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CKJ Review

CKJ REVIEW

Are we ready for an adipocentric approach in people living with type 2 diabetes and chronic kidney disease?

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ABSTRACT

We are entering a new era in the management of adiposity-based chronic disease (ABCD) with type 2 diabetes (T2D) and related chronic kidney disease (CKD). ABCD, T2D and CKD can affect almost every major organ system and have a particularly strong impact on the incidence of cardiovascular disease (CVD) and heart failure. ABCD and the associated insulin resistance are at the root of many cardiovascular, renal and metabolic (CKM) disorders, thus an integrated therapeutic framework using weight loss (WL) as a disease-modifying intervention could simplify the therapeutic approach at different stages across the lifespan. The breakthrough of highly effective WL drugs makes achieving a WL of >10% possible, which is required for a potential T2D disease remission as well as for prevention of microvascular disease, CKD, CVD events and overall mortality. The aim of this review is to discuss the link between adiposity and CKM conditions as well as placing weight management at the centre of the holistic CKM syndrome approach with a focus on CKD. We propose the clinical translation of the available evidence into a transformative Dysfunctional Adipose Tissue Approach (DATA) for people living with ABCD, T2D and CKD. This model is based on the interplay of four essential elements (i.e. adipocentric approach and target organ protection, dysfunctional adiposity, glucose homeostasis, and lifestyle intervention and de-prescription) together with a multidisciplinary person-centred care. DATA could facilitate decision-making for all clinicians involved in the management of these individuals, and if we do this in a multidisciplinary way, we are prepared to meet the adipocentric challenge.

Keywords: adipocentric approach, chronic kidney disease, dysfunctional adipose tissue, incretins, type 2 diabetes

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INTRODUCTION

Adiposity-based chronic disease (ABCD) is a diagnostic term for overweight/obesity that explicitly recognises the chronic nature of the disease and the underlying adiposity that drives the pathophysiology and complications that cause morbidity and mortality [1].

ABCD, type 2 diabetes (T2D), belonging to the group of metabolic diseases, and chronic kidney disease (CKD) can damage almost every major organ system and have a particularly strong impact on the incidence of cardiovascular disease (CVD) and heart failure (HF). Recently, the connection between these clinical entities has been defined as a health disorder leading to poor health outcomes, the Cardiovascular–Kidney–Metabolic Syndrome (CKM syndrome), due to its clear impact on the health of the global population [2]. The CKM syndrome is a systemic disorder that can lead to multi-organ dysfunction and a high rate of adverse cardiovascular outcomes and includes both individuals at risk of CVD due to the presence of metabolic disease, CKD or both, and individuals with existing CVD that is potentially related to or complicated by metabolic risk factors or CKD [2].

ABCD and the associated insulin resistance are at the root of many CKM syndrome harms [2, 3], thus, a holistic therapeutic framework using weight loss (WL) as a disease-modifying intervention would facilitate its management at different stages across the lifespan.

In this review, we discuss the adiposity link between T2D, CKD and CVD, and place weight management at the centre of the integral CKM syndrome approach with a focus on CKD. Additionally, we propose the clinical translation of the available evidence into a transformative Dysfunctional Adipose Tissue Approach (DATA) for people living with ABCD, T2D and CKD, while highlighting gaps, areas of uncertainty and controversies meriting ongoing investigation.

ABCD, T2D, CKD AND CVD: THE ADIPOSITY CONNECTION

Size, site and cyte

To date, several fundamental gaps remain in our scientific insight into the interactions of dysfunctional adipose tissue and renal–cardiovascular systems. Subcutaneous white adipose tissue (SAT) is a uniquely plastic organ that can expand or shrink in response to caloric supply and demand, and its extension may occur via cellular hypertrophy and, to a lesser extent, hyperplasia [4]. However, the capacity for SAT expandability and its metabolic flexibility has a limit. It is now recognized that in the presence of dysfunctional SAT, the resulting lipid spillover must be stored as visceral adipose tissue as well as in normally lean tissues, through a process known as ectopic fat deposition [5]. The enlarged visceral fat deposit is infiltrated by proinflammatory macrophages, and this process is accompanied by an altered secretion of adipocytokines, leading to chronic low-grade inflammation with both local and systemic adverse metabolic consequences [5]. Pro-oxidative and pro-inflammatory mediators exacerbate the pathophysiological processes involved in atherosclerosis-CVD, as well as inducing alterations in renal haemodynamics resulting in glomerular hyperfiltration, glomerulosclerosis, renal tubular inflammation, tubulointerstitial atrophy and renal fibrosis [6, 7].

It is known that the 'size' (hypertrophy and hyperplasia), 'site' (ectopic location) and 'cyte' (degree of inflammation and function of the adipose tissue) are crucial in the adipose connection [8]. At the cellular level, the degree of transcription and a higher expression of triacylglycerol (TAG) synthesis, as well as TAG hydrolysis, are markers of the metabolic flexibility—good health—of an individual's SAT [9]. The above notwithstanding, from an eminently practical point of view, a person with T2D has become too heavy for their own body, leading to more fat in the liver, pancreas and kidneys than the individual can tolerate.

Obesity-related kidney disease comprises both obesity-related glomerulopathy, a consequence of glomerular hyperfiltration (subnephrotic proteinuria, glomerulomegaly with or without focal glomerulosclerosis) and fatty kidney disease, secondary to ectopic fat contributing to CKD [10]. In the kidney, ectopic fat is often deposited in the perirenal space, renal sinus and renal parenchyma, and is significantly associated with CKD in patients with T2D, independent of anthropometric, metabolic factors and other fat indicators [10–14]. Excess lipids accumulate in the renal parenchyma and cause damage to various cells, including podocytes, mesangial cells and proximal tubular epithelial cells [15], as well as causing oxidative stress, inflammation and fibrosis which leads to kidney damage [16].

In this context, it is clearly expected that substantial WL will be the most effective measure to improve or resolve adipose tissue dysfunction, including renal involvement. Indeed, changes in renal fat deposition may explain the renoprotective effect of bariatric surgery or certain glucagon-like peptide 1 (GLP1) receptor agonist (RA) treatments [13, 17].

Weight-related heterogeneity in people living with T2D

The Personal Fat Threshold hypothesis postulates that individual thresholds for lipid overspill and loss of SAT metabolic flexibility differs from person to person, and explains the apparent weight-related heterogeneity in people with T2D (PWT2D), with individual differences in the capacity to store fat in metabolically safe depots [18]. Body fat quality and location matter—even people with a body mass index (BMI) of <27 kg/m^2 could achieve remission of T2D with dietary WL, accompanied by the same underlying pathogenic mechanisms as in heavier people [18]. Therefore, this adipocentric or Dysfunctional Adipose Tissue Approach (DATA) should not be arbitrarily limited by a BMI cut-off point ≥ 30 kg/m^2 or even higher.

Waist circumference is a better indicator of visceral adiposity than BMI or waist-to-hip ratio and would be relevant in people with a BMI of <30 kg/m^2 to avoid underdiagnosis of excess abdominal fat excess and high cardiometabolic risk [19]. However, it should be noted that most of the available evidence on the effects of WL strategies is based on percentage of WL [20, 21], only BMI is part of the selection criteria for clinical trials [22–24] and the position statements of the main scientific societies [3, 25, 26] continue to prioritize percentage of WL targets without specific recommendations for changes in body composition. Therefore, despite more advanced techniques to target body fat being an evolving issue, BMI strongly correlates with body fat and associated comorbidities and remains a useful tool for general clinical practice.

The role of GIP and GLP1 in adipose tissue

GLP1 receptor (GLP1R) and glucose-dependent insulinotropic polypeptide receptor (GIPR) are widely expressed in multiple organs beyond the pancreas. Both the GIPR and GLP1R are expressed in the central nervous system, wherein receptor activation produces anorectic effects enabling WL [27]. GIPR, but not

GLP1R, is expressed within adipose tissue. GIP stimulates blood flow to white adipose tissue (WAT), lipoprotein lipase activity, insulin sensitization, glucose and free fatty acid uptake, *de novo* lipogenesis and lipolysis. GIP also regulates WAT macrophage-dependent inflammation. In brown adipose tissue (BAT), GIP regulates thermogenesis-related genes and upregulates lipid, amino acid and glucose catabolic processes [28]. Conversely, GLP1 indirectly promotes BAT activation and thermogenesis via central nervous system pathways in animals [29]. Whether GIPR agonism produces substantial WL in humans still remains uncertain [28].

WEIGHT MANAGEMENT AT THE CORE: WHAT IS THE EVIDENCE?

Intensive lifestyle intervention and bariatric surgery

T2D disease remission, prevention of microvascular disease and CKD, CVD events and mortality may require over 10% WL based on case–control studies of intensive lifestyle intervention (ILI) and meta-analyses of the bariatric surgery literature [30].

The DiRECT trial (The Diabetes Remission Clinical Trial) evaluated an ILI in PWT2D and demonstrated the strong correlation between the magnitude of WL and the likelihood of T2D remission, showing that a 15% WL, achieved in 7% of patients, can lead to remission in patients with early T2D at 24 months [21]. The Look AHEAD study also evaluated an ILI in PWT2D aimed at 7% WL. Interestingly, although the primary endpoint of cardiovascular events was not significantly different between groups at the end of the study [20], a *post hoc* analysis of Look AHEAD found that those individuals (few) who achieved a reduction in body weight (BW) >10% in the first year of the study had a 21% lower incidence of major adverse cardiovascular events (MACE) [31]. This evidence suggests that you need double-digit WL to reduce these hard endpoints, such as cardiovascular events and mortality.

WL is consistently associated with a reduction in urinary albumin excretion in PWT2D [32], through changes in renal blood flow, reduced inflammation, oxidative stress and hypoxia [33]. In the Look AHEAD study, even a moderate WL of 6% was associated with a 31% reduction in the incidence of very high-risk CKD [i.e. G3aA3 and G3bA2 to G5 Kidney Disease: Improving Global Outcomes (KDIGO) categories] [34]. Newly-onset renal impairment, defined as an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2, was reduced by 21% [95% confidence interval (CI) 0.66–0.96] and new-onset macroalbuminuria was also reduced by 19% (95% CI 0.66–0.01), albeit of marginal significance [34].

The benefits associated with WL in terms of T2D remission and micro-macrovascular complications are most pronounced in the early stages of the disease [35]. This may in part be related to the fact that hyperglycaemia 'per se' leads to long-lasting advanced glycation end products and epigenetic modifications, and subsequent upregulation of proinflammatory and profibrotic genes [2, 5, 30]. This may suggest that the benefits of this intensive adipose-focused approach are greater in the early stages of the disease. Finally, the timing of the benefits of different outcomes with large-scale WL is variable. Large-scale WL rapidly (within days to weeks) improves glycaemia, triglyceride levels, hepatic steatosis and blood pressure [36]. Potential cardiac remodelling in HF and renal remodelling, or changes in renal function, are likely to be intermediate in response to WL, whereas CVD is expected to be reduced over a longer period.

Consideration of the benefits of WL at different stages of CKD is valuable. Targeted WL early in the disease course may provide greater lifelong benefits. Although WL after bariatric or metabolic surgery appears to confer renal benefits in obese CKD patients without T2D [37–39], current evidence is still scarce and limited, preventing definitive conclusions for recommending specific interventions in the CKD population without T2D. Future high-quality studies focusing on hard outcomes such as CKD progression or renal failure are needed to clarify whether intentional WL offers additional benefits on the renal and cardiovascular risk profile in the long term. If WL does improve CKD outcomes, mechanistic studies would be useful to better understand both the rate and mechanisms of benefit, such as haemodynamic, cellular or other effects (see Table 1).

Highly effective weight loss pharmacotherapy

The DiRECT and Look AHEAD trials, amongst others, have shown that WL ≥10% and maintenance are difficult to achieve with lifestyle changes alone due to compensatory increases in appetite as well as reductions in energy expenditure. Until recently, bariatric surgery was the only intervention that consistently achieved WL ≥15% ensuring maintenance, but surgical procedures are difficult to scale up to treat the entire population. The breakthrough of highly effective WL pharmacotherapy, such as tirzepatide and semaglutide, allows for the goal of WL ≥10% of baseline BW to be achieved and maintained [3, 30, 40]. Preliminary results also suggest that tirzepatide and semaglutide improve renal outcomes in PWT2D with increased CV risk. These benefits are mainly related to a reduction in the risk of developing macroalbuminuria, but may also result from a reduction in the rate of eGFR decline over time [41, 42] (see Fig. 1 and Table 2).

In CV outcomes trials in PWT2D, GLP1RAs have not yet been shown to meaningfully reduce renal outcomes, beyond a reduction in albumin excretion [43]. However, *post hoc* analyses of people with T2DM treated with liraglutide, semaglutide and dulaglutide in the LEADER, SUSTAIN-6 and REWIND trials show a modest reduction in the rate of eGFR decline, particularly in people with eGFR <60 mL/min/1.73 m^2 [44, 45].

In addition, an analysis of real-world data showed a reduced rate of major renal events [hazard ratio (HR) 0.76 (95% CI 0.68–0.85)] in people treated with GLP1RAs for 6 years [46]. The long-term renal safety and renoprotective potential of weekly subcutaneous semaglutide 1 mg is being evaluated in a completed clinical trial in PWT2D with reduced eGFR and elevated ACR in the FLOW study (NCT03819153) [47], which was stopped due to interim efficacy data (see Table 3).

To date, the results of weekly subcutaneous semaglutide at a dose of 2.4 mg in the SELECT study (NCT03574597) [24] and the STEP-HFpEF study (NCT04788511) [48] have positioned this molecule as the high-intensity WL therapy of choice in non-diabetic ABCD people without diabetes and with established CVD or HF with preserved ejection fraction (HFpEF). The SELECT trial in patients with pre-existing CVD and overweight or obesity but without diabetes, reported a HR of 0.80 (95% CI 0.72–0.90) for MACE with a mean difference in percentage change in BW of −8.51% (95% CI −8.75 to −8.27) [24]. Whereas in the STEP-HFpEF study [48] in non-PWT2D with heart failure with preserved ejection fraction (HFpEF) and obesity showed a mean difference in the KCCQ Clinical Summary Score of 7. 8 points (95% CI 4.8–10.9) and a mean difference in percentage change in BW of –10.7% (95% CI −11.9 to −9.4), as dual primary

Table 1: Ongoing mechanistic studies of incretin-based therapies in people with CKD.

Clinical trial	Drug	Phase	Population	Main outcome	Secondary outcomes	State/date of end of the study
REMODEL (NCT04865770): A Research Study to Find Out How Semaglutide Works in the Kidneys Compared to Placebo, in People With Type 2 Diabetes and Chronic Kidney Disease [90]	Semaglutide 1 mg SC OW vs placebo SC OW (52 weeks)	3	T2D, eGFR 30-75 mL/min/1.73 m^2 and UACR ≥20 and ≤5000 mg/g ($n = 105$)	Change in kidney oxygenation, inflammation (cortex, medulla) and global perfusion by MRI (Week 0 and 52)	Kidney biopsy: gene expression assessed by single nucleus RNA sequencing, change in glomerular membrane width (Weeks 0 and 52) MRI: change in ADC (cortex, medulla), change in mean, change in mean arterial flow (Weeks 0 and 52) Urinalysis: change in natriuresis, albumin excretion rate, creatinine clearance	Ongoing/2024-11-18
SMART (NCT04889183): SeMaglutide and Albuminuria Reduction Trial in Obese Individuals Without Diabetes [91]	Semaglutide SC with increasing doses until 2.4 mg SC OW vs placebo SC OW (24 weeks)	3	Non-diabetic individuals with BMI ≥27 kg/m^2, eGFR ≥30 mL/min/1.73 m^2, UACR ≥30 mg/g and ≤3.5 g/g ($n = 98$)	Change from baseline to week 24 in UACR (Weeks 0 and 24)	eGFR and mGFR (Weeks 1 and 24) Change in UACR and eGFR during washout (Week 24 and 28) Change in BW and hip circumference (Weeks 1 and 24) Systolic and diastolic blood pressure (Weeks 1 and 24) Extracellular fluid measured by bio-impedance (Weeks 1 and 24) Liver stiffness measured by fibroscan (Weeks 1 and 24) CRP (Weeks 1 and 24)	Ongoing/2024-10
GLIMP (NCT05254418): Effects of GLP1RA on Ectopic Fat Deposition in Chronic Kidney Disease [92]	Dulaglutide 1.5 mg SC OW for 12 weeks	2	Patients with stage 3–4 CKD (eGFR 15–59 mL/min/1/73 m^2, BMI ≥25 kg/m^2 and ≤40 kg/m^2 with or without DM	To test the hypothesis that GLP1RA decreases intermuscular fat deposition in patients with stage 3–4 CKD as assessed by MRI	Changes in skeletal muscle mitochondrial function as assessed by phosphocreatine recovery time constant by ^{31}P magnetic resonance spectroscopy Changes in physical performance as assessed by 6-min walk test Safety and feasibility of dulaglutide treatment as evaluated by subject interview, continuous glucose monitoring, adverse events, laboratory tests, vital signs, ECG and allergic/hypersensitivity reaction	Ongoing/2024-09-01

Abbreviated names of the studies are in bold. SC, subcutaneous; OW, once a week; UACR, urine albumin–creatinine ratio; MRI, magnetic resonance imaging; ADC, apparent diffusion coefficient; RARI, renal artery resistive index; mGFR, measured glomerular filtration rate; CRP: C-reactive protein; GLP1RA, glucagon-like peptide-1 receptor agonists.

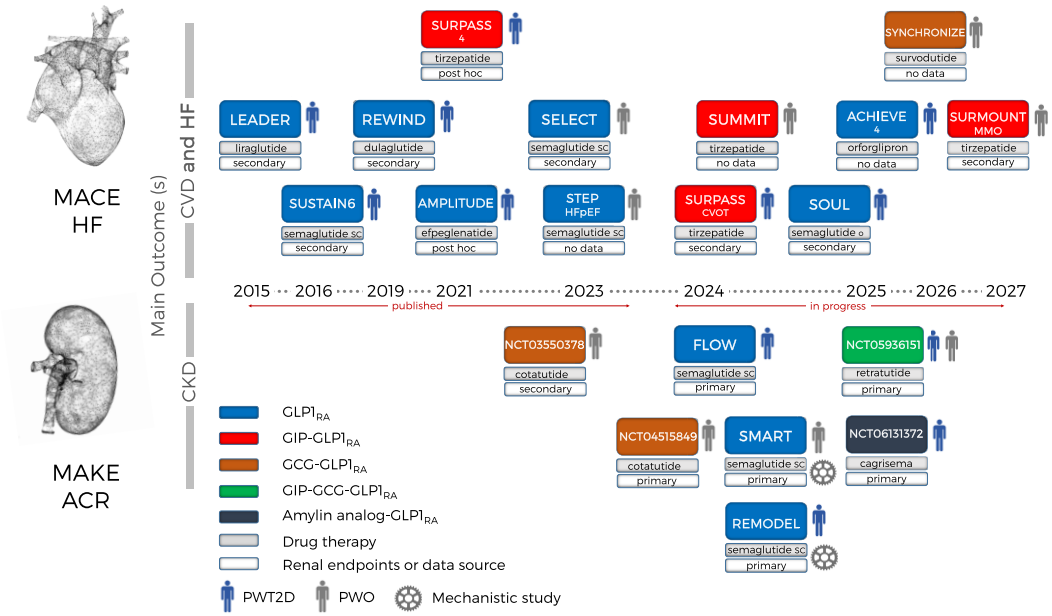

Figure 1: A timeline of published and ongoing clinical trials of incretin-based therapies with kidney, metabolic and CV outcomes. MACE defined as cardiovascular death, myocardial infarction or ischaemic stroke); HF events defined as time to first HF event, heart failure-related symptoms and physical function; MAKE (major adverse kidney events) defined as new-onset kidney injury, i.e. persistent albuminuria/proteinuria and/or decline in GFR <60 mL/min/1.73 m^2, persistent evidence of worsening kidney disease, development of ESRD with estimated GFR <15 mL/min/1.73 m^2 with or without initiation of renal replacement therapy, and renal death; SC, subcutaneous administration; O, oral administration; Cagrisema, cagrilintide plus semaglutide; renal endpoints or data source: secondary, secondary endpoints include some renal events; primary, primary endpoints include some renal events; post-hoc refers to a statistical analysis performed after a trial has been completed and the data collected; no data, no renal data published on clinicaltrilas.gov or included as a secondary endpoint; PWO, people who are overweight (BMI ≥27 kg/m^2) with clinical disease or BMI ≥30 kg/m^2. Semaglutide sc maximum dose 2.4 mg per week, except SUSTAIN 6, FLOW, REMODEL (1.0 mg per week). All studies versus placebo except SURPASS CVOT (versus dulaglutide 1.5 mg), NCT06131372 (versus semaglutide SC 2.4 mg, cagrinlitide 2.4 mg and placebo), NCT04515849 (versus semaglutide SC 1.0 mg and placebo). Further information and references of published and ongoing trials are given in Tables 1–3.

endpoints. Interestingly, in the STEP-HFpEF trial, the magnitude of benefit was directly related to the extent of the WL [49], and we await the subanalysis data from the SELECT trial.

Tirzepatide is the first approved dual GLP-1 and GIPRA for glucose lowering in T2D. There are no specific studies available or ongoing to evaluate the clinical impact of tirzepatide in patients with CKD. However, a post-hoc analysis of prespecified renal endpoints has been reported in SURPASS-4 [41, 50]. Tirzepatide reduced albuminuria and total eGFR decline [between-group difference 2.2 (95% CI 1.6–2.8)] and almost halved the risk of a prespecified composite renal endpoint (eGFR decline ≥40%, renal death, renal failure or new-onset macroalbuminuria) in PWT2D and high CV risk when compared with insulin glargine [HR 0.41 (95% CI 0.26–0.66)] in the overall population and in patients with A2 albuminuria. Effects of tirzepatide on the ACR and eGFR slope were essentially similar after taking into account HbA1c and BW changes [50]. The decrease in new-onset macroalbuminuria (and of the composite outcome that contained it) was apparent in both patients on and off sodium-glucose cotransporter 2 inhibitors (SGLT2i). The ongoing SURPASS-CVOT trial (NCT04255433) comparing tirzepatide with dulaglutide in PWT2D also has secondary endpoints of urinary albumin to creatinine ratio (ACR) and new or worsening nephropathy, which may be informative for the development of CKD-focused trials (see Table 3). Whereas, SURMOUNT-MMO trial (NCT05556512), with a secondary hierarchical composite of renal death or end-stage renal disease (ESRD), sustained decline in eGFR and eGFR slope, will inform us of its nephroprotective capacity in overweight type 2-obese non-diabetic people.

Non-weight loss direct effects of highly effective weight loss drugs

Genetics and epidemiology suggest that excess adiposity over time (i.e. accumulated exposure over years) causally contributes to kidney damage [51, 52]. However, it remains unclear to what extent the benefits associated with higher doses of GLP1RAs and dual GLP1 and GIPRAs in clinical outcomes are mainly related to WL, reduction of comorbid risk factors or other direct beneficial mechanisms of these drugs.

GLP1R is known to be expressed in the kidney and to be localized to a subset of vascular smooth muscle cells within afferent arterioles [28]. GLP1 acutely increases sodium and water excretion and reduces blood pressure and albumin excretion in human studies, which contribute to renoprotection [53]. Conversely, the effect of GIP on the kidney has not been studied in detail and further studies are needed [54].

THERAPEUTIC TRANSLATION: DYSFUNCTIONAL ADIPOSE TISSUE APPROACH (DATA)

Current guidelines

The adipocentric approach initiative should be driven by updating treatment guidelines with a specific focus on substantial, sustained WL as the primary treatment goal for dysfunctional adiposity in PWT2D with overweight/obesity and CKD, coupled with comorbidity-guided adjuvant therapy, as well as replacing

Table 2: Published major clinical trials of incretin-based therapies and renal outcomes.

Clinical trial	Drug	Phase	Population	Main renal outcomes	Secondary renal outcomes; HR (95% CI)	Published date
LEADER (NCT01179048): Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [93]	Liraglutide 1.8 mg QD vs PCB	3	T2D with high CV risk	NA	New onset of persistent macroalbuminuria; persistent doubling of serum creatinine; need for continuous renal replacement therapy; death due to renal disease; **HR 0.78** (95% CI 0.67–0.92); $P = .003$	28 July 2016
SUSTAIN-6 (NCT01720446): Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes [22]	Semaglutide (0.5 or 1.0 mg) SC OW vs PCB	3	T2D with high CV risk	NA	Persistent macroalbuminuria, persistent doubling of serum creatinine and eGFR of <45 mL/min/1.73 m^2, need for continued renal replacement therapy; **HR 0.64** (95% CI 0.46–0.88); $P = .005$	16 September 2016
REWIND (NCT01394952): Researching Cardiovascular Events With a Weekly Incretin in Diabetes [44]	Dulaglutide 1.5 mg SC OW vs PCB	3	T2D with high CV risk	NA	New macroalbuminuria, sustained decline in eGFR of 30% or more since baseline, continuous renal replacement therapy; **HR 0.85** (95% CI 0.77–0.93); $P = .0004$	10 June 2019
AMPLITUDE-O (NCT03496298): Effect of Efpeglenatide on Cardiovascular Outcomes [94]	Efplegenatide 4 or 6 mg SC OW vs PCB	3	T2D with high CV risk	NA	Composite renal endpoint: incident macroalbuminuria (defined as UACR $\geq$300, plus an increase in UACR of at least 30% from baseline), a sustained decrease in eGFR of at least 40% for 30 days or more, renal-replacement therapy for 90 days or more, and a sustained eGFR of <15 mL/min/1.73 m^2 for 30 days or more; **HR 0.68** (95% CI 0.57–0.79); $P < .001$	2 September 2021

Table 2: Continued

Clinical trial	Drug	Phase	Population	Main renal outcomes	Secondary renal outcomes; HR (95% CI)	Published date
NCT03550378: Efficacy and safety of cotadutide, a dual glucagon-like peptide-1 and glucagon receptor agonist, in a randomized phase 2a study of patients with type 2 diabetes and chronic kidney disease [95]	Cotadutide SC QD increasing doses until 300 μg daily vs PCB SC QD (32 days)	2a	T2D, BMI $\geq$25 kg/m^2 and $\leq$45 kg/m^2, eGFR 30–59 mL/min/1.73 m^2, UACR $\geq$30 mg/g and $\leq$3.5 g/g ($n = 41$)	NA	In a subgroup of patients with baseline micro- or macroalbuminuria, ACR was reduced; **HR 0.51** (90% CI 0.27–0.88) at Day 32 with cotadutide vs PCB; $P = .0504$ No differences in change of eGFR *Post hoc*: no statistically significant differences in urinary or plasma inflammatory biomarkers (pH, IL-18, monocyte chemoattractrant protein, TNF-alpha, BUN, uric acid, renin, aldosterone, kidney-injury marker-1	24 July 2022
SELECT (NCT03574597): Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity	Semaglutide 2.4 mg SC OW vs PCB	3	Overweight (BMI $\geq$27 kg/m^2) with clinical conditions or BMI $\geq$30 kg/m^2	NA	A 5-component composite nephropathy endpoint consists of: onset of persistent macroalbuminuria (UACR above 300 mg/g), persistent 50% reduction in eGFR compared with baseline (randomization), onset of persistent eGFR $<$15 mL/min/1.73 m^2, initiation of chronic renal replacement therapy (dialysis or transplantation) or renal death; **HR 0.78** (95% CI 0.63–0.96); *P*-value: NA	14 December 2023

Abbreviated names of the studies are in bold. QD, once daily; PCB, placebo; SC, subcutaneous; OW, once a week; NA, not applicable; IL, interleukin; BUN, blood urea nitrogen; TNF-R, tumour necrosis factor receptor.

Table 3: Ongoing major clinical trials with incretin-based therapies and kidney, metabolic and CV outcomes.

Clinical trial	Drug	Phase	Population	Main outcomes	Secondary outcomes	State/study completion date (estimated)
FLOW (NCT03819153): A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease [47]	Semaglutide 1 mg SC OW vs PCB	3	T2D, eGFR ≥50–≤75 mL/min/1.73 m^2 and UACR >300–<5000 mg/g or eGFR ≥25–<50 mL/min/1.73 m^2 and UACR >100–<5000 mg/g	Time to first kidney failure (persistent eGFR <15 mL/min/1.73 m^2 or initiation of chronic kidney replacement therapy), persistent ≥50% reduction in eGFR or death from kidney or CV causes	Annual rate of change in eGFR (total eGFR slope); Time to First Occurrence of a component event of MACE-3; Time to occurrence of all-cause death	Closed, pending publication
NCT04515849: A Study of Cotadutide in Participants Who Have Chronic Kidney Disease With Type 2 Diabetes Mellitus [96]	Cotadutide at 100, 300 vs 600 µg SC QD vs semaglutide 1 mg SC OW vs PCB	2b	BMI >25 kg/m^2 with CKD (eGFR 20-90 mL/min/1.73 m^2 and micro- or macroalbuminuria as defined by UACR >50 mg/g)	Change and percentage change in UACR versus PCB (Week 14).	Change in HbA_{1c}, fasting glucose from baseline, 10-day average glucose levels as measured by CGM, body weight and safety and tolerability (Weeks 14 and 26)	Closed, pending publication
SOUL (NCT03914326): A Heart Disease Study of Semaglutide in Patients With Type 2 Diabetes [97]	Oral semaglutide 14 mg QD vs PCB	3	T2D with atherosclerotic CVD [CAD, CVD, symptomatic PAD] and/or CKD (eGFR <60 mL/min/1.73 m^2)	Time to first occurrence of a component event of MACE-3	First occurrence of composite outcome comprising CV death, kidney-related death, persistent ≥50% reduction from baseline in eGFR, persistent eGFR (CKD-EPI) <15 mL/min/1.73 m^2 or initiation of chronic kidney replacement therapy (dialysis or kidney transplantation); occurrence of CV death; first occurrence of major adverse limb events, a composite outcome consisting of hospitalization for acute or chronic limb ischaemia	Ongoing/2024-07-29
SURPASS-CVOT (NCT04255433): A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes [98]	Tirzepatide SC OW vs dulaglutide 1.5 mg SC OW	3	T2D and confirmed CVD	Time to first occurrence of a component event of MACE-3	Change from baseline in UACR; time to first occurrence of new or worsening nephropathy	Ongoing/2024-10-17

Table 3: Continued

Clinical trial	Drug	Phase	Population	Main outcomes	Secondary outcomes	State/study completion date (estimated)
SURMOUNT-MMO (NCT05556512): A Study of Tirzepatide (LY3298176) on the Reduction on Morbidity and Mortality in Adults With Obesity [99]	Tirzepatide SC OW vs PCB	3	BMI ≥27 kg/m^2 with clinical conditions or BMI ≥30 kg/m^2	Time to first occurrence of any component event of composite, all-cause death, nonfatal MI, nonfatal stroke, coronary revascularization, or heart failure events that results in hospitalization or urgent visits	Hierarchical composite of renal death or ESRD, sustained decline in eGFR, and eGFR slope; time to first occurrence of a component event of MACE-3	Ongoing/2027-10-07
SUMMIT (NCT04847557): A Study of Tirzepatide (LY3298176) in Participants With Heart Failure With Preserved Ejection Fraction and Obesity [100]	Tirzepatide SC OW vs PCB	3	BMI ≥30 kg/m^2 and stable HF (NYHA class II–IV) and LVEF ≥50%	Hierarchical composite of all-cause mortality, HF events, 6MWD and KCCQ-CSS category	No renal outcomes	Ongoing/2024-07-30
SYNCHRONIZE™—CVOT (NCT06077864): A Study to Test the Effect of BI 456906 on Cardiovascular Safety in People With Overweight or Obesity [101]	Survodutide (3.6 mg, 6 mg) SC OW vs PCB	3	BMI ≥27 kg/m^2 with established CVD and/or at least 2 weight-related complications or risk factors for CVD or BMI ≥30 kg/m^2 with established CVD or CKD, and/or at least 2 weight-related complications or risk factors for CVD	Time to first occurrence of any of the adjudicated components of the composite endpoint consisting of: CV death, non-fatal stroke, non-fatal MI, ischaemia-related coronary revascularization, or HF events	No renal outcomes	Recruiting/2026-03-12
NCT06131372: A Research Study to See if Kidney Damage in People With Chronic Kidney Disease and Type 2 Diabetes Living With Overweight or Obesity Can be Reduced by CagriSema Compared to Semaglutide, Cagrilintide and PCB [102]	CagriSema 2.4 mg/2.4 mg vs semaglutide 2.4 mg vs cagrilintide 2.4 mg (all SC OW) vs PCB	2	T2D, BMI >27 kg/m^2, eGFR 15–90 mL/min/1.73 m^2 and UACR ≥100 and <5000 mg/g	Change in UACR	Change in eGFR	Ongoing/2025-10-13

Table 3: Continued

Clinical trial	Drug	Phase	Population	Main outcomes	Secondary outcomes	State/study completion date (estimated)
NCT05936151: A Study of Retatrutide (LY3437943) on Renal Function in Participants With Overweight or Obesity and Chronic Kidney Disease With or Without Type 2 Diabetes [103]	Retatrutide SC OW vs PCB	2b	BMI ≥27 kg/m^2 and CKD, with or without T2D	Change from Baseline in eGFR	Change from Baseline in UACR; change in mean arterial flow	Ongoing/2025-11-25
ACHIEVE-4 (NCT05803421): A Study of Daily Oral Orforglipron (LY3502970) Compared With Insulin Glargine in Participants With Type 2 Diabetes and Obesity or Overweight at Increased Cardiovascular Risk [104]	Oral orforglipron oral QD vs glargine SC	3	T2D, BMI ≥25 kg/m^2 at increased CV risk (CAD, PAD, CVD or CKD presumed to be of atherosclerotic origin), congestive HF NYHA II to III	Time to first occurrence of a component event of MACE-4	No renal outcomes	Ongoing/2025-04-24

Abbreviated names of the studies are in bold. Main outcomes and secondary outcomes limited to cardiovascular or renal outcomes. For more information see the studies. SC, subcutaneous; OW, once a week; PCB, placebo; MACE-3, a composite of CV death, nonfatal MI or nonfatal stroke; QD, once daily; CGM, continuous glucose monitoring; CAD, coronary artery disease; PAD, peripheral artery disease; NYHA, New York Heart Association; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; LVEF, left ventricular ejection fraction; 6MWD, 6-min Walk Test Distance; KCCQ, Kansas City Cardiomyopathy Questionnaire; CSS, Clinical Summary Score; MACE-4, myocardial infarction, stroke, hospitalization for unstable angina, or cardiovascular death; MI, myocardial infarction.

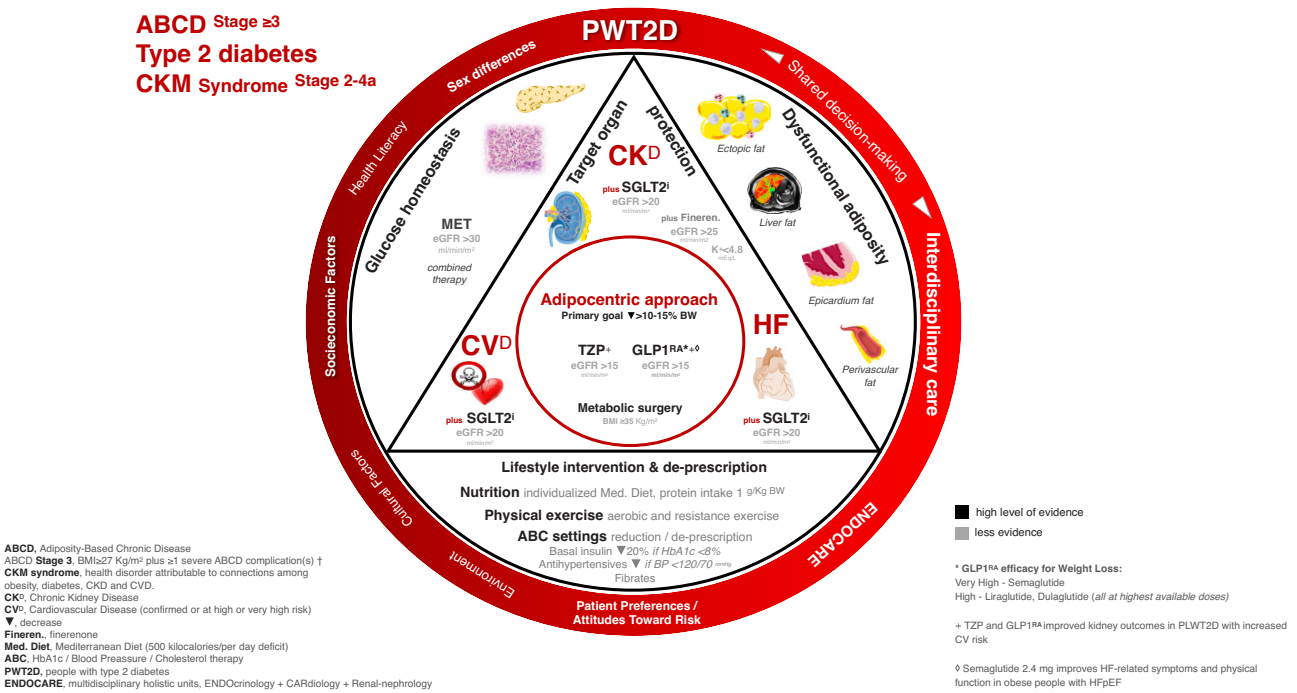

Figure 2: Holistic adipocentric approach for PWT2D, ABCD and CKD. The square circle illustrates the interplay of the four essential elements and the patient-centred approach in the DATA. CKM is a health disorder attributable to connections among obesity, diabetes, CKD and CVD; CKM stages: stage 2, dysfunctional adipose tissue with metabolic risk factors or CKD; stage 3, subclinical CVD; stage 4a, clinical CVD without renal failure (i.e. eGFR >15 mL/min/m^2). HF is HF confirmed or at risk. pEF, preserved ejection fraction. Physical exercise, including at least 150 min/week of aerobic exercise and at least 3 sessions/week of resistance training (exercise snacks/breaks, or short sessions of resistance exercise, performed every day, can also be considered). 'Exercise snacks' or minimal-dose resistance training, defined as lower volumes per session (i.e. ≤2 exercises per major muscle group and ≤2 sets per exercise) combined with lower weekly training frequency and higher intensities/loads, or higher weekly training frequency and lower intensities/loads. This approach requires minimal to no equipment (i.e. BW, resistance bands or portable weights) and may improve adherence [79]. †Severe ABCD complication(s) include T2D, hypertension, obstructive sleep apnoea, obesity–hypoventilation syndrome, nonalcoholic fatty liver disease, gastroesophageal reflux disease, asthma, venous stasis disease, severe urinary incontinence, debilitating arthritis or considerably impaired quality of life.

the long-standing exclusive focus on glycaemic control. The current reality of CKD-specific clinical practice guidelines is far from this objective.

A consensus report from the American Diabetes Association (ADA) and the KDIGO provides clear direction for implementing care to improve clinical outcomes in people with T2D and CKD [55]. All PWT2D and CKD should be treated with a comprehensive weight optimisation plan. Physicians should consider advising/encouraging people with obesity and CKD to target WL, particularly in people with eGFR ≥30 mL/min per 1.73 m^2 [25]; however, to our knowledge, there are no clear recommendations for WL targets. The role of GLP1RAs with proven CV benefit is only recommended for PWT2D and CKD who are not achieving their individualized glycaemic target with metformin and/or an SGLT2i, or who are unable to use these drugs [55], and there is no reference to therapies such as dual GIP–GLP1RAs. There is also no explicit reference in the public review draft KDIGO 2023 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.

The ADA—European Association for the Study of Diabetes (EASD) Standards of Care consider that weight management is an impactful component of glucose-lowering management in T2D [26, 56]. A sustained loss of >10% of BW confers disease-modifying effects and the possible remission of T2D, and may also improve long-term CV outcomes and mortality [26]. In overweight or obese PWT2D, the preferred pharmacotherapy should be a GLP1RA or dual GIP–GLP1RA with greater efficacy in reducing BW (i.e. semaglutide or tirzepatide), especially considering their additional weight-independent benefits (e.g. glycaemic and cardiometabolic). However, in the specific chapter on CKD and risk management, there is no dedicated section on target WL [57].

Finally, the 2022 AACE Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan and the 2023 update advocate a complication-centred model of care for people with ABCD [3, 58]. In the context of ABCD, a minimum threshold of >5%–≥10% is required to have a positive impact on glycaemia, BP and lipids, and WL of ≥15% may help to mitigate other ABCD complications [58].

Dysfunctional Adipose Tissue Approach (DATA)

Our current management proposal is based on the interplay of four essential elements and the person-centred care (see Fig. 2). The basic elements are (i) an adipocentric approach and target organ protection around which all other key factors such as (ii) dysfunctional adiposity, (iii) glucose homeostasis and (iv) lifestyle intervention and de-prescription intervene.

(i) Adipocentric approach and target organ protection.

From a practical perspective, when considering the approach to a person with T2D and CKD, the HbA1c target should be forgotten for decision making and weight management should be placed at the centre of the treatment algorithm, focusing

on the individual double-digit WL target and tolerability as main determinants of the WL drug titration. Of course, HbA1c remains a crucial aspect of overall management, but, given the high metabolic efficacy of these molecules, with up to 97% of participants in the tirzepatide phase 3 development programme achieving an HbA1c <7% [59], this metabolic control goal can be bypassed.

DATA brings weight management to the forefront of the treatment algorithm, prioritizing molecules with very high WL efficacy, combined with a comorbidity-based selection of agents such as SGLT2is and finerenone, together with drugs responsible for the control of other cardiovascular risk factors, such as high-potency statins and renin–angiotensin–aldosterone system inhibitors.

Given the global supply chain issues for subcutaneous GLP1RAs, oral semaglutide could also be an option. Real-world data show that it is effective and safe in an unselected population, with one-third reaching WL >10% and near two-thirds achieving HbA1c <7% [60].

This adipocentric, disruptive approach could be applicable to 60%–70% of PWT2D (excluding clusters or phenotypes with insulinopenia) [61], with ABCD stage 3 or higher (at least BMI ≥27 kg/m^2 plus one or more severe ABCD complication) [3] and CKM syndrome stages 2 to 4a (stage 2, dysfunctional adipose tissue with metabolic risk factors or CKD; stage 3, subclinical CVD; stage 4a, clinical CVD without ESRD) [2].

SGLT2is are the glucose-lowering agents of choice in patients with T2D and CKD from the perspective of protecting target organs [56, 62, 63], particularly in CKD, but one-fourth of patients treated with these molecules progress to KDIGO risk status, regardless of baseline risk category [64], and DATA is fully complementary to address residual risk.

(ii) Dysfunctional adiposity.

The systemic effects associated with dysfunctional ectopic adiposity, together with the local source of mediators, can lead to compressive organ damage around the kidney, contributing to hypertension and abnormal blood pressure variability [6, 7]. The development of steatotic liver disease associated with metabolic dysfunction further amplifies systemic inflammation and insulin resistance, which become self-perpetuating [65]. In addition, epicardial, pericardial ectopic and perivascular fat promotes arrhythmogenesis, myocardial dysfunction and coronary atherosclerosis [66, 67]. In this context, substantial WL is the best approach to reverse or slow the progression of the problem. This WL, regardless of the therapy used, leads to a loss of all adipose tissue, including abdominal-ectopic, with a direct correlation in the improvement of parameters related to cardiovascular and renal risk [23, 68, 69].

(iii) Glucose homeostasis.

Early, intensive adjuvant combination pharmacotherapy with impact on glucose homeostasis is recommended for most PWT2D, prioritizing insulin-sensitising drugs such as metformin or pioglitazone unless contraindicated [56, 63]. In certain clinical scenarios, adjunctive use of insulin may be necessary.

(iv) Lifestyle intervention and de-prescription intervene.

Lifestyle measures include promoting a Mediterranean-style diet, ensuring adequate protein intake according to individual needs, and physical activity. Depending on the WL and the baseline treatment used, an initial reduction in basal insulin dose of at least 20% and discontinuation of prandial insulin, should be considered [70]. Blood pressure needs to be monitored and antihypertensive treatment would also be reduced [23]. Drugs with effect in lipids but without CV benefits, such as fibrates, can be discontinued.

Person-centred care is an essential aspect of DATA. The preferences and attitudes of PWT2D about treatment options and the potential effects of WL need to be addressed, and the potential benefits and adverse effects of medications should be discussed. Gender differences, social determinants of health and the promotion of interdisciplinary care are also important. If we include all these factors in the shared decision-making process, clinical outcomes are likely to be better and adherence and persistence may be improved [71].

Although our scientific understanding still presents several gaps of knowledge on dysfunctional adipose tissue and renal cardiovascular interactions, this transformative proposal for an adipocentric approach to ABCD with T2D/CKM syndrome aims to refocus clinical practice to effectively incorporate weight management, prevent or mitigate metabolic risk factors, delay the progression of CKD and reduce the associated cardiovascular risk.

Sex differences in DATA and CKD

Sex matters in medical science. This particularly applies to CKM syndrome, which displays key differences between women and men. However, underrepresentation of women in randomized trials has led to an evidence gap in clinical practice. There are few and unclear data regarding sex differences on CKM syndrome. Early reports reinforced by later studies suggest that at a younger age, men with diabetes have an increased risk of CVD and CKD as compared with women, but once the disease is present and progresses over the years, it seems that renal events and cardiovascular-related mortality tend to equilibrate [72]. These differences have been partially related to the differential activation of the renin–angiotensin system and the relative protective effect exerted by oestrogens in young women. Taking all of these results into account, it seems that female sex is a protective factor for diabetic CKD; however, this only applies to younger, premenopausal women, where oestrogen levels are highest [73].

LIMITATIONS, UNCERTAINTIES AND FUTURE DIRECTIONS

There are several questions that need to be addressed in this area. The most important is to investigate whether intentional WL with highly effective WL pharmacotherapy affects renal function, development of ESRD and mortality in patients with pre-existing CKD, independently of its effect on T2D, hypertension and hyperlipidaemia. This is important in light of the 'obesity paradox' reported in dialysis patients: obese patients live longer than non-obese patients [74]. In addition, future studies should use consistent measures to assess obesity and early kidney damage, given the obvious limitations associated with BMI and the so-called CKD blind spot [75]. Work is underway to identify earlier biomarkers of CKD, mainly by analysing urine, which is thought to reflect early renal events better than plasma or serum [76]. When they become available, they should be included as indirect measures of early kidney damage in clinical trials with and without people with CKD.

One of the main challenges for the future lies in the prevention and management of sarcopenic obesity in chronic diseases as T2D or CKD, a catabolic condition associated with

muscle loss and decreased protein synthesis [77, 78]. The increasing rates of obesity and sedentarism amongst people living with CKD, and the association of high adiposity and muscle impairment with higher morbidity, mortality and worse clinical prognosis, reinforce the need for standardized criteria for diagnosis and research [77]. Future research should not only include assessment of sarcopenic obesity in the initial evaluation, but should also be carefully monitored during any pharmacological or non-pharmacological intervention, and prevention strategies based on both supervised physical activity programmes (aerobic, resistance exercises, 'exercise snacks') [79], nutrition support and muscle-directed therapies should be evaluated. Although protein recommendations are between 0.6–0.8 g/kg BW a day [10%–20% of total energy expenditure (TEE)], for overweight or obese PWT2D with eGFR ≥60 mL/min per 1.73 m^2, a protein intake of 1 g/kg BW a day (23%–32% of TEE) can be recommended in the short term (up to 12 months) in context of a low-calorie diet [80, 81].

The evidence needs to be considered in the context of public health approaches to T2D and CKD. The future challenge for clinical research will be to identify the best combination of present and future highly effective WL pharmacotherapy, with other traditional (SGLT2is, RAA renin–angiotensin–aldosterone system inhibitors, healthy lifestyle) and non-traditional (finerenone) nephroprotective interventions, and to develop cost-efficacy and real-world effectiveness studies. These studies should include robust and standardized clinical objectives (major adverse kidney events and MACE) and patient experience (patient-reported experience and patient-reported outcome measures), as well as considering direct and indirect costs in the short, medium and long term, without limiting the outcome measure to quality-adjusted life years. The evidence mentioned is needed to encourage national health systems and insurers to cover expensive treatments and to adopt care models that support integration of care, viewing the DATA not as an expense but as an investment to achieve long-term savings by minimizing costly downstream metabolic, renal and cardiovascular complications.

The available data strongly suggest that understanding the long-term benefits and mechanisms of action of GLP1RA, GIP-GLP1RA and GIP-GLP1-Glucagon (GCG) RA combinations will be of great importance to the metabolic community in the coming years. There are exciting new developments on the horizon (see Fig. 1 and Table 1).

Amongst the subcutaneous agents, three molecules stand out. CagriSema (combining the GLP1RA semaglutide with the long-acting amylin analogue cagrilintide) achieved a WL of −15.6% in PWT2D [82]. Cotatutide (a dual GLP1 and GCGRA), showed a 46% reduction in ACR and a WL of 7.3% in a phase 2b study in PWT2D and CKD with ACR ≥50 mg/g [83]. Finally, retatrutide (a novel single peptide derived from the GIP peptide backbone with agonist activity at GIPR, GLP1R and GCGR) achieved a WL of −17% in PWT2D and 24% in people with obesity in phase 2 studies [84, 85]. Two points of direct clinical relevance are the elimination of WL non-responders and the opening of the WL window of over 30% in one-fourth of patients.

Regarding oral therapies, semaglutide at doses of 25 and 50 mg in phase 3b studies in PWT2D and obese individuals achieved WL between 7% and 17%, superimposable to semaglutide 2.4 mg [86, 87], while orforglipron (a chemically synthesized, non-peptide, partial, biased agonist of human GLP1R) achieved average WLs between 10% and 15% in the same populations in phase 2 studies [88, 89].

CONCLUSIONS

We are entering in a new era in the management of ABCD with T2D/CKM syndrome, with a growing arsenal of treatment options. Physicians need to move towards more integrative management of these diseases as a single entity, and we believe that if we do this in a multidisciplinary way, we are ready to meet the upcoming adipocentric challenge. However, there are still important gaps in our knowledge of the interactions between dysfunctional adipose tissue and the renal cardiovascular system, and ongoing studies will provide further insight into this topic. In absence of more evidence, the 'art of medicine' and clinical experience will come into play in deciding how and when to combine these tools for maximum benefit. But science will have to be coupled with pragmatic and well-considered implementation strategies with the goal of overcoming inertia, and our proposed adipocentric approach could facilitate decision making for any clinician involved in the management of these individuals.

Fortunately for PWT2D with overweight/obesity and CKD, ongoing trials of tirzepatide and semaglutide, amongst others, with major adverse renal and CV events as the primary composite outcome, will soon tell us whether the scientific community has found the philosopher's stone in this DATA or if we are only one step closer to solving the puzzle.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

O.M.-P. received honoraria as a speaker and consulting fees from Eli Lilly, Boehringer-Ingelheim, AstraZeneca and Novo Nordisk. R.R.-G. received speaker honoraria sand consulting fees from Eli Lilly, AstraZeneca, Dexcom and Novo Nordisk. I.M.-P. received honoraria as a speaker from Eli Lilly, Boehringer-Ingelheim and Novo Nordisk. M.L.-M. received support for attending meetings and/or travel from Novo Nordisk. M.J.S. received honoraria as a speaker and consulting fees from Novo Nordisk, Jansen, Mundipharma, AstraZeneca, Esteve, Fresenius, Eli Lilly, Boehringer-Ingelheim, Vifor, ICU, Pfizer, Bayer, Travere Therapeutics, GE Healthcare, GSK and Otsuka. She is also one of the former Editors-in-Chief of *CKJ*.

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