the pairings; body-composition vs eGFR by urinary cystatin C or serum creatinine) [31]. A null finding here is significant since this study specifically recruited patients for measuring whether adiposity/inflammation-mediated change was a driver of cystatin C-eGFR discordance during semaglutide treatment. It should, therefore, be regarded as a biologically plausible, but still open, mechanism that results in inflammation-cystatin C in incretin-treated patients.

### 3.4 Metabolic Status

Weight loss with incretins is accompanied by better glycaemic control and insulin sensitivity and, in theory,

may impact both biomarkers via muscle protein turnover and adipokine/inflammatory pathways. Indirect supporting evidence comes from a cross-sectional study of young adults in which insulin levels, visceral fat, and high-sensitivity CRP had an independent association with eGFR based on cystatin C in women and visceral fat and leptin with eGFR based on creatinine in men, suggesting that metabolic/partiotrophic signals have a differential effect on these two markers [16]. However, none of the studies isolated an effect specific to metabolic status (such as insulin sensitization and glycaemic control) alone between incretin-treated and non-treated groups to conclude that specific metabolic changes are responsible for creatinine-cystatin C discordance apart from the two pathways mentioned above (mediated by inflammation and weight loss). Therefore, this pathway is included as a potential (though not proven) contributor supported by indirect (non-incretin), cross-sectional evidence.

## 4. Evidence From Pharmacologic Weight-Loss Trials

There are only a few randomized controlled trials (RCTs) and substudies that have assessed both creatinine and cystatin C-based eGFR and/or measured GFR simultaneously during incretin-based weight loss interventions (2020-2026); large outcome RCTs mostly assessed one or the other.

A lower annual eGFR decline was observed in patients treated with semaglutide, and there was a composite kidney outcome relative risk reduction of 24% in the FLOW trial (n=3533, T2D with CKD) with only creatinine data reported (no cystatin C measurement) [8]. Although different effects on body composition explain the discrepancy in biomarkers, the SELECT cardiovascular outcome trial of semaglutide in obesity without diabetes did not provide any data on cystatin C in the main publication of the trial.[1] A trial reported pooled data from SELECT, FLOW, and SOUL (n=30,787), with a pooled kidney composite hazard ratio of 0.84 (95% confidence interval [CI] 0.77 to 0.91) for semaglutide [9], but this had been pooled from several trials without specifically isolating the discordance in biomarker.

When two markers are being evaluated, there is some disagreement regarding the direction and amount of discordance. In SURPASS-4 (tirzepatide versus insulin glargine, type 2 diabetes), eGFR by both creatinine and cystatin C markers also decreased over 52 weeks in tirzepatide versus insulin glargine, but the between-group difference did not correlate with body-weight change [32]. The pooled kidney-parameter analysis of the SURMOUNT-1/2 trials demonstrated that tirzepatide resulted in a larger improvement in eGFR, based on cystatin C, than placebo in SURMOUNT-1 (obesity without type 2 diabetes) but was not different than placebo in SURMOUNT-2 (obesity with type 2 diabetes) [10]. In a trial involving obese patients with heart failure with preserved ejection fraction (HFpEF) (SUMMIT, n=731), eGFR decreased with tirzepatide at 12 weeks, based on creatinine, but not on cystatin C, although at 52 weeks, an increase in eGFR was observed by both methods, albeit with marked individual-level differences between the markers, likely related to effects of reduction in fat and protein mass on creatinine synthesis vs cystatin C synthesis [33]. The discordance hypothesis has been tested directly only once in the SMART trial (semaglutide, CKD with overweight/obesity, no diabetes, n=101; the GFR measured by iohexol) [31] where changes in body composition were considered a response to semaglutide and independently of the changes in GFR-measured by creatinine and cystatin C. In patients with type 2 diabetes and albuminuria, small, but significant, rise in creatinine levels during semaglutide treatment was associated with better performance of the combined filtration markers (creatinine, cystatin C, beta-trace protein, beta-2-microglobulin) than technetium-99m diethylenetriaminepentaacetic acid (99mTc-DTPA) plasma clearance methodology on measuring GFR, when compared with measured GFR as a reference [34]. The opposite direction of concordance and discordance was observed in the shorter, 16-week study above cited: In the arm with exenatide-plus-dapagliflozin, cystatin C-eGFR declined significantly (-10.4 mL/min/1.73 $m^2$, P<0.001), whereas creatinine-eGFR did not, and the authors related this to acute, haemodynamic changes different from that of muscle-mass loss [35]. A study on liraglutide in heart failure with reduced ejection fraction (HFrEF) showed that an increase in cystatin C but not a decline in renal-function outcome was linked with therapy with the GLP-1 receptor agonist [36].

No large RCTs have used paired outcomes of creatinine and cystatin C-derived eGFR and mGFR following specific interventions with semaglutide or tirzepatide in the obesity only (non-diabetic, non-HF) population. The limited number of direct dual-marker studies that have been performed to date (n=48-160) have mostly been in type 2 diabetes populations, with CKD or HF, and the results have been uneven from trial-to-trial both in the direction and magnitude. The evidence base remains limited, which argues against any blanket statement regarding the direction of the creatinine-cystatin C discordance with incretin-based weight loss.

## 5. Is Discordance True GFR Change or a Shift in Non-GFR Determinants?

The available studies do not answer this question definitively; the answer probably depends on the patient, the drug, the duration of treatment and the extent of muscle loss and inflammation change. There are several observations that counsel caution in translating an increase or decrease in one biomarker (eGFR) to an increase or decrease in the GFR. This SMART trial result is not to be interpreted as an artifact of all eGFR equations as there is quite a bit of lean mass and fat mass loss reported in this trial with no correlation between any change in GFR and any change in eGFR. Second, the time-dependency and transience of the discordance between the markers is aptly described in the SUMMIT trial, with early decreases in creatinine and late (after 20 days) 'catch-up' creatinine [33]. Third, the consistent pattern of bias against measured GFR following substantial weight loss in the body of available mechanistic-analog bariatric surgery data supports the plausibility of a similar artifact, where GLP-1/tirzepatide-specific data on measured GFR are lacking [27,28]. Finally, literature on sarcopenia/cachexia, most of which is not in oncology or oncology populations (Other than incretin treated) suggests that lower levels or less levels of muscle mass are associated with greater eGFR when calculated using creatinine but less eGFR

when calculated using cystatin C and GFR [24,25,37]. A similar effect is plausible in incretin-treated patients, but the amount of lean-mass loss with these drugs varies between studies.

Thus, an increase in eGFR based on creatinine levels after weight loss with incretin therapy does not necessarily reflect improvement in renal function, particularly in those with a substantial decrease in muscle mass, and any decrease in eGFR that may occur after administering some of the agents, such as in SUMMIT, should not be assumed to also reflect a decline in GFR in the absence of supportive data. It provides a little more but not definitive (cystatin C itself is a adiposity and inflammation factor) certainty that there is a real change in filtration when the eGFR by cystatin C is in parallel with the eGFR creatinine values over time.

## 6. Clinical Implications

### 6.1 CKD classification and staging

As the selection of equation affects the CKD stage assignment, with rates of reclassification of approximately 10% in the overall cohort and 9 of 16 (56%) among patients with clinically confirmed CKD in the discordant subgroup, as reported above [21]. Physicians need to be aware that when the CKD stage is listed in a patient with weight loss while receiving incretins, the stage may not be stable and/or may differ from that listed before beginning use of incretins, even when there is a genuine difference in the state of the patient's renal function.

### 6.2 Longitudinal renal monitoring

A decrease in creatinine production is associated with a moving, non-GFR baseline during a prolonged period of significant and persistent weight loss and muscle loss, as reported in elderly patients after orthopaedic surgery [38]. Some of this variability in eGFR-creatinine in clinical use for monitoring patients in active incretin-based weight loss may be due to differences in weight loss, and hence not necessarily due to differences in kidney disease activity.

### 6.3 Interpreting apparent eGFR improvement or decline

An increase in eGFR following substantial weight loss leads to the question of whether this represents a reduction in the generation of creatinine as a result of loss of lean mass, a true haemodynamic/metabolic benefit (as seen in the FLOW and pooled semaglutide kidney outcome trials, where hard clinical outcomes, including kidney failure, have been used in conjunction with eGFR trends [8,9]), or a combination of both. Similarly, the decrease in eGFR at treatment initiation with tirzepatide in SUMMIT would need to be followed over time before it can be judged whether it reflects a nephrotoxic effect.

### 6.4 Medication Dosing

The impact of factors on which eGFR equation to choose directly affects renally-cleared drugs with narrow therapeutic index [39]. Among the patients receiving palliation, 53% had clinically significant, relevant eGFR discrepancies between creatinine and cystatin C (median discrepancy of 17 mL/min/1.73 m2), with non-clinically relevant discrepancies occurring in over a third of the patients receiving two or more renally excreted drugs, which prompted the authors to suggest selective cystatin C use prior to initiation of such drugs [40]. Costa et al., (2026) [41] found that creatinine-based eGFR had large bias and poor accuracy in an oncology population with sarcopenia, regardless of obesity status, whereas combined creatinine-cystatin C-based and multi-marker eGFR equations achieved optimal accuracy; the authors suggested using combined-marker eGFR or measured GFR specifically “when clinically relevant decisions are needed.” In addition, if giving incretins for active weight loss, the most care should be taken of patients on nephrotoxic or renally-dosed drugs due to the same mechanism: alterations in body composition and changes in creatinine production.

### 6.5 Nephrotoxic drug assessment

Because the above eGFR based on creatinine may underestimate or overestimate the real change in GFR during a muscle depletion period, the physician evaluating possible nephrotoxicity in a patient receiving incretins for weight loss should (where possible) investigate the results using other methods (urinalysis/albuminuria, creatinine-cleared eGFR or measured GFR), but should not rely on the creatinine-eGFR trend alone to exclude or formally confirm drug-induced adverse effects on the kidney.

### 6.6 Patients in whom combined eGFR or measured GFR may be preferable

Consider using combined creatinine-cystatin C eGFR (and sometimes measured GFR) in patients with large or rapid weight and muscle loss on incretin therapy, patients with low baseline muscle mass or frailty, patients where knowing GFR is critical for a treatment or dosing decision (chemotherapy, administration of contrast, assessment of a transplant donor, or use of narrow-therapeutic-index renally cleared drugs) [41-45], and patients with other conditions that can affect cystatin C alone (uncontrolled thyroid disease, corticosteroid therapy, active malignancy, or marked systemic inflammation), where the use of cystatin C alone for interpretation should be considered with caution [13].

## 7. Limitations of the Current Evidence Base

The main limitation of this review is that there is a lack of large, long-duration, comprehensive, and detailed body composition and inflammatory marker data specifically in the context of semaglutide or tirzepatide treatment and that these details have not been evaluated within a population that excludes diabetes, CKD, or heart failure. A number of smaller substudies and/or post hoc analyses of mixed/comorbid populations provide available direct evidence, but this evidence is discordant in terms of what is measured and for how long the follow-up periods are. Much of this mechanistic explanation of muscle mass-driven and inflammation-driven discordance, therefore, is literature from the field of bariatric surgery, general adiposity-cystatin C cross-sectional studies, and studies in other populations, rather than from prospective, incretin-specific studies. Conclusions extrapolated from these settings should therefore be treated as physiologically plausible hypotheses rather than as findings established for GLP-1 receptor agonists and tirzepatide.

## 8. Summary of Evidence

All included studies are human studies (randomized controlled trials, cohort studies, cross-sectional studies, guideline/consensus statements, or case reports); no animal or in vitro evidence was used in this review.

## 9. Conclusion

The non-GFR determinants of creatinine-based eGFR (muscle mass and protein intake) and of cystatin C-based eGFR (adiposity, inflammation, endocrine status) are both plausibly affected by incretin-based weight-loss therapeutics, but through distinct pathways. Trials of GLP-1 receptor agonists and tirzepatide provide direct evidence of discordance, but its direction, size and clinical importance are inconsistent across trials. In addition, at least one well designed trial that examined body composition, with measurement of the change in GFR, did not demonstrate an association between the change in composition and discordance between GFR measurements. Current evidence suggests that single eGFR values (using creatinine or cystatin C) are not a useful indicator of actual progression or regression of kidney function with weight loss. A combined creatinine-cystatin C eGFR is recommended to be used in clinical decision-making settings where knowledge of the GFR is important. Additionally, factors that might also affect the outcome, such as changes in body composition, nutrition, and inflammation must be taken into account when measuring the changes in an eGFR over time. Additional studies are required to confirm the possible association between detailed body-composition assessment, inflammatory markers, and dual-marker eGFR and measured GFR during progression of weight-reduction therapy with incretins.

## References


1. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023;389(24):2221-2232. doi:10.1056/NEJMoa2307563
2. Look M, Skarbaliene J, et al. Body composition changes during weight reduction with tirzepatide in the SURMOUNT-1 study of adults with obesity or overweight. Diabetes Obes Metab. 2025;27(5):2720-2729. doi:10.1111/dom.16275
3. Arslan S. Medical nutrition in the glucagon-like peptide-1 (GLP-1) era: protein strategies, micronutrient monitoring, and lean mass preservation. Clin Nutr ESPEN. 2026;73:103305. doi:10.1016/j.clnesp.2026.103305
4. Kanbay M, et al. Effects of GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists on inflammatory and metabolic biomarkers in type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab. 2026;28(10):9002-9013. doi:10.1111/dom.71106
5. Ren Y, et al. The effect of GLP-1 receptor agonists on circulating inflammatory markers in type 2 diabetes patients: a systematic review and meta-analysis. Diabetes Obes Metab. 2025;27(7):3607-3626. doi:10.1111/dom.16366
6. Bray JJH, Foster-Davies H, Salem A, et al. Glucagon-like peptide-1 receptor agonists improve biomarkers of inflammation and oxidative stress: a systematic review and meta-analysis of randomised controlled trials. Diabetes Obes Metab. 2021;23(8):1806-1822. doi:10.1111/dom.14399
7. Inflammatory biomarker response to GLP-1 receptor agonists versus other glucose-lowering medications in patients with type 2 diabetes: a systematic review and meta-analysis. Front Endocrinol. 2026;16:1734549. doi:10.3389/fendo.2025.1734549
8. Perkovic V, Tuttle KR, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. N Engl J Med. 2024;391(2):109-121. doi:10.1056/NEJMoa2403347
9. Mann JFE, et al. Effect of semaglutide on kidney outcomes in the SELECT, FLOW, and SOUL trials: a prespecified pooled analysis. Lancet Diabetes Endocrinol. 2026;14(10):818-830. doi:10.1016/S2213-8587(26)00134-8
10. Heerspink HJL, et al. Kidney parameters with tirzepatide in obesity with or without type 2 diabetes. J Am Soc Nephrol. 2025;36(11):2190-2200. doi:10.1681/ASN.0000000764
11. Gil-Lopez F, et al. Evaluation of kidney function in cirrhosis: methods and pitfalls. Diagnostics (Basel). 2026;16(13):2088. doi:10.3390/diagnostics16132088
12. Delgado C, Baweja M, Crews DC, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN task force on reassessing the inclusion of race in diagnosing kidney disease. J Am Soc Nephrol. 2021;32(12):2994-3015. doi:10.1681/ASN.2021070988
13. Patel S, et al. Cystatin C in chronic kidney disease: enhancing diagnostic accuracy and patient outcomes. Postgrad Med. 2026;138(2):136-145. doi:10.1080/00325481.2026.2634426
14. Laucyte-Cibulskiene A, Nilsson PM, Engström G, Christensson A. Increased fat mass index is associated with decreased glomerular filtration rate estimated from cystatin C. Data from Malmö Diet and Cancer cohort. PLoS One. 2022;17(7):e0271638. doi:10.1371/journal.pone.0271638
15. Cong X, Chen X, Shen Q, Wu Y, Wang Q, Chen L. Serum cystatin C levels increase with increasing visceral fat area in patients with type 2 diabetes mellitus. Sci Rep. 2024;14:18638. doi:10.1038/s41598-024-69623-w
16. Sineglazova AV, et al. Sex differences in early stages of cardiorenometabolic syndrome in young adults. Cureus. 2025;17(10):e93900. doi:10.7759/cureus.93900
17. Mizuta M, Fukuda M, Fujii M, et al. Chronic kidney disease with Sjögren's syndrome and hyperthyroidism: discrepant creatinine- and cystatin C-based eGFR. Intern Med. 2026. doi:10.2169/internalmedicine.7902-26
18. Gutiérrez OM, Sang Y, Grams ME, et al. Association of estimated GFR calculated using race-free equations with kidney failure and mortality by Black vs non-Black race. JAMA. 2022;327(23):2306-2316. doi:10.1001/jama.2022.8801
19. Furth SL, et al. The relationship between obesity and chronic kidney disease: conclusions from a KDIGO Controversies Conference. Kidney Int. 2025;109(3):442-464. doi:10.1016/j.kint.2025.09.019
20. Awdishu L, Karger AB, Shlipak MG, Estrella MM. Use of cystatin C in tandem with creatinine to improve GFR estimation and clinical decision making. J Am Soc Nephrol. 2026;37(9):2042-2054. doi:10.1681/ASN.0000001201
21. Osredkar J, Klemenčič I, Kumer K, Pajek J, Knap B. Comparison of creatinine-, cystatin C-, and combined creatinine-cystatin C-based equations for estimating glomerular filtration rate: a real-world analysis in patients with chronic kidney disease. Int J Mol Sci. 2025;27(1):364. doi:10.3390/ijms27010364
22. Hage M, et al. Assessment of GFR estimation methods in patients with obesity. J Clin Endocrinol Metab. 2026;111(3):679-688. doi:10.1210/clinem/dgaf510
23. Sangla F, Marti PE, Verissimo T, Pugin J, de Seigneux S, Legouis D. Measured and estimated glomerular filtration rate in the ICU: a prospective study. Crit Care Med. 2020;48(12):e1232-e1241. doi:10.1097/CCM.0000000000004650
24. Groothof D, Post A, Polinder-Bos HA, et al. Muscle mass and estimates of renal function: a longitudinal cohort study. J Cachexia Sarcopenia Muscle. 2022;13(4):2031-2043. doi:10.1002/jcsm.12969
25. Hanna PE, Ouyang T, Tahir I, et al. Sarcopenia, adiposity and large discordance between cystatin C and creatinine-based estimated glomerular filtration rate in patients with cancer. J Cachexia Sarcopenia Muscle. 2024;15(3):1187-1198. doi:10.1002/jcsm.13469

26. Al Ozairi E, et al. Weight loss-dependent changes in body composition and bone health in people with obesity and type 1 diabetes treated with liraglutide, semaglutide, or tirzepatide. Diabetes Metab Res Rev. 2026;42(6):e70213. doi:10.1002/dmrr.70213
27. Chang AR, George J, Levey AS, Coresh J, Grams ME, Inker LA. Performance of glomerular filtration rate estimating equations before and after bariatric surgery. Kidney Med. 2020;2(6):699-706. doi:10.1016/j.xkme.2020.08.008
28. Friedman AN, et al. Measurement, estimation, and correlates of the GFR before and after bariatric surgery. J Am Soc Nephrol. 2025;37(1):110-119. doi:10.1681/ASN.0000000797
29. Teixeira Silva PR, et al. Effects of high-protein diets on renal function and body composition in adults without chronic kidney disease: a systematic review and meta-analysis of randomised trials. Diabetes Obes Metab. 2026;28(9):7672-7683. doi:10.1111/dom.70996
30. Li J, Yang L, Yang B, et al. Dietary patterns and kidney health: an umbrella review of systematic reviews and meta-analyses. Nutr Rev. 2026;84(9):1903-1921. doi:10.1093/nutrit/nuaf208
31. Heerspink HJL, Soler M, Beernink JM, et al. Effects of semaglutide on body composition and GFR: a prespecified analysis of the SMART trial. Clin J Am Soc Nephrol. 2026;21(7):1149-1158. doi:10.2215/CJN.0000001051
32. Heerspink HJL, Sattar N, Pavo I, et al. Effects of tirzepatide versus insulin glargine on cystatin C-based kidney function: a SURPASS-4 post hoc analysis. Diabetes Care. 2023;46(8):1501-1506. doi:10.2337/dc23-0261
33. Packer M, Zile MR, Kramer CM, et al. Interplay of chronic kidney disease and the effects of tirzepatide in patients with heart failure, preserved ejection fraction, and obesity: the SUMMIT trial. J Am Coll Cardiol. 2025;85(18):1721-1735. doi:10.1016/j.jacc.2025.03.009
34. Yahya R, Iversen E, Sivalingam S, et al. Effect of semaglutide on measured vs estimated glomerular filtration rate. Nephrol Dial Transplant. 2026. doi:10.1093/ndt/gfag154
35. van Ruiten CC, van der Aart-van der Beek AB, IJzerman RG, et al. Effect of exenatide twice daily and dapagliflozin, alone and in combination, on markers of kidney function in obese patients with type 2 diabetes: a prespecified secondary analysis of a randomized controlled clinical trial. Diabetes Obes Metab. 2021;23(8):1851-1858. doi:10.1111/dom.14410
36. Redouane B, Greene SJ, Fudim M, et al. Effects of liraglutide on worsening renal function among patients with heart failure with reduced ejection fraction: insights from the FIGHT trial. Circ Heart Fail. 2020;13(5):e006758. doi:10.1161/CIRCHEARTFAILURE.119.006758
37. Kusunoki H, Tsuji S, Kusukawa T, et al. Relationships between cystatin C- and creatinine-based eGFR in Japanese rural community-dwelling older adults with sarcopenia. Clin Exp Nephrol. 2020;25(3):231-239. doi:10.1007/s10157-020-01981-x
38. Iacomelli I, Giordano A, Rivasi G, et al. Low creatinine potentially overestimates glomerular filtration rate in older fracture patients: a plea for an extensive use of cystatin C? Eur J Intern Med. 2020;84:74-79. doi:10.1016/j.ejim.2020.06.016
39. Awdishu L, et al. KDIGO 2024 clinical practice guideline on evaluation and management of chronic kidney disease: a primer on what pharmacists need to know. Am J Health Syst Pharm. 2025;82(12):660-671. doi:10.1093/ajhp/zxaf044
40. Pelz S, Kobelt I, Schettle M, Hertler C, Blum D. Discrepancies between creatinine- and cystatin C-based eGFR estimation in palliative care patients and their implications on drug dosing. J Palliat Med. 2026;29(6):723-732. doi:10.1177/10966218261423788
41. Costa E Silva VT, Sise ME, Inker LA, et al. Impact of computed tomography-derived body composition analysis on the performance of GFR estimating equations in patients with cancer. Clin J Am Soc Nephrol. 2026;21(2):261-272. doi:10.2215/CJN.0000000878
42. Gama RM, et al. Measuring or estimating glomerular filtration rate in potential kidney donors: a comparative study. Clin Kidney J. 2026;19(9):sfag250. doi:10.1093/ckj/sfag250
43. Sinhmar P, Girimaji NS, Kumar D. Evaluation of kidney function in living kidney donor candidates. Curr Opin Organ Transplant. 2026;31(3):111-116. doi:10.1097/MOT.0000000000001282
44. Yajima S, Nakanishi Y, Ogasawara RA, et al. Value of cystatin C-based sarcopenia index in patients undergoing surgery for renal tumors. Clin Genitourin Cancer. 2024;22(3):102051. doi:10.1016/j.clgc.2024.02.002
45. Tuccinardi D, Masi D, Watanabe M, et al. Precision obesity medicine: a phenotype-guided framework for pharmacologic therapy across the lifespan. J Endocrinol Invest. 2025;48(12):2761-2798. doi:10.1007/s40618-025-02700-7

**Table 1. Summary of key evidence on creatinine-cystatin C eGFR discordance during incretin-based weight loss.**

| Review section / topic | Key references | Study type | Level of evidence |
|---|---|---|---|
| **Introduction: Incretin Pharmacology and Weight-Loss Effects** | | | |
| Semaglutide cardiovascular/weight-loss trial (SELECT) | [1] | RCT | I |
| Tirzepatide body-composition substudy (SURMOUNT-1 DXA) | [2] | RCT (prespecified substudy) | I |
| GLP-1 nutrition / lean-mass-preservation strategies | [3] | Narrative review | III |
| Precision, phenotype-guided obesity pharmacotherapy framework | [45] | Narrative review | III |
| GLP-1 / dual-agonist anti-inflammatory effects | [4-7] | Meta-analysis of RCTs | I |
| **Physiologic Basis: Creatinine-Based eGFR** | | | |
| NKF-ASN task force / race-free CKD-EPI 2021 equation | [12] | Task force consensus statement | III |
| Race-free equation and kidney failure/mortality outcomes | [18] | Multi-cohort study | II |
| Creatinine limitations in altered body composition (cirrhosis) | [11] | Narrative review | III |
| eGFR equation accuracy vs measured GFR in obesity | [22] | Prospective validation cohort | II |
| **Physiologic Basis: Cystatin C-Based eGFR** | | | |
| Cystatin C biology and non-GFR determinants | [13] | Narrative review | III |
| Fat mass index and cystatin C-based eGFR | [14] | Cohort study | II |
| Visceral fat and serum cystatin C in type 2 diabetes | [15] | Cross-sectional study | III |
| Sex differences, cardiorenometabolic syndrome and cystatin C | [16] | Cross-sectional study | III |
| Thyroid dysfunction and creatinine-cystatin C discordance | [17] | Case report | V |
| **Physiologic Basis: Combined Creatinine-Cystatin C eGFR** | | | |
| Cystatin C-in-tandem-with-creatinine review | [20] | Narrative review | III |
| Combined equation preserves risk discrimination (8 US cohorts) | [18] | Multi-cohort study | II |
| KDIGO 2024 guideline incorporation of cystatin C | [39] | Guideline primer | III |
| KDIGO Obesity-CKD Controversies Conference | [19] | Consensus conference report | III |
| Real-world CKD reclassification across equations | [21] | Retrospective comparative study | III |
| **Measured GFR as Reference Standard** | | | |
| Measured vs estimated GFR in kidney donors | [42] | Retrospective comparative study | III |
| Measured vs estimated GFR in ICU patients | [23] | Prospective study | II |
| **Mechanistic Basis for Discordance: Muscle Mass Loss** | | | |
| Muscle mass and longitudinal eGFR discordance (PREVEND) | [24] | Longitudinal cohort study | II |
| Sarcopenia/adiposity and eGFR discordance in cancer | [25] | Cross-sectional study | III |
| Body-composition change under incretin therapy (real-world DXA) | [26] | Observational study | III |
| GFR equations before/after bariatric surgery (single-centre) | [27] | Prospective observational study | II |
| Pooled measured-GFR analysis, bariatric surgery | [28] | Pooled observational analysis | II |

| Review section / topic | Key references | Study type | Level of evidence |
|---|---|---|---|
| Cystatin C-based sarcopenia index, renal tumour surgery | [44] | Retrospective observational study | III |
| Sarcopenia and cystatin C/creatinine ratio, older adults | [37] | Cross-sectional study | III |
| Muscle-mass loss and creatinine drift, fracture patients | [38] | Prospective cohort study | II |
| **Mechanistic Basis for Discordance: Dietary Intake** | | | |
| High-protein diet effects on eGFR/creatinine | [29] | Meta-analysis of RCTs | I |
| Dietary patterns and kidney health | [30] | Umbrella review of meta-analyses | I |
| **Evidence From Pharmacologic Weight-Loss Trials** | | | |
| FLOW trial (semaglutide, CKD/type 2 diabetes) | [8] | RCT | I |
| Pooled SELECT/FLOW/SOUL kidney outcomes | [9] | Pooled RCT analysis | I |
| SURPASS-4 post hoc analysis (tirzepatide, cystatin C) | [32] | RCT post hoc analysis | I |
| SURMOUNT-1/2 kidney-parameter pooled analysis (tirzepatide) | [10] | Pooled RCT analysis | I |
| SUMMIT trial (tirzepatide, HFpEF, explicit discordance) | [33] | RCT | I |
| SMART trial (semaglutide, body composition/measured GFR) | [31] | RCT | I |
| Measured vs estimated GFR, semaglutide (type 2 diabetes + albuminuria) | [34] | RCT post hoc analysis | I |
| DECREASE trial (exenatide + dapagliflozin) | [35] | RCT secondary analysis | I |
| FIGHT trial (liraglutide, HFrEF) | [36] | RCT post hoc analysis | I |
| **Clinical Implications** | | | |
| Drug-dosing implications of eGFR discrepancy, palliative care | [40] | Retrospective cohort study | III |
| CT body-composition analysis and eGFR-equation accuracy, oncology | [41] | Prospective cohort study | II |
| Living kidney donor evaluation, combined equations | [43] | Narrative review | III |