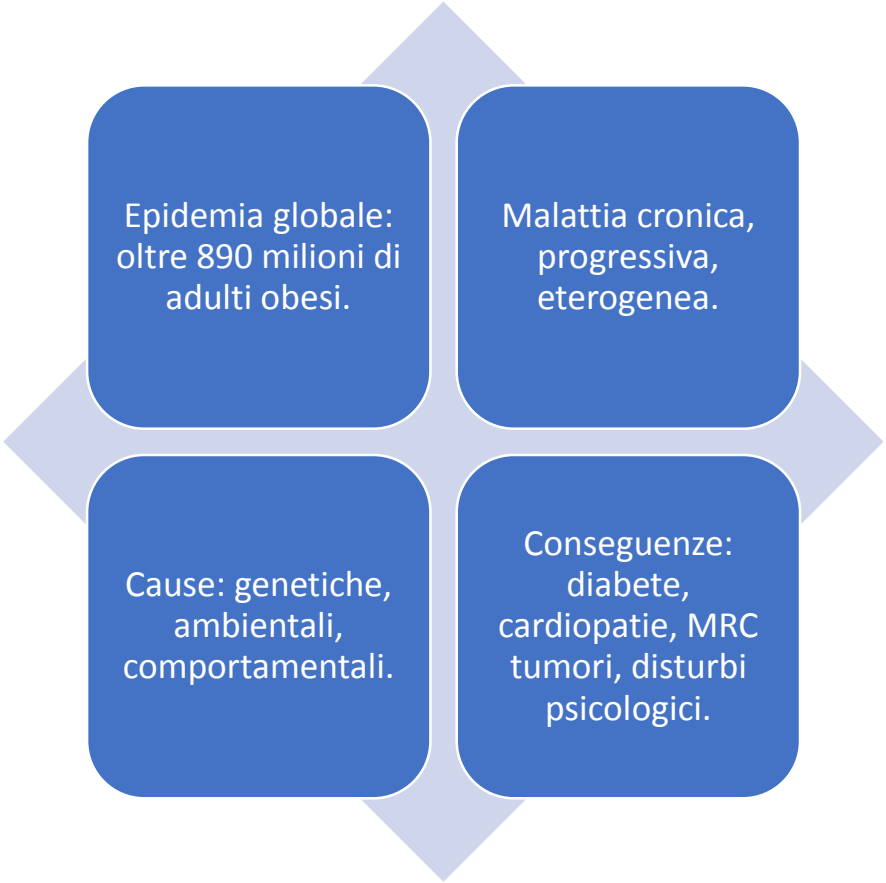
Diabete mellito ed obesità nel dializzato in lista di attesa per trapianto o in rientro dal TX

G. Castellano, MD, PhD

Università Statale di Milano

Obesità: una sfida globale complessa



www.thelancet.com **Vol 404 September 7, 2024**

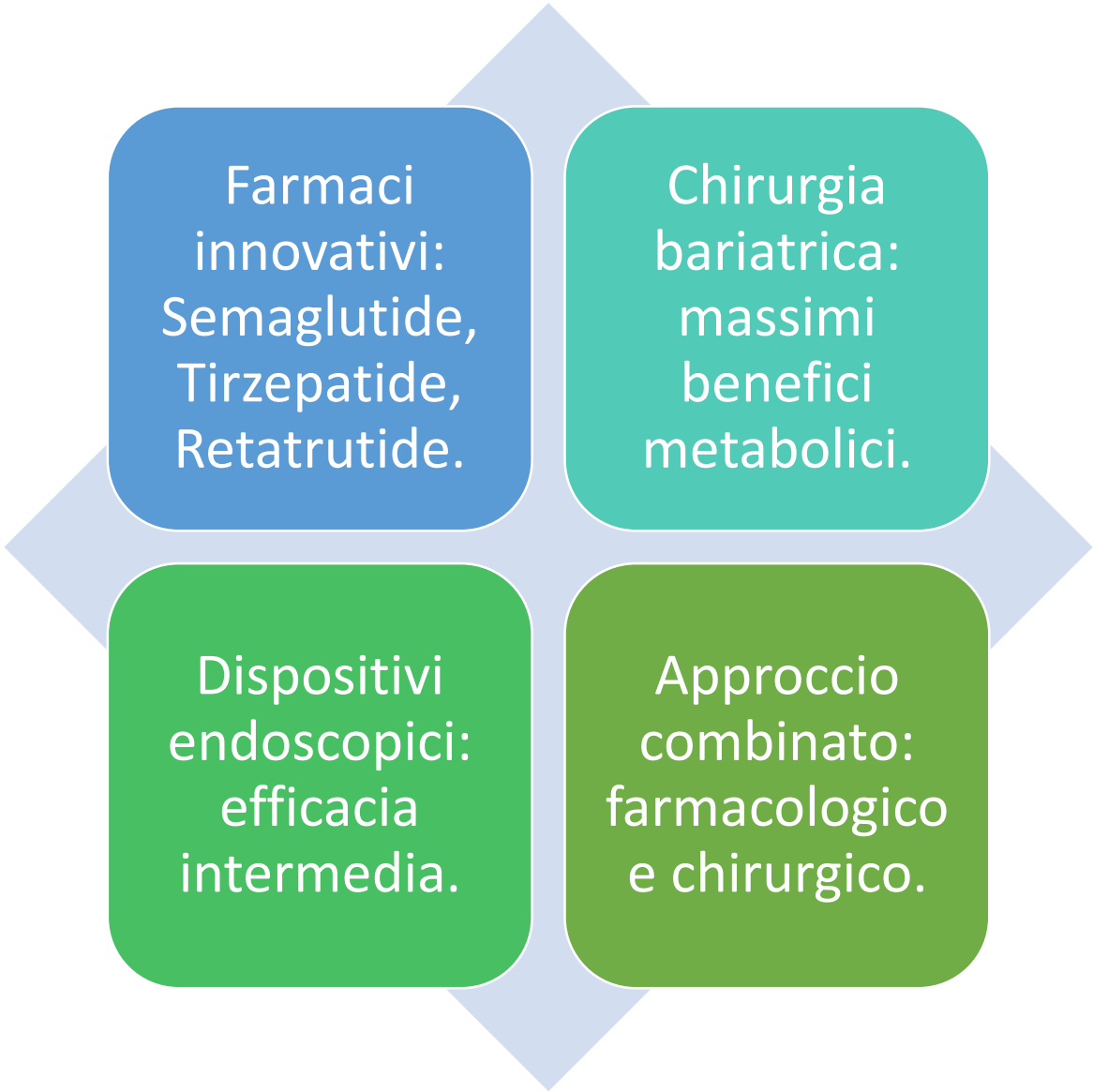
Diagnosi e gestione clinica

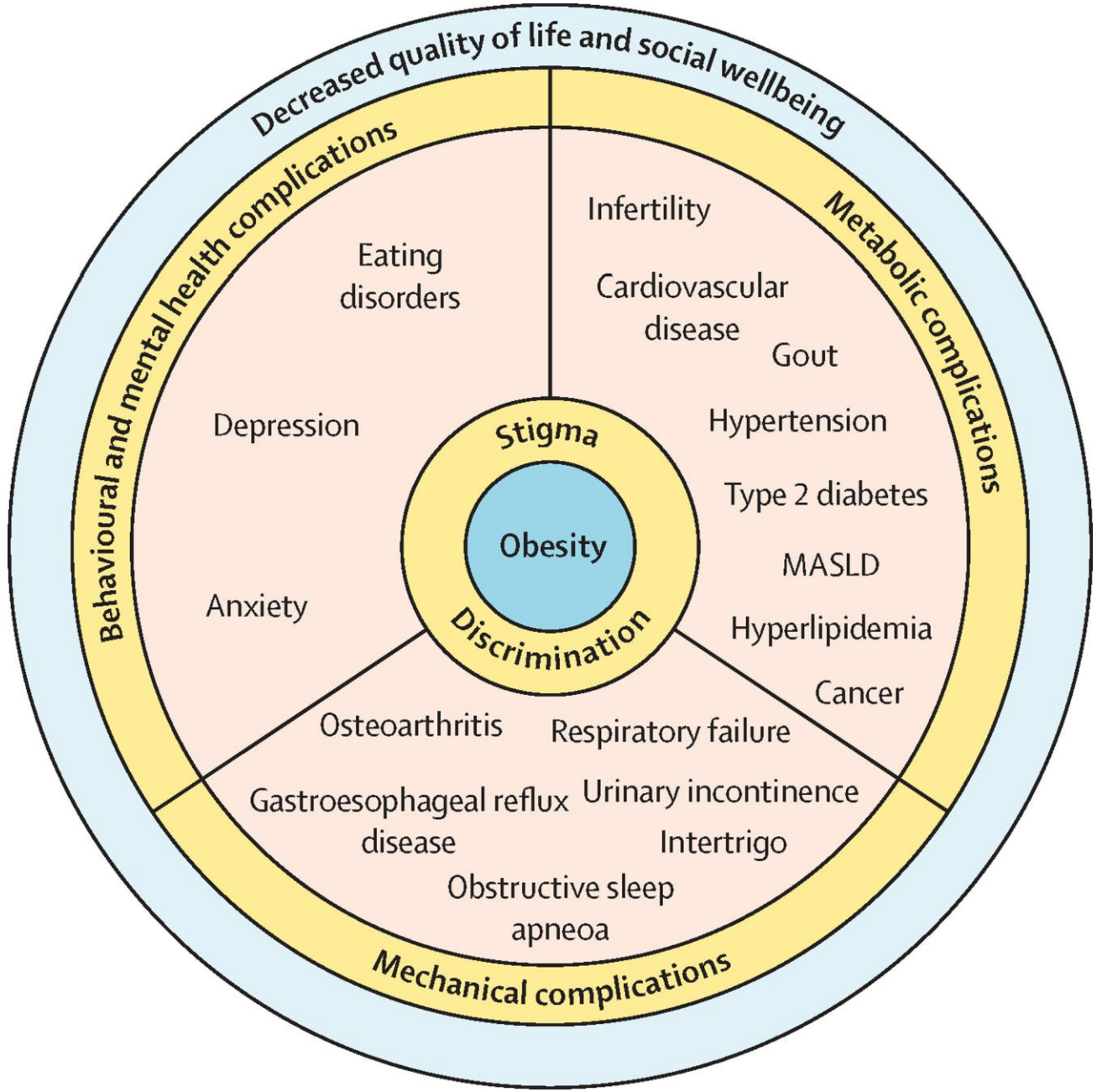
BMI UTILE MA IMPRECISO: SERVE VALUTAZIONE PERSONALIZZATA.

OBIETTIVO: MIGLIORARE LA SALUTE, NON SOLO PERDERE PESO.

GESTIONE: STILE DI VITA, FARMACOTERAPIA, CHIRURGIA.

Trattamenti: innovazioni e terapie combinate




Decreased quality of life and social wellbeing
Behavioural and mental health complications
Metabolic complications
Mechanical complications
Eating disorders
Depression
Anxiety
Infertility
Cardiovascular disease
Gout
Hypertension
Type 2 diabetes
MASLD
Hyperlipidemia
Cancer
Osteoarthritis
Respiratory failure
Gastroesophageal reflux disease
Urinary incontinence
Intertrigo
Obstructive sleep apneoa
Stigma
Obesity
Discrimination

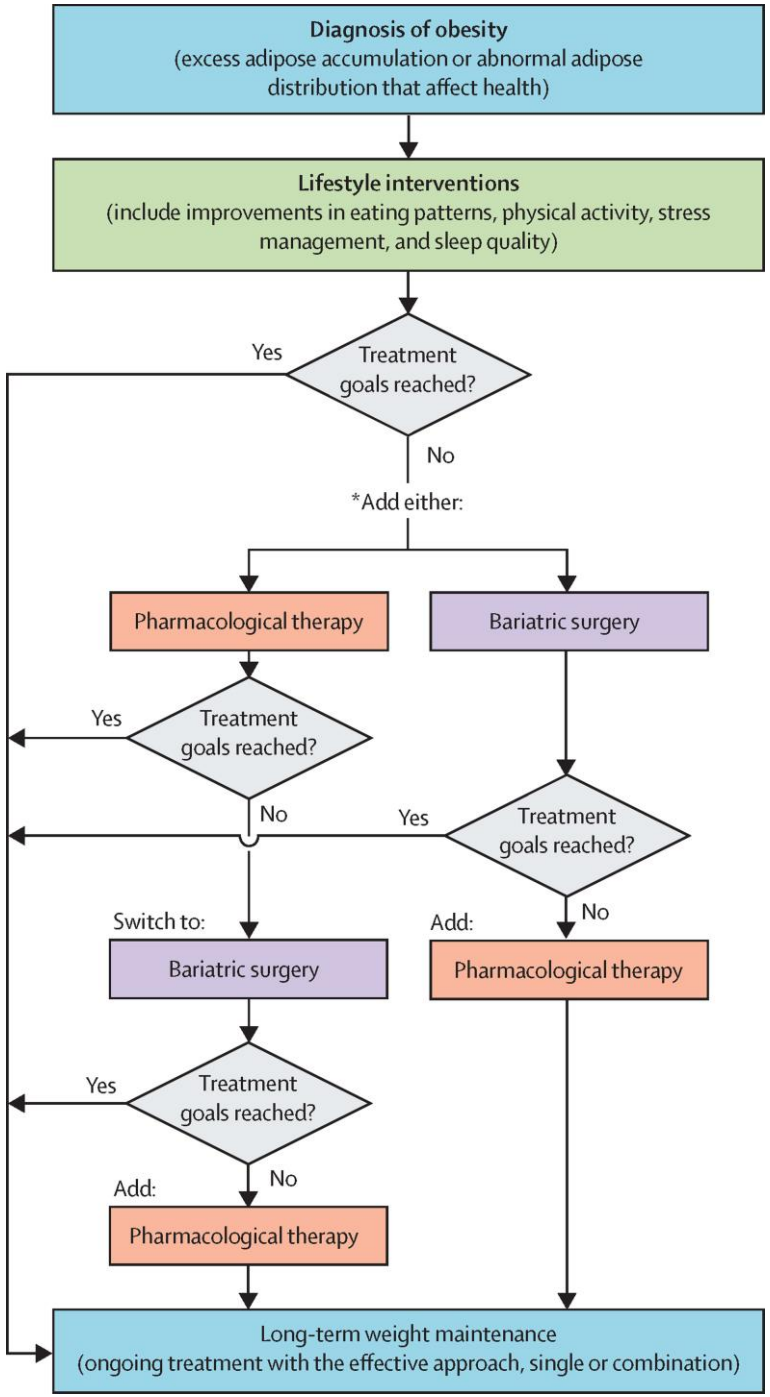
Visione futura: approccio cronico e integrato

Necessità di trattamenti continuativi.

Garantire accesso equo alle cure.

Combinare prevenzione e cura individuale.

Definire target personalizzati e strategie integrate.


Diagnosis of obesity
(excess adipose accumulation or abnormal adipose distribution that affect health)
Lifestyle interventions
(include improvements in eating patterns, physical activity, stress management, and sleep quality)
Yes
Treatment goals reached?
No
*Add either:
Pharmacological therapy
Bariatric surgery
Yes
Treatment goals reached?
No
Yes
Treatment goals reached?
No
Switch to:
Bariatric surgery
Add:
Pharmacological therapy
Yes
Treatment goals reached?
No
Add:
Pharmacological therapy
Long-term weight maintenance
(ongoing treatment with the effective approach, single or combination)

Contesto e necessità

Obesità: condizione complessa, causa principale di diabete tipo 2 e comorbidità.

Limiti attuali: approccio "one size fits all" inefficace.

Precision medicine: necessità di stratificazione personalizzata.

Lukasz Szczerbinski, Jose C Florez

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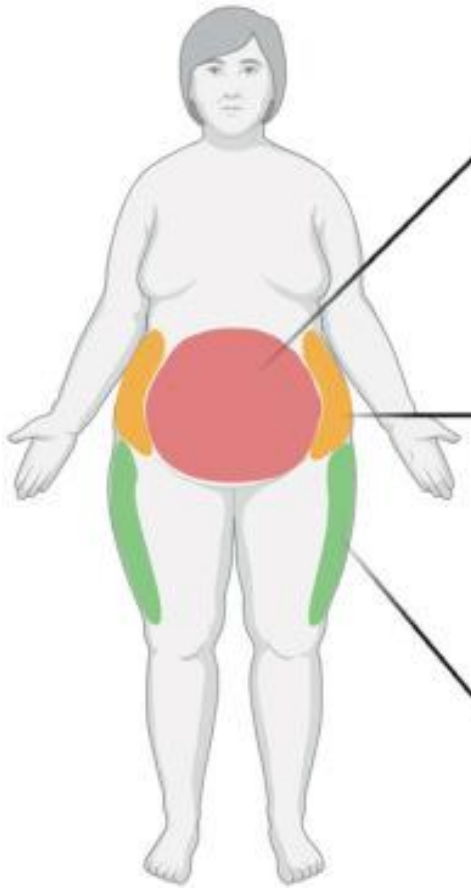

VAT
- VAT volume substantially higher in males
- VAT adj associated with increased risk of type 2 diabetes and coronary artery disease

VATadj loci
AMBRA1, CEBPA, CEBPA-DT*, CPEB4, EBF2, GPR158, HLA-B, HLA-DQB1, HLA-DRB5, JAZF1, LINC00310, LINC01101, LINC01948, LINC02953, MTOR, PEPD, PIK3C2B, PNKD, WT1-AS

ASAT
- ASAT volume substantially higher in females
- ASAT adj associated with neutral risk of type 2 diabetes and coronary artery disease

ASATadj loci
ADAMTSL3, ARL17A, ARL17B, CACNA1S, CENPW, DMRT2, FST, KLF14, LINC01230, MIR6085, OPTC, PDE4C, SOCS3, TBX15, UBE2Q2P1

GFAT
- GFAT volume substantially higher in females
- GFAT adj associated with decreased risk of type 2 diabetes and coronary artery disease

GFATadj loci
ABCA1, CCDC92, COBLL1†, COLEC11, DLG1, EYA1, FAM13A, FGF2, FGFR2, GTF2H3, H6PD, HOXC13, ITPR2, KAT5, KNTC1, LINC01214, LINC02227, LINC02537, LOC101928306, LOC646736, LY86, MAFB, MAFF, MTMR11, NYAP2, OSMR-DT, PDCL2, PDGFC, PEMT, PEPD, PLCB3, PPARG, PRKAG3, PRR5L, SETD2, SHBG, SLC44A1, SMIM20, SSPN

Lukasz Szczerbinski, Jose C Florez
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	Hungry brain	Emotional hunger	Hungry gut	Slow burn
				
Main obesity phenotype	Abnormal satiation*	Abnormal hedonic eating†	Abnormal satiety‡	Low predicted energy expenditure
Features (compared with a non-phenotype group)	• Consume 62% more calories before reaching fullness	• 2·3 times higher anxiety levels	• 31% faster gastric emptying rate	• 12% lower predicted resting energy expenditure • Reduced muscle mass • Less active
Proposed targeted LIFESTYLE therapy	• Time-restricted eating	• Low-calorie diet with intensive behavioural group therapy	• Low-calorie diet with pre-meal protein supplements	• Low-calorie diet with post-workout protein supplementation and high-intensity interval training
Proposed targeted PHARMACOTHERAPY	• Phentermine plus topiramate extended release	• Oral naltrexone plus bupropion sustained release	• Liraglutide	• Phentermine

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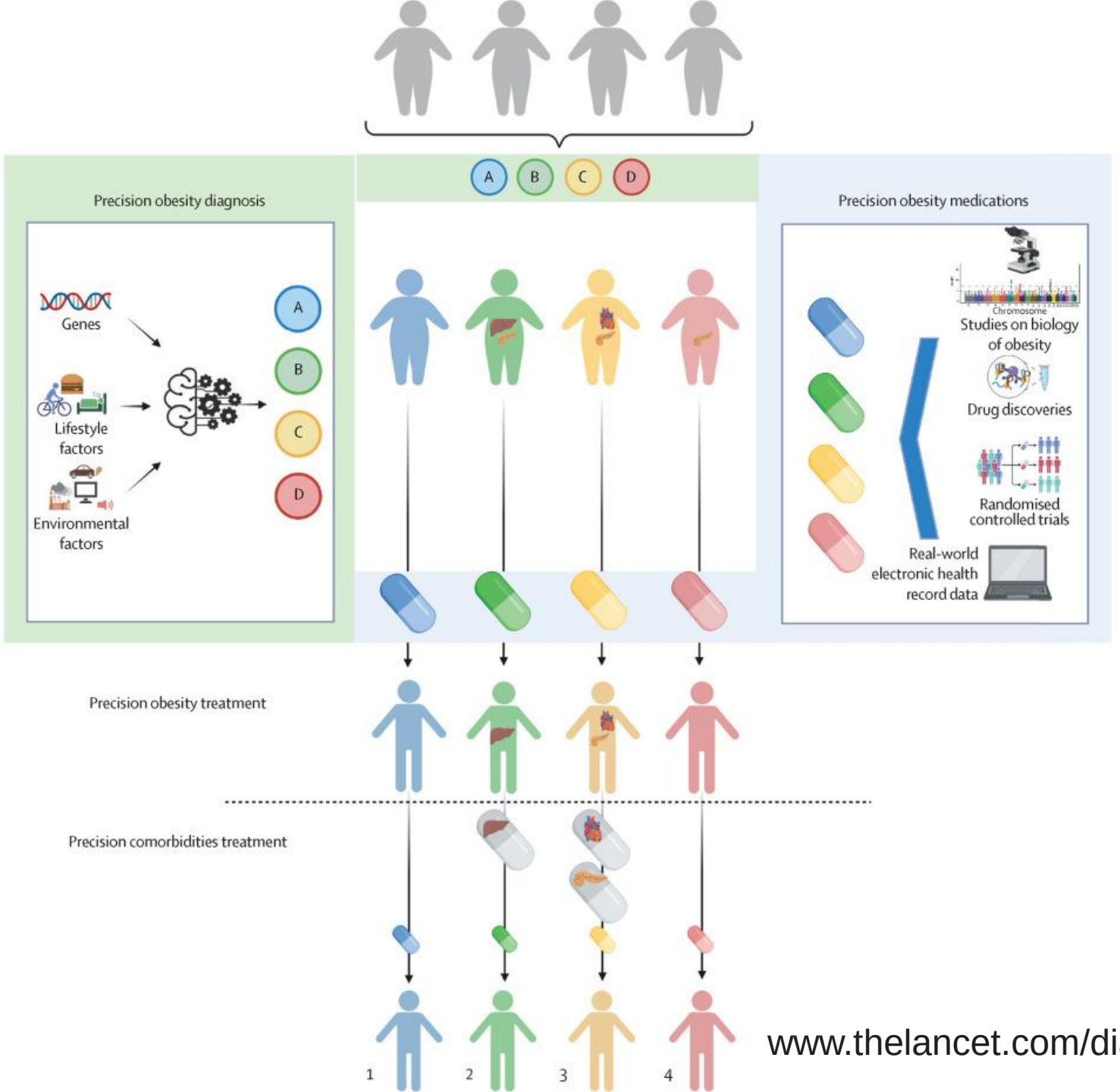

Lukasz Szczerbinski, Jose C Florez

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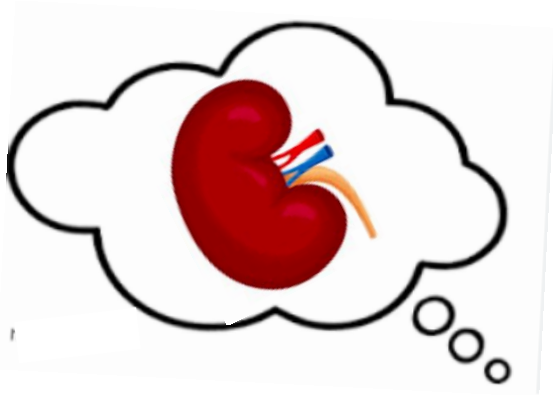
Obesity in kidney transplant (KTx) candidates: the problem



- Prevalence of obesity in KTx candidates: 6% - 30%
- In our chort **8%** of active waitlisted patients have BMI 30-34 Kg/m^2
- Optimal management strategies are not well defined
- Thresholds for accepting people for transplantation remain a source of controversy
- There is disagreement about how to validly assess obesity (BMI? waist circumference? waist:hip ratio?)

Management of obesity in kidney transplant candidates and recipients: A clinical practice guideline by the DESCARTES Working Group of ERA

Nephrol Dial Transplant (2022) 37: i1–i15

We suggest accepting people with ESKD and a **BMI of 30–34 kg/m^2** for kidney transplantation if they are otherwise considered suitable (2C). There are insufficient data to make a recommendation in the higher BMI categories (–D)

We recommend counselling patients living with obesity about **possible increased risk of perioperative complications** such as delayed graft function, wound-related morbidity, acute rejection and diabetes after transplantation (1C)

We suggest that kidney transplantation, either from a deceased or living donor, is the **optimal treatment for people with a BMI of 30–39 kg/m^2** and ESKD who are otherwise considered suitable for kidney transplantation (2C)

Interventions for obesity in KTx candidates

Diet

The optimal dietary management in obese KTx candidates is not defined (no RCT)

Patients on dialysis

- *Dietary restrictions* (potassium and phosphate) limit access to diets that are rich in vegetables and proteins

- *Calories restriction* favors PEW

Patients on conservative therapy

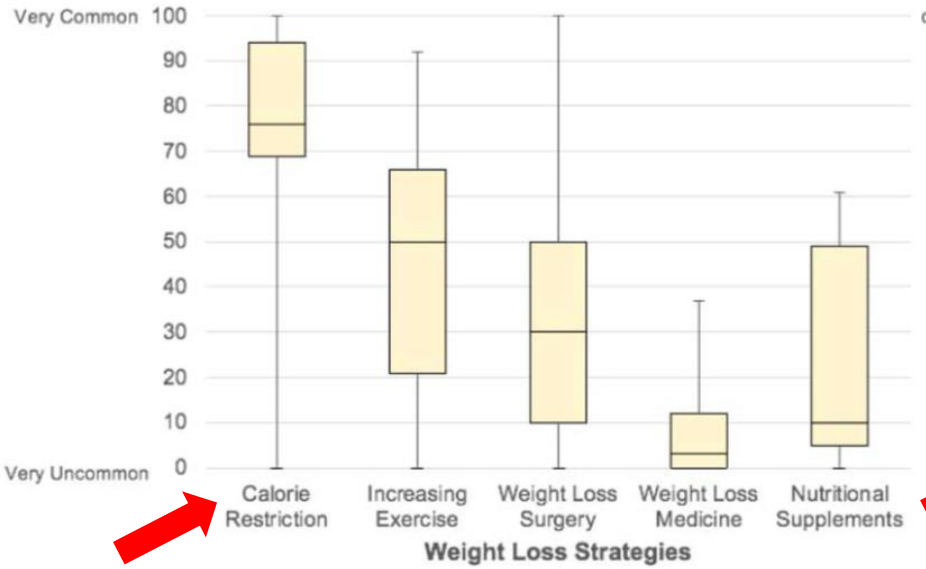
- Some RCT in obese stage 2-4 CKD patients

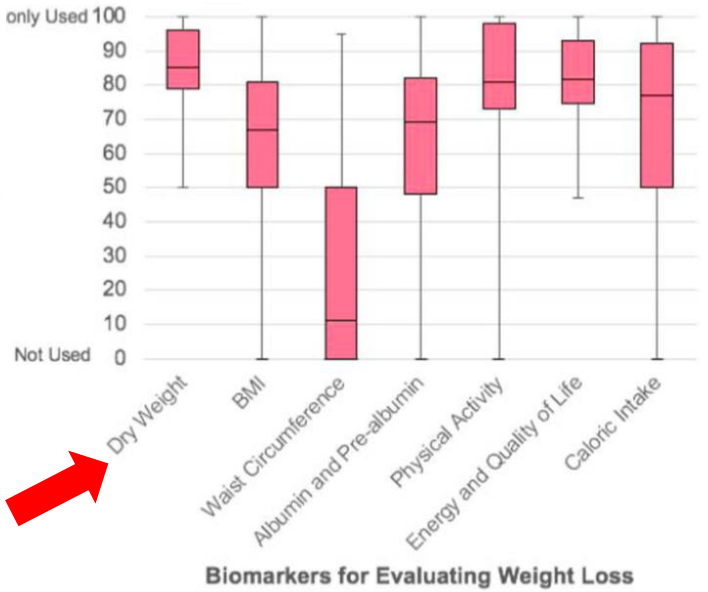
- Ipocaloric /ketogenic diet

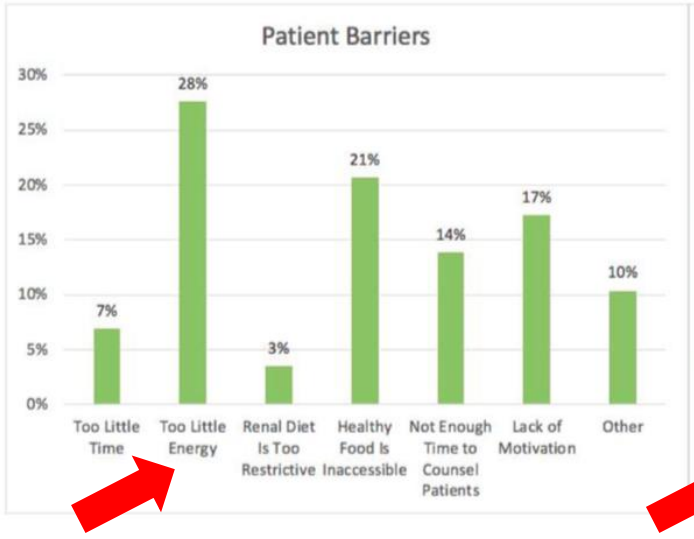
Approaches to Obesity Management in Dialysis Settings: Renal Dietitian Perspectives

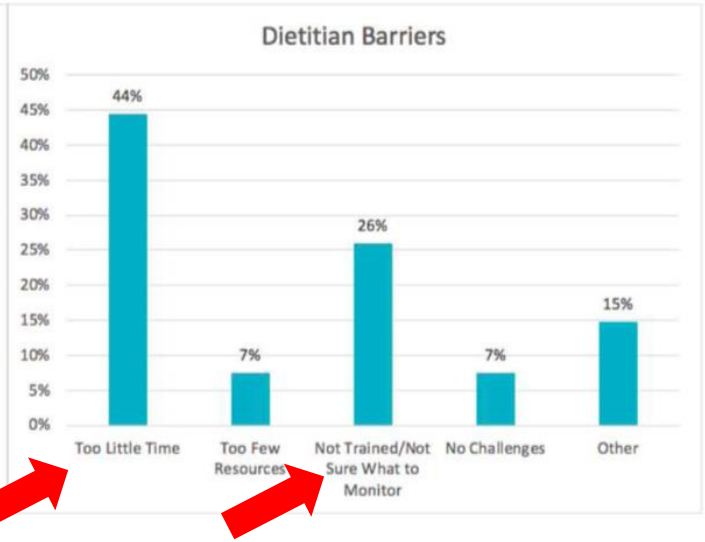
Suresch et al. J Ren Nutr. 2020 November ; 30(6): 561–566

- Access to KTx was the main reason that dialysis patients with obesity desired weight loss (90%)
- 68% of respondents indicated that **<10%** of their patients with obesity successfully lost weight
- This pilot survey suggests that **current approaches to obesity management in dialysis settings are variable**
- **Guidelines are needed** to support people with dialysis-dependence and obesity who desire or require weight loss









THE RENAL ASSOCIATION founded 1950

GUIDELINES Open Access

Baker *et al. BMC Nephrology (2022) 23:75*

Clinical practice guideline exercise and lifestyle in chronic kidney disease

Implementing weight loss in the haemodialysis population

We suggest the following guidance for encouraging and monitoring weight loss in haemodialysis patients:

- In individuals receiving haemodialysis it is reasonable for a registered dietitian to use clinical judgement to determine the most effective way to measure body weight or composition. For guidance, please see the recent KDOQI clinical practice guideline for nutrition in CKD: 2020 update [165].
- The standard weight status categories that have been defined by the World Health Organisation (WHO) according to BMI ranges for adults can be used in the haemodialysis population; these include $<18.5\,kg/m^2$ for underweight; 18.5 to $24.9\,kg/m^2$ for normal weight; 25.0 to $29.9\,kg/m^2$ for overweight; and $\geq 30\,kg/m^2$ for obese.
- BMI as maker for weight loss in the haemodialysis population is limited as it cannot differentiate between fat and muscle mass. Measures of body composition may be more informative
- Weight loss should be discussed with persons who would be eligible for transplant except for their degree of obesity.
- Weight loss programmes should be individualised wherever possible and take into account body composition, the aim of interventions should be to increase muscle mass in conjunction with reducing fat mass. Muscle mass loss should be avoided in programmes of weight loss.
- Programmes of weight loss require a multidisciplinary approach (which should include other healthcare providers such as dietitians, physiotherapists and health psychologists), and should evaluate nutritional needs along with comorbid conditions. This should be in conjunction with the promotion of physical activity and/or exercise.

RCT on diet interventions for obese CKD patients

First Author, year	Study population	Intervention, follow-up time	Weight outcomes
Morales, 2003	RCT of 30 adults w/proteinuria >1 g/d and creatinine <2 mg/dL (47% diabetic nephropathy, mean age 56y, BMI 33.4 kg/m2) **stage2-3 CKD**	Arm 1: **Hypocaloric diet;** Arm 2: Standard diet; Duration: 5 months	**5-month weight decreased in diet arm (87.5 to 83.9 kg)** and increased in control arm (96.1 to 98 kg)
Howden, 2013	RCT of 72 adults w/**eGFR 25-60 (stage 3-4)** and 1 uncontrolled CVD risk factor (28% diabetes, mean age 61, BMI 33 kg/m2)	Arm 1: lifestyle intervention (**lifestyle program**, supervised aerobic and resistance training); Arm 2: usual care (control); Duration: 12 months	**12-month changes greater in lifestyle intervention arm** vs. control for weight (−1.8 vs. +0.7 kg)
Tirosh (DIRECT), 2013	RCT of 322 adults w/BMI ≥27 kg/m2, T2DM, or CAD excluded serum creatinine ≥2.0 mg/dL (14% T2DM, albuminuria, mean age 52 y, BMI 31 kg/m2)		**Overall: weight loss (primary) at 2 years highest for low-carb −4.7kg, Mediterranean −4.4 kg, then low-fat arm −2.9 kg.**
Goraya, 2014	RCT of 108 non-diabetic adults ≥18 y w/ **stage 3 CK** ≥200 mg/g, K≤4.6 mEq/L (mean age 54 y, weight 84 kg)	0%; Arm 2: NaHCO3 0.3 mEq/Kg/d; Arm 3: usual care; Duration: 3 years	**At 3 years, weight loss greater in fruit/ vegetable arm (−4.0 kg)** than usual care arm (−1.9) and HCO3 arm (no change)
Ikizler, 2018	Pilot RCT at 4 US sites of 122 overweight/obese adults w/**stage 3-4 CKD** (25% diabetes, mean age 60 y, BMI 31-36 kg/m2)	Arm 1: **Caloric restriction** (CR) and supervised aerobic exercise; Arm 2: Aerobic exercise only; Arm 3: CR only; Arm 4: Control (usual care); Duration: 4 months	Compared to control, **weight improved after 4 months in CR/exercise arm (−2.4 kg) and CR only arm (−1.8)** but not exercise only (0.5 kg)

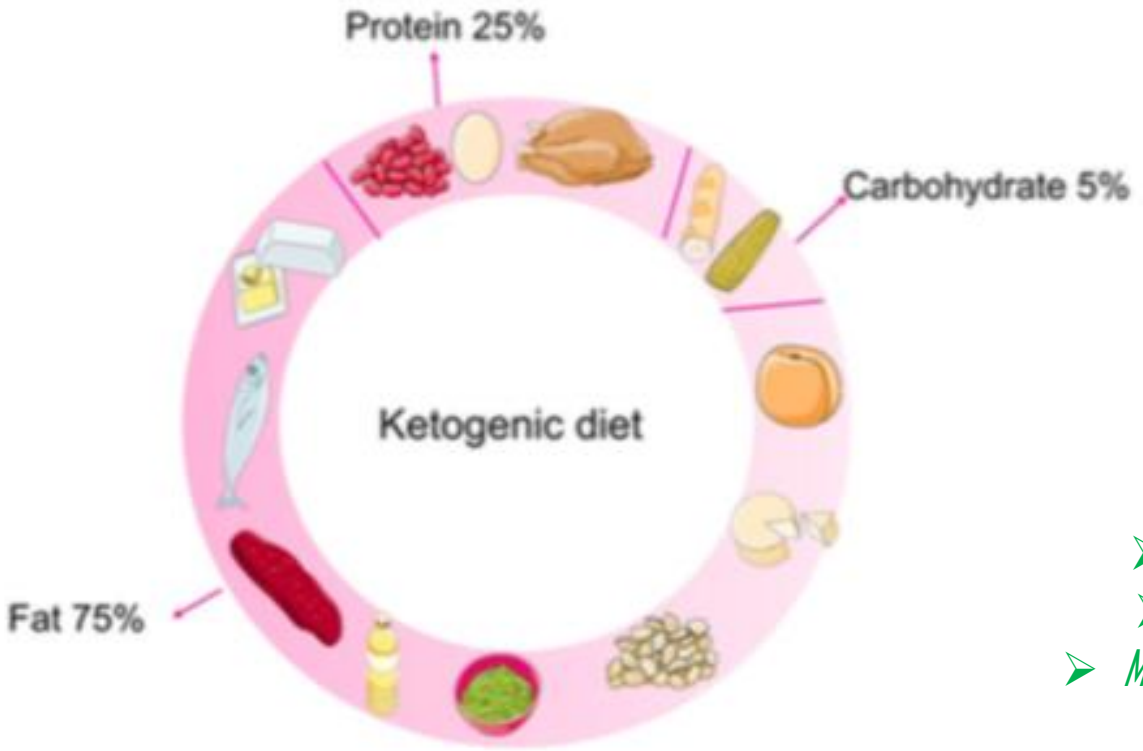
Stage 2-4 CKD
Limited effect
(weight loss 2 - 4 Kg)

Modified from Am J Kidney Dis. 2021 March ; 77(3): 427–439

Ketogenic Diet for obese CKD patients

Carbohydrate restriction (< 50 gr/day) + moderate protein consumption + increase in fat intake

Carbohydrate resctriction induces ketosis

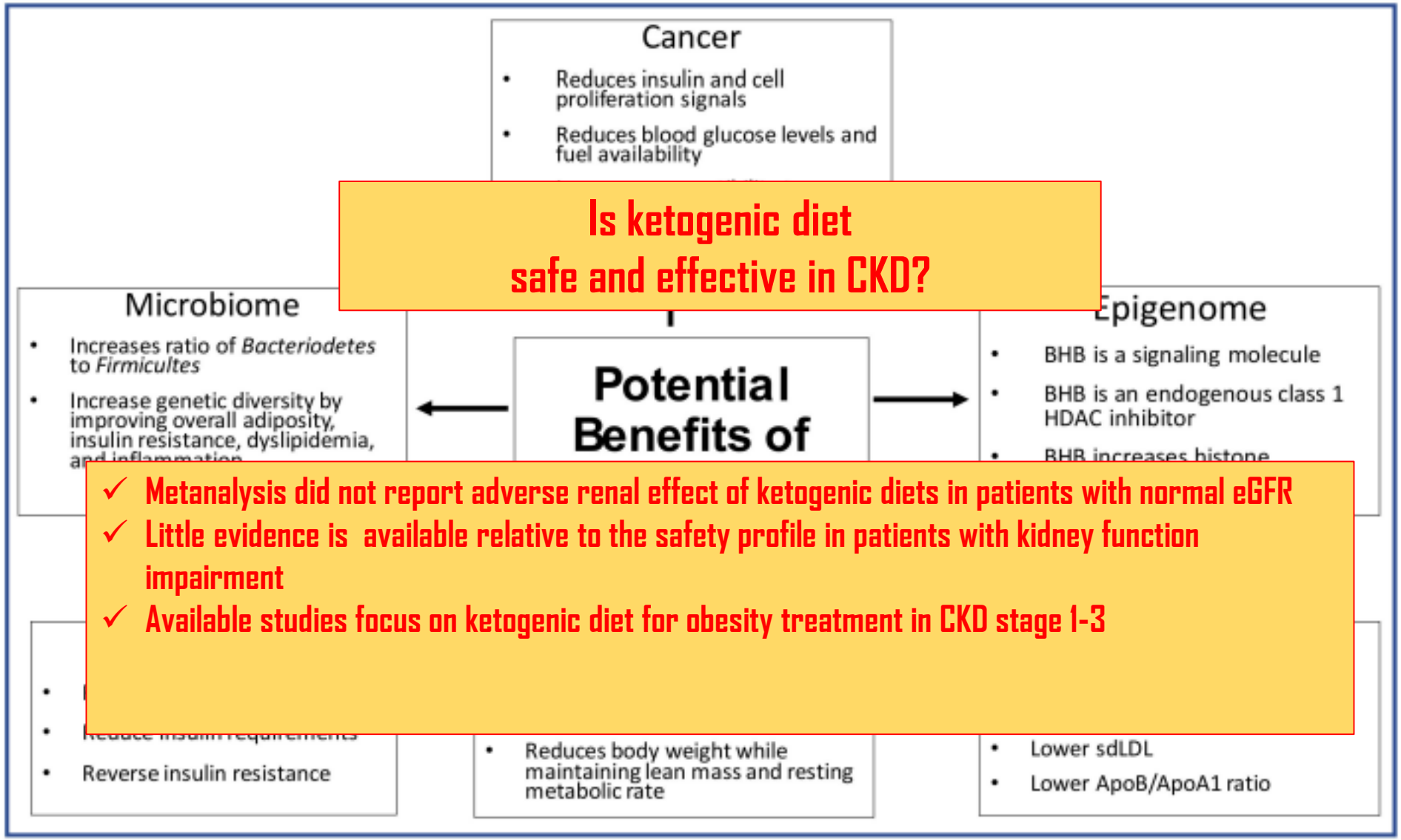


Very Low Calories Ketogenic Diet (VLCKD)

- ✓ 500–800 calories/day
- ✓ 20 g carbohydrates/day
- ✓ 1–1.5 g protein/Kg/day
- ✓ 15–30 g fat/day

- ➢ *Rapid weight loss*
- ➢ *Satiety induction*
- ➢ *Muscle mass preservation*

VLCKDs are currently recommended as an effective and feasible dietary intervention for obesity



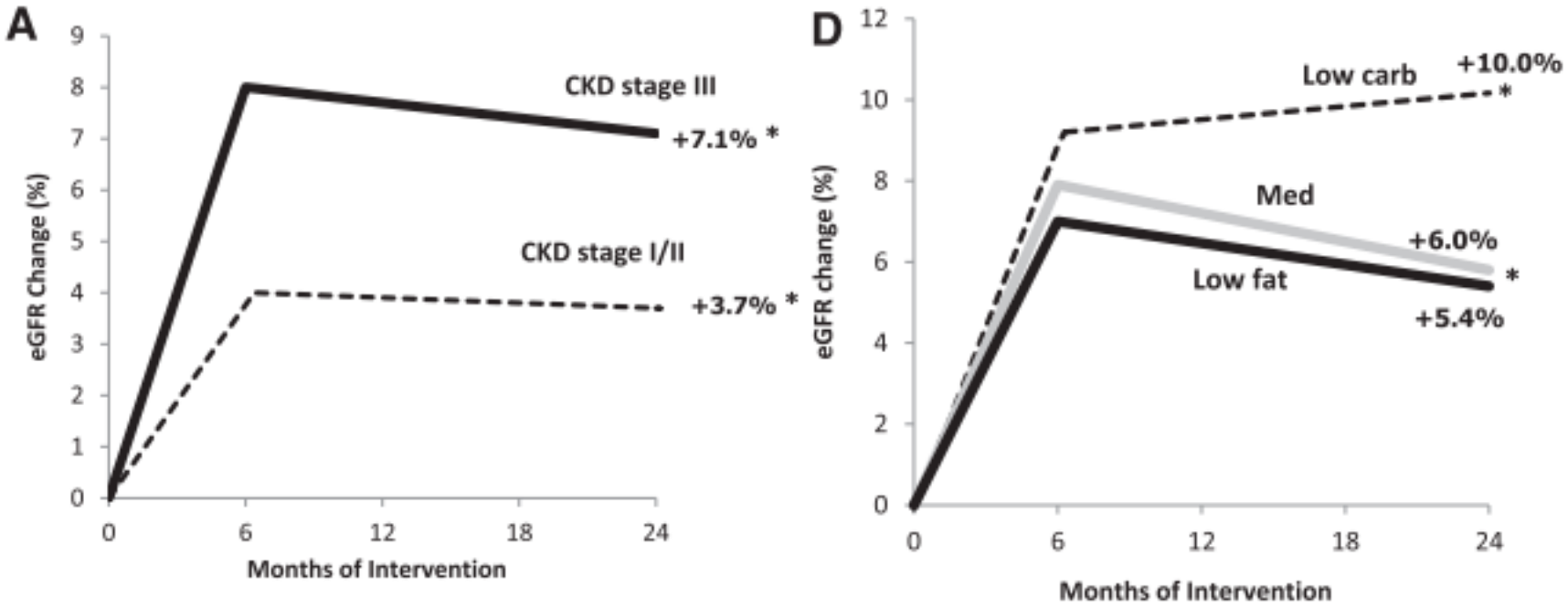
Dowis K et a. The Potential Health Benefits of the Ketogenic Diet: A Narrative Review. Nutrients 2021, 13, 1654.

Renal Function Following Three Distinct Weight Loss Dietary Strategies During 2 Years of a Randomized Controlled Trial

Amir Tirosh et al. Diabetes Care. 2013 Aug

Comparison of a **low-carbohydrate high-protein ketogenic diet (20 gr carbohydrates/day, not restricted calories)** with a **low-fat (30% fat, 10% saturated fat, 1500-1800 Kcal/day)** and **Mediterranean diet (< 35% fat, 1500-1800 Kcal/day)** in 322 moderately obese subjects and that **included 99 patients with stage 3 CKD** over a 2-year follow-up

Mean weight loss
- 2.9 kg Low-fat
-4.4 kg Mediterranean
-4.7 kg Ketogenic
($p < 0.001$)



A low-carbohydrate diet is as safe as Mediterranean or low-fat diets in preserving/improving renal function among moderately obese participants with **stage 3 CKD**

nutrients

MDPI

Bruci et al. Nutrients **2020**, *12*, 333;

Article

Very Low-Calorie Ketogenic Diet: A Safe and Effective Tool for Weight Loss in Patients with Obesity and Mild Kidney Failure

Prospective study

3 months Very Low-Calorie (450-800 Kcal) Ketogenic diet
(20 g cabohydrates, 1-1.4 g protein/Kg, 15-30 g fat) in 38 pts with obesity and CKD stage 2 (eGFR 60-89 ml/min/1.73 m^2)

Significant reduction in body weight (nearly 20%), BMI, fat mass
Improvement in metabolic parameters
In 27.7% normalization of eGFR
No difference compared to 54 obese pts with eGFR > 90 ml/min/1,73 m^2

	MCKD (eGFR 60–89)						
Variable	Baseline			End of Diet			*p*
Weight (Kg)	89.92	±	17.84	75.28	±	13.95	<0.0001
BMI (kg/m2)	33.01	±	6.01	27.56	±	4.68	<0.0001
Fat Mass (Kg)	33.05	±	9.96	22.31	±	7.99	<0.0001
Fat Free Mass (Kg)	56.88	±	12.55	52.97	±	10.72	<0.0001
Skeletal Muscle Mass (Kg)	37.54	±	9.00	34.40	±	8.13	<0.0001
TBW (Lt)	42.98	±	9.76	40.03	±	8.47	<0.0001
ECW (Lt)	19.74	±	4.50	18.78	±	3.90	<0.0001
ICW (Lt)	23.20	±	5.67	21.23	±	5.19	<0.0001
SBP (mmHg)	137.6	±	12.2	132.2	±	9.2	<0.0001
DBP (mmHg)	81.4	±	6.7	77.4	±	4.6	<0.0001
Creatinine (mg/dL)	0.93	±	0.16	0.88	±	0.17	0.002
eGFR (ml/min/1.73m^2)	76.32	±	10.44	82.21	±	15.14	0.002
BUN (g/L)	0.39	±	0.11	0.41	±	0.11	0.052
Glucose (mg/dL)	91.59	±	11.0	86.60	±	10.02	0.005
HbA1c (%)	5.60	±	0.46	5.39	±	0.40	0.007

**When conducted under the supervision of healthcare professionals,
a VLCKD is an effective and safe treatment for weight loss in patients with obesity, including those affected by mild kidney failure**

Safety and efficacy of very low carbohydrate diet in patients with diabetic kidney disease—A randomized controlled trial

PLOS ONE

Zainordin NA, et al. PLoS ONE 2021; 16(10)

RCT in 30 pts with type 2 DM, **stage 2-3 CKD** (median eGFR 59mL/min/1.73 m_2) and mild obesity (BMI 30.6 kg/m_2)

A 12-week **very low-carbohydrate (<20 g), moderate low-protein (44 g) diet compared with a normal-carbohydrate (90 g), low- protein (29 g) diet.** Caloric and fat intake similar between groups (740-790 Kcal/day, and 30-35 g/day)

Significant reduction in HbAIc, fasting glucose, insulin dose and weight by <10% , with no worsening of renal function

Weight
- 4 kg

BMI,
- 1.5 Kg/m2

Waist circumference
- 4 cm

	VLCBD group (n:14)	Control Groups (n:16)	*p-value*
Baseline	74.5 (23.2)	89.65 (29.1)	0.244
Week 12	72.5 (21.9)	90.6 (29)	**0.042**
Change	-4.0 (3.9)	0.2 (4.2)	**<0.001**
p-value within group	**0.002**	0.955	
Baseline	29.23 (7.26)	32.21 (8.93)	0.154
Week 12	27.45 (6.34)	32.15 (9.72)	**0.038**
Change	-1.5 (1.18)	0.074 (1.54)	**<0.001**
p-value within group	**0.002**	0.910	
Baseline	97 (16.8)	112 (19)	0.143
Week 12	95 (14.5)	108 (18)	**0.006**
Change	-4.0 (5.25)	-2.0 (3.6)	0.167
p-value within group	**0.003**	**0.009**	

Physical activity

No RCT specifically focused on the effect of exercise for weight-loss in obese KTx candidates

According to several metanalyses, regular physical activity may have many beneficial effects in ESRD, improving aerobic capacity, muscolar strenght, cardiovascular health, and health-related QoL

Patients on dialysis

- Most studies focus on exercise effect in normoweight/underweight patients

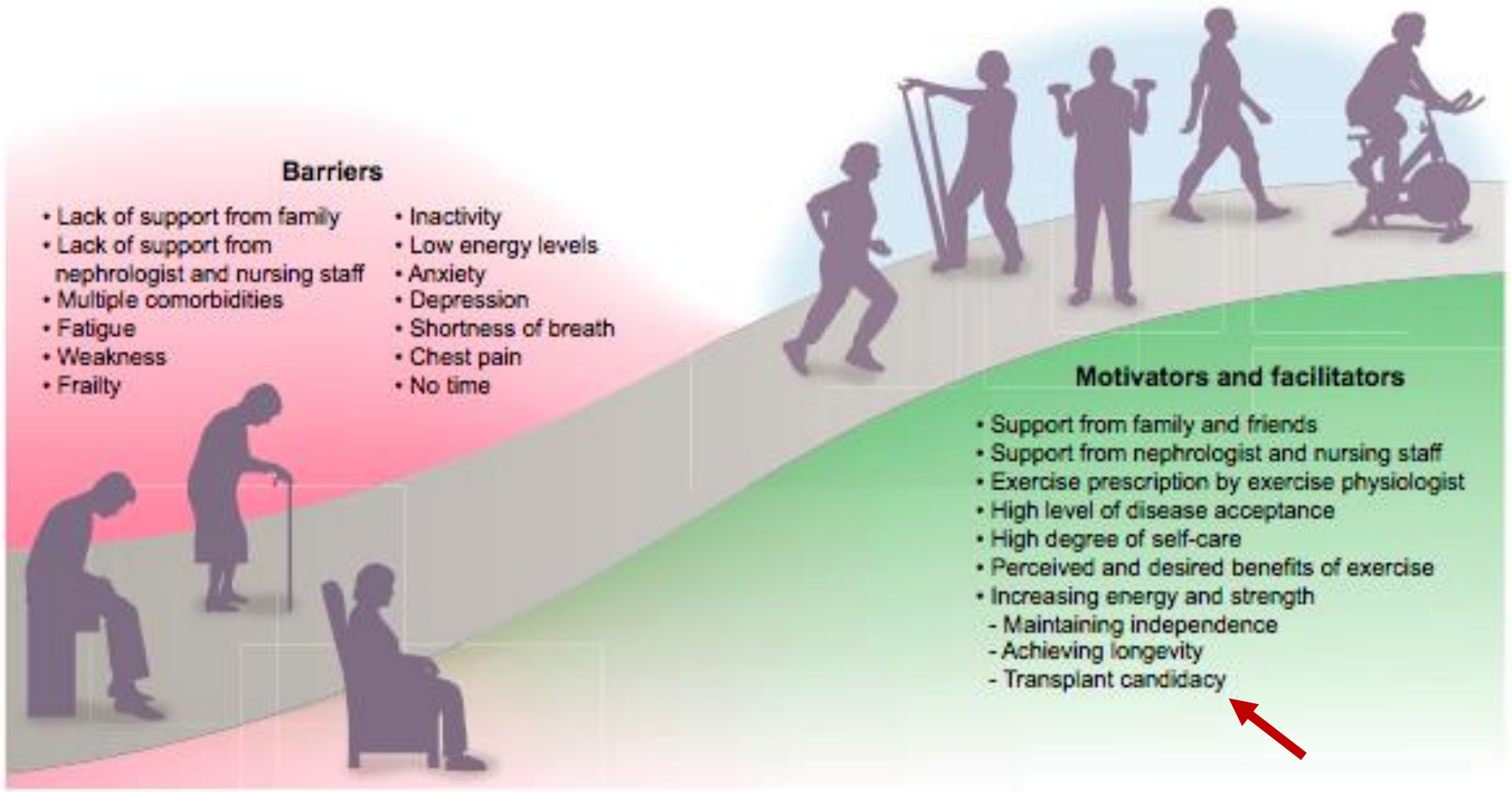
Patients on conservative therapy

- Some RCT in stage 3-4 CKD obese patients show a modest benefit of exercise on weight loss

Ekramzadeh et al. The Effect of Nutrition and Exercise on Body Composition, Exercise Capacity, and Physical Functioning in Advanced CKD Patients. *Nutrients* 2022, *14*,2129

Mei Huang, et al. Exercise Training and Outcomes in Hemodialysis Patients: Systematic Review and Meta-Analysis. *Am J Nephrol* 2019;50(4): 240–254.

Barriers, facilitators and motivators affecting interest and willingness to engage in exercise training



Clyne N, et al. Exercise training in chronic kidney disease-effects, expectations and adherence. Clin Kidney J. 2021 May 6;14(Suppl 2):ii3-ii14

Randomized controlled trial to evaluate the impact of aerobic exercise on visceral fat in overweight chronic kidney disease patients

Nephrol Dial Transplant (2014) 29: 857–864

N. 27

Overweight/obese BMI 30.4 ± 3.8 kg/m^2,

CKD 3-4

Centre-based aerobic exercise group (n = 10)

Home-based aerobic exercise group (n=8)

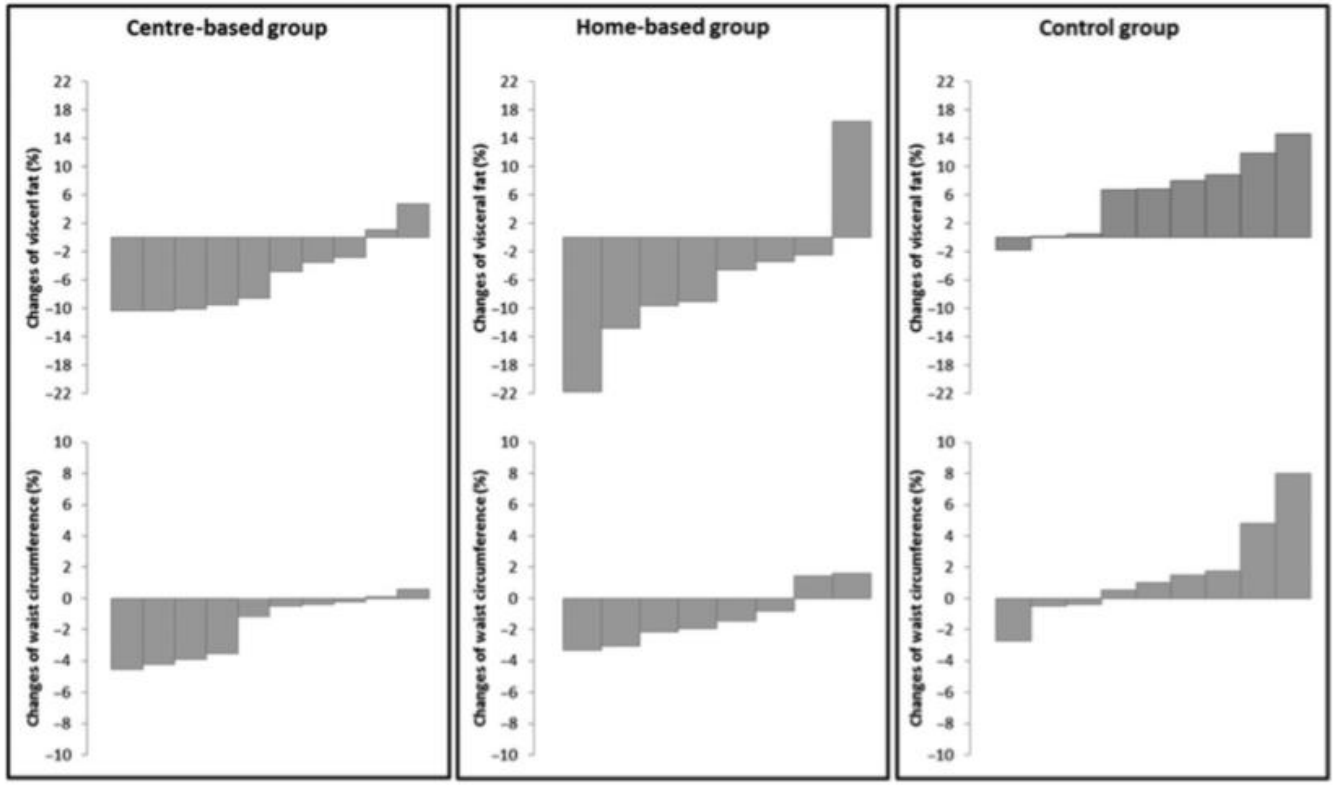
Control group (n=9)

Training three times per week for 12 weeks

Renal specific diet (energy: 25-30 Kcal/Kg/day; protein intake: 0.6-0-8 g/Kg/day)

In the centre-based group, visceral fat and waist circumference decreased 6.4 ± 6.4 mm (P < 0.01) and 2.0 ± 2.3 cm (p = 0.03) and leg lean mass increased 0.5 ± 0.4 kg (p < 0.01)

Percentage variation in visceral fat and waist circumference after 12 weeks



N. 180

Obese (BMI 33±6 Kg/m^2)

CKD 3-4 (eGFR 41±10 ml/min/1.73 m^2)

Lifestyle intervention group:

+ 150 min/wk of individualized moderate-intensity aerobic and resistance exercise + Mediterranean-style diet

Significant but small reductions in weight, BMI, and waist circumference in the lifestyle intervention group

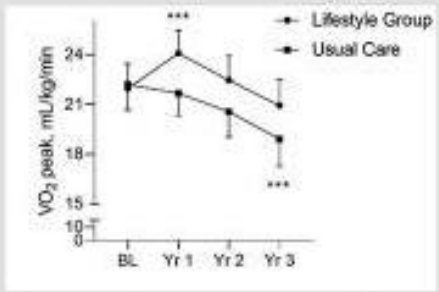
Effect of a Three-year Lifestyle Intervention in patients with Chronic Kidney Disease: A Randomized Controlled Trial

JASN
2022 Feb;33(2):431-441

METHODS

- Randomized 3-year lifestyle intervention
- Intervention comprised care from a nurse led, multi-disciplinary team
- Change in cardiorespiratory fitness (VO_2peak), physical function, markers of cardiovascular health & physical activity levels were evaluated

OUTCOME



VO_2 peak increased at year 1, & remained elevated compared with usual care at year 3.

The intervention favorably affected;

- ✓ Exercise capacity
- ✓ Physical function
- ✓ Physical activity levels
- ✓ Weight gain

No statistical group differences in;

- ❖ Kidney function
- ❖ Blood pressure
- ❖ Cholesterol
- ❖ Glycemic control

	Usual Care				Lifestyle Intervention				*P*
Variable	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Value**
Weight, kg	95 (91 to 99)	97 (92 to 101)[a]	98 (94 to 103)[b]	98 (94 to 103)[b]	93 (88 to 97)	91 (86 to 95)[a]	91 (87 to 96)	92 (88 to 96)	0.001
BMI, kg/m^2	34 (32 to 35)	34 (33 to 36)[a]	35 (33 to 36)[b]	35 (33 to 36)[c]	33 (32 to 35)	32 (31 to 34)[a]	33 (31 to 34)	33 (31 to 34)	0.001
Waist, cm	110 (107 to 113)	111 (107 to 114)	113 (109 to 116)[a]	113 (110 to 117)[c]	109 (105 to 112)	106 (103 to 110)[a]	107 (104 to 111)	109 (105 to 113)	0.026

RESEARCH ARTICLE Open Access

Effect of a pedometer-based walking intervention on body composition in patients with ESRD: a randomized controlled trial

Sheshadri A et al. BMC Nephrol. 2020, 21, 100

N 54
ESRD (10 PD and 44 HD)
BMI 26.9 (25.3, 32.8) intervention group
BMI 31.6 (26.4-34.6) control group (p=ns)

Randomized to standard care or a 6-month program consisting of 3 months of pedometers and weekly step count targets and 3 months of post-intervention follow-up

At 6 months, participants in the intervention had a **significantly greater increase from baseline in total-body muscle mass** of 0.7 kg/m^2 (95% CI 0.3, 1.13), **decrease in fat mass** (− 4.3 kg [95% CI -7.1, − 1.5]) and **decrease in BMI** (− 1.0 kg/m^2 [95% CI -1.8, − 0.2]
Each increase of 1000 steps from 0 to 3 months was associated with a 0.3 kg decrease in fat mass (95% CI 0.05, 0.5; p= 0.02) from 0 to 6 months

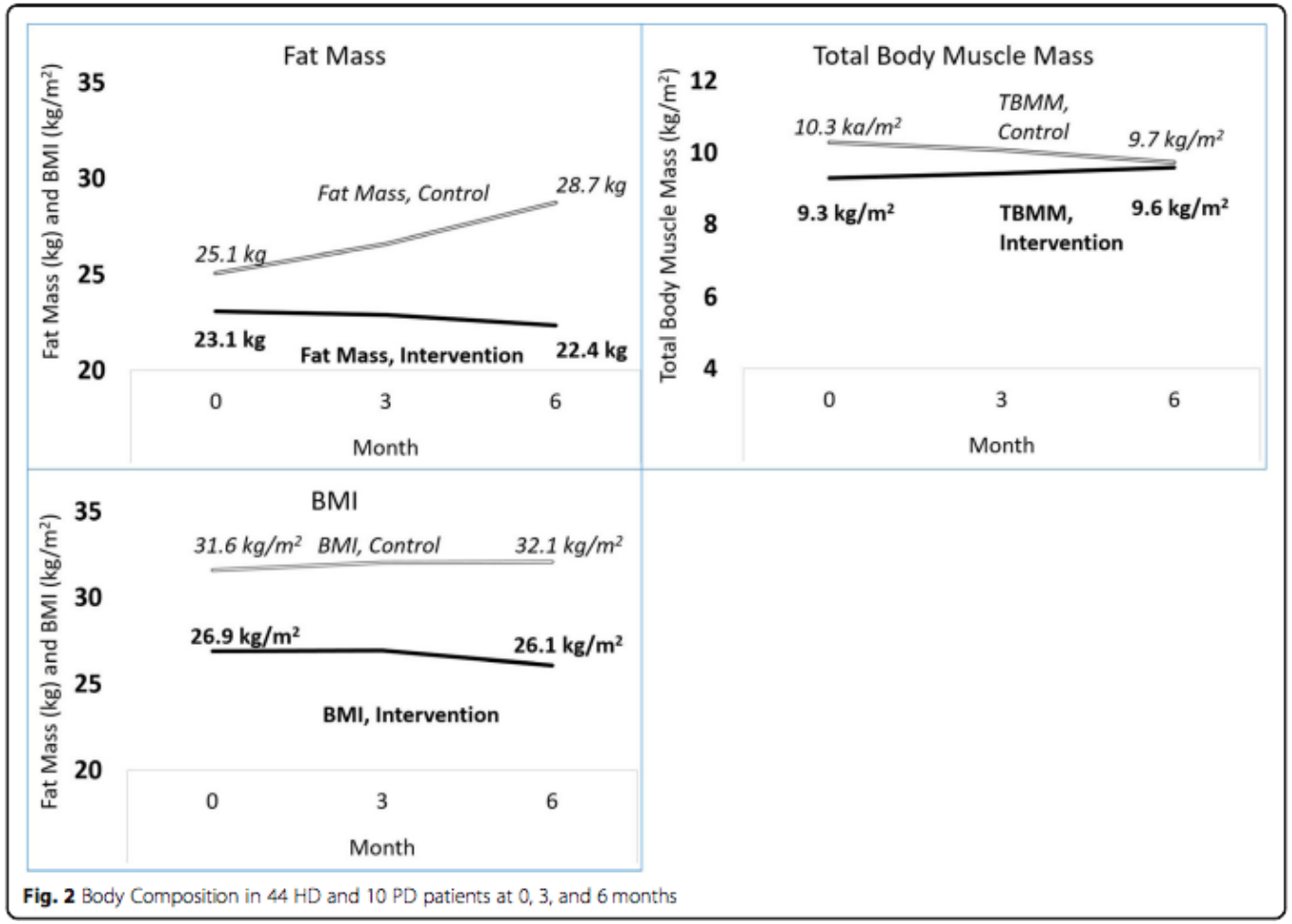


Fig. 2 Body Composition in 44 HD and 10 PD patients at 0, 3, and 6 months

Medications

Among FDA/EMA approved anti-obesity medications, some could be used in obese KTx candidates:

- ***Orlistat*** (gastric and pancreatic lipase inhibitor): no dosing adjustemens for eGFR
- ***Liraglutide*** and ***semaglutide*** (GLP-1 analogues): limited data in ESRD
- ***Tirzepatide*** (GIP/GLP-1 dual agonist): limited data in advanced CKD

Chakhtoura M, et al. Pharmacotherapy of obesity: an update on the available medications and drugs under investigation. EClinicalMedicine. 2023 Mar 20;58:101882

Nephrol Dial Transplant (2008) 23: 263–268
doi:10.1093/ndt/gfm511
Advance Access publication 31 October 2007

Original Article

NDT
Nephrology Dialysis Transplantation

A structured weight management programme can achieve improved functional ability and significant weight loss in obese patients with chronic kidney disease

CKD 3-5 patients *with a BMI ≥30kg/m2 or 28 plus comorbidities*

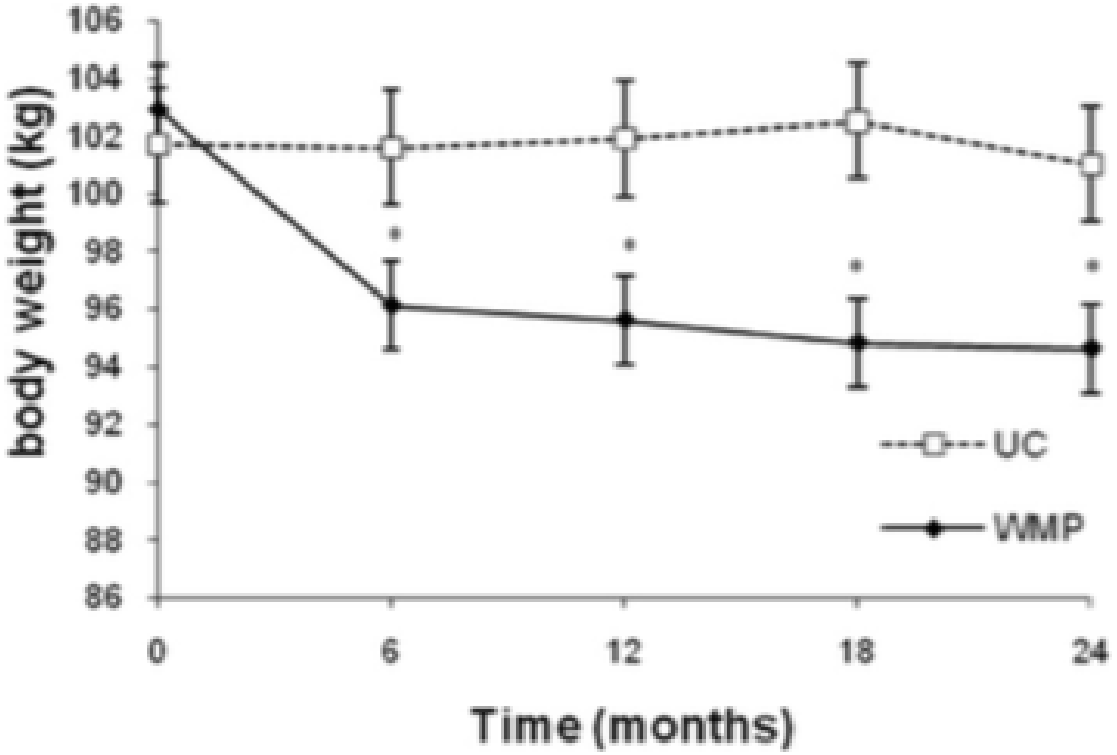
Table 1. Baseline characteristics (mean ± SD) of patients who completed 12 months in the WMP and the control group.

Characteristic	WMP ($n=32$)	Control ($n=22$)
Weight (kg)	102.9 (±17.7)	101.68 (±20.7)
Body mass index (kg/m^2)	35.7 (±4.5)	34.1 (±4.2)
GFR (ml/min)	44.8 (±26)	38.8 (±35.1)

50% on dialysis (18% PD and 32% HD)
All pts on dialysis were otherwise suitable for kidney transplant but not listed because of BMI

1. Low fat, reduced energy diet (-500 Kcal/day)
2. Individualized exercise prescription
3. Orlistat 120mg tds

Primary outcome : change in body weight and BMI at 12 months



35% from the weight-management program group vs **6%** from the usual-care group **were accepted for kidney transplant listing**

Helen L MacLaughlin et al .*American Journal of Kidney Diseases,* Vol 55, 2010: pp 69-76

CPE Participation in a Structured Weight Loss Program and All-Cause Mortality and Cardiovascular Morbidity in Obese Patients With Chronic Kidney Disease

Primary end point :all-cause mortality, or the first occurrence of a cardiovascular event.
Secondary end point: **placement on the waiting list for KTx**

- ✓ After 12 months, the mean weight change in WMP group was **- 4.3 kg** and **- 1.9 kg** in CON group (*p 0.001*)
- ✓ Participation in WMP predicted a **longer event-free period for the combined event of all-cause mortality and cardiovascular morbidity,** compared with the CON group

Table 1. Baseline Characteristics of Obese Patients with Chronic Kidney Disease Referred to a Structured Weight Loss Program

Characteristic	Weight Management Program (n = 169)	Control (n = 169)	P
Age (y)	52.3 + 12.9	53.3 + 12.7	.5
Sex			
Male (%)	51	58	.2
Female (%)	49	42	
Ethnicity			
White	81	79	.8
Black	65	70	
Asian	19	15	
Other	4	5	
Kidney function			
eGFR >15 mL/min/1.73 m^2	128	130	.8
eGFR <15 mL/min/1.73 m^2 including hemodialysis	41	39	
Diabetes (%)	38	49	.03
Hypertension (%)	92	96	.2
Body mass index (kg/m^2)	36.6 (±5.3)	34.5 (±5.1)	.2
Smoking status			
Never smoked	120	104	.2
Previous smoker	31	30	
Current smoker	19	18	
Status unknown	12	24	

eGFR, estimated glomerular filtration rate.

Table 4. Multivariable Logistic Regression for Factors Related to Qualifying for Listing for Kidney Transplantation in Obese Patients with Chronic Kidney Disease Referred to a Weight Loss Program

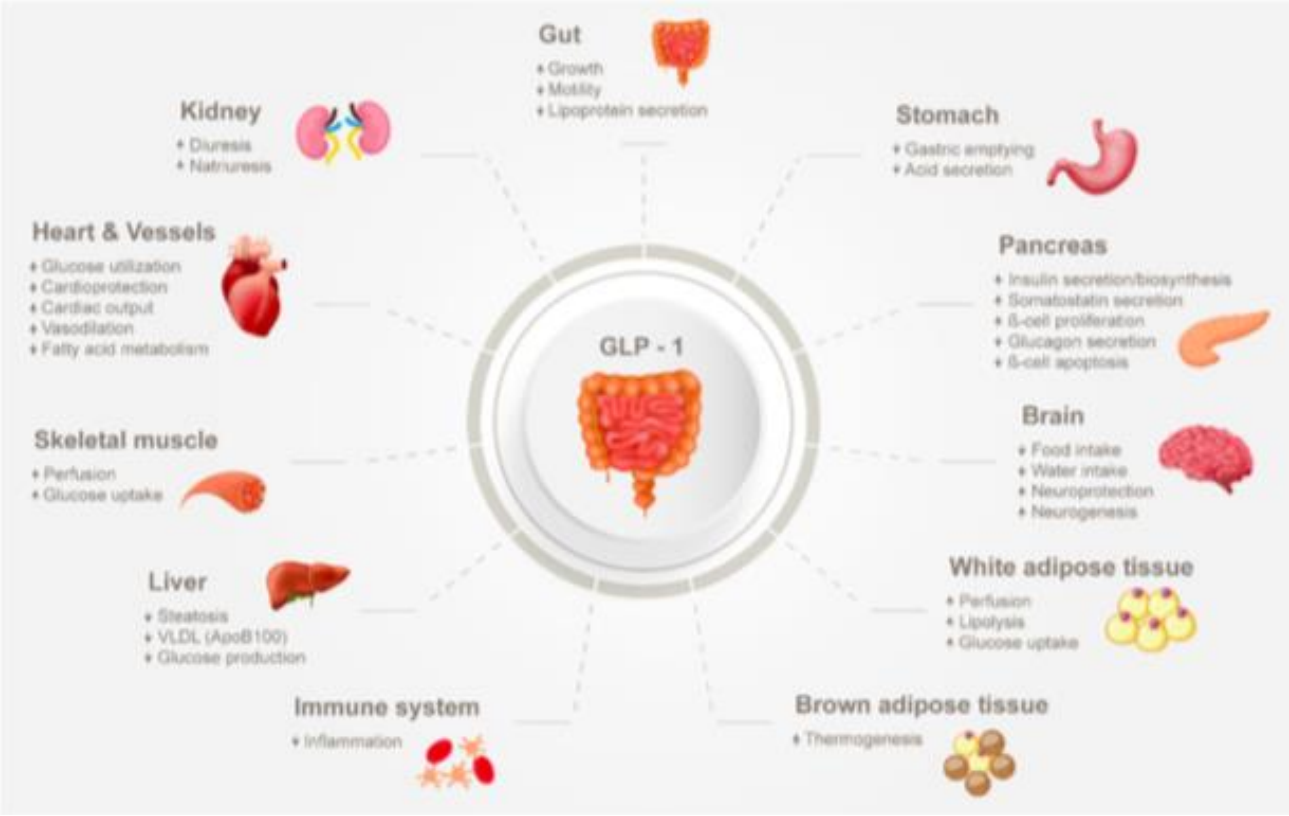
Parameter	Odds Ratio (β)	95% CI for β	P
Group (WMP compared to CON)	1.060	0.39 to 2.87	.9
Lower baseline BMI	0.672	0.56 to 0.80	<.001
Weight loss during first 12 months	0.872	0.80 to 0.95	.003
Age	0.972	0.97 to 1.02	.3
Sex	0.55	0.20 to 1.50	.2
Ethnicity	0.652	0.23 to 1.85	.4

BMI, body mass index; CI, confidence interval; CON, control group; WMP, weight management program.

MacLaughlin at al, J Ren Nutr 2015; 25: 472–479

GLP-1 RAs and obesity in CKD

GLP-1 RAs can potentially be safely used in all CKD classes, although there are limited data for severe CKD (eGFR < 15 ml/min)

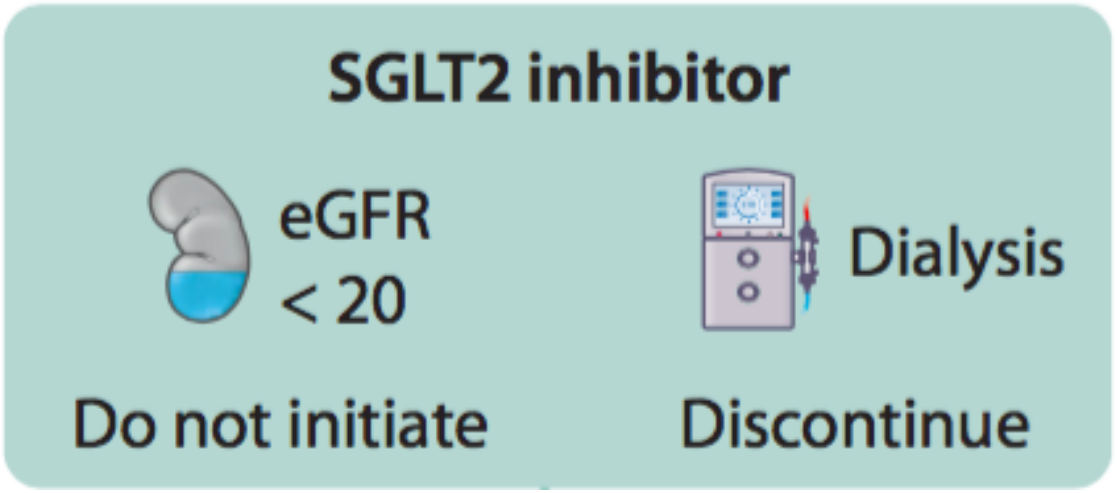


GLP-1 RA	Dose	CKD adjustment
Dulaglutide	0.75 mg and 1.5 mg once weekly	No dosage adjustment Use with eGFR >15 ml/min per 1.73 m^2
Exenatide	10 µg twice daily	Use with CrCl >30 ml/min
Exenatide extended-release	2 mg once weekly	Use with eGFR >45 ml/min per 1.73 m^2
Liraglutide	1.2 mg and 1.8 mg once daily	No dosage adjustment Limited data for severe CKD
Lixisenatide	10 µg and 20 µg once daily	No dosage adjustment Limited data for severe CKD Not recommended with eGFR <15 ml/min per 1.73 m^2
Semaglutide (injection)	0.5 mg and 1 mg once weekly	No dosage adjustment Limited data for severe CKD
Semaglutide (oral)	3 mg, 7 mg, or 14 mg daily	No dosage adjustment Limited data for severe CKD

No RCT for obesity treatment in KTx candidates!

SGLT2-is and obesity in CKD

- **Caloric loss from glucosuria** (300 Kcal/die) typically results in 1 to 3 kg weight loss, most of which is fat, and greater weight loss is observed in patients with higher baseline HbA1c
- **Average weight loss of 0.8-1.5 kg in CKD stages 3–4 (RCT vs placebo)**
- **Sotagliflozin** (dual SGLT1 and 2 inhibitor) in obese diabetic **stage 4 CKD** reduce weight **by 1.4 Kg** vs placebo at 26 weeks (95% CI -2.8 to -0.008; P=0.049)

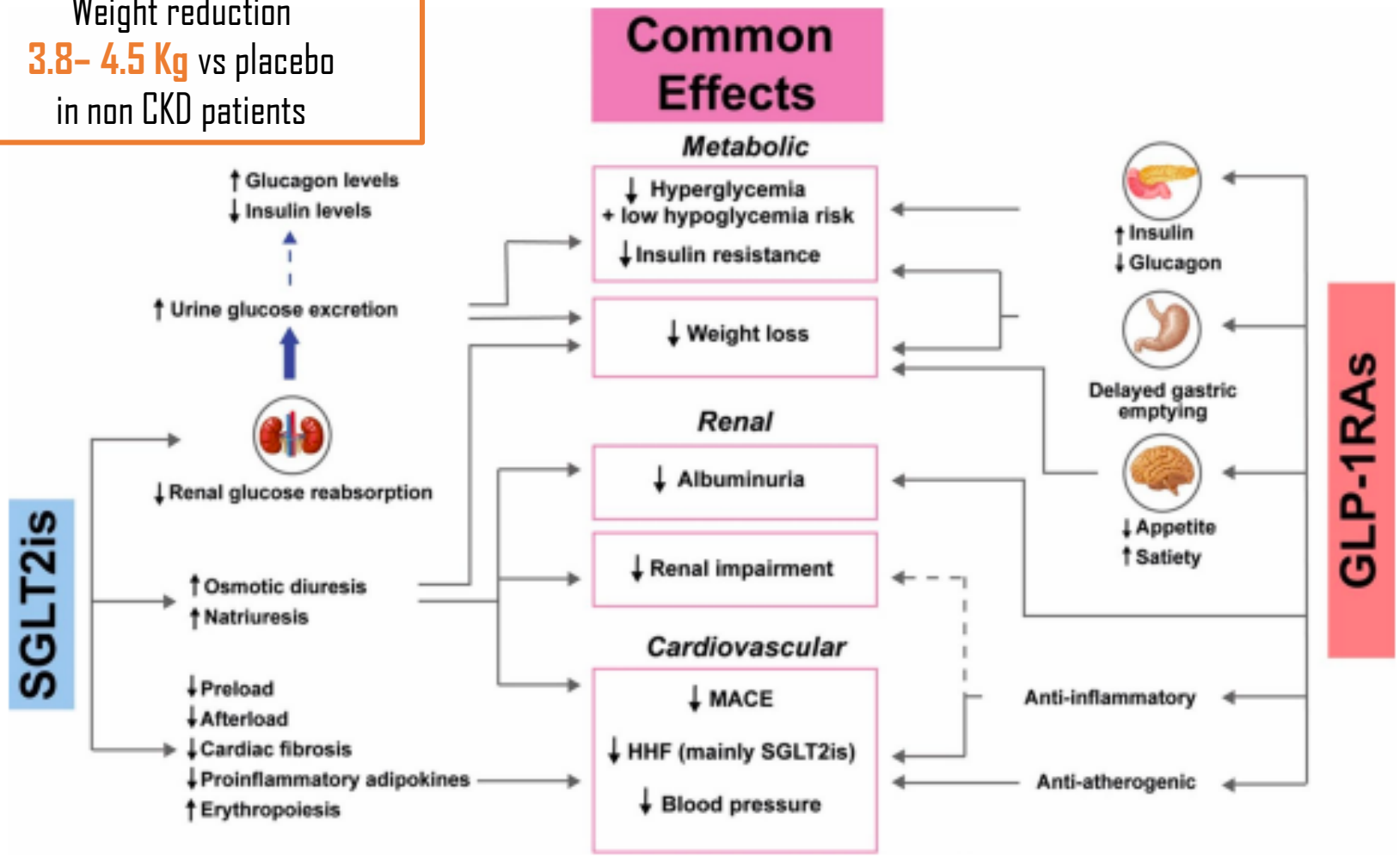


No RCT for obesity treatment in KTx candidates!

Angelidi AM, et al Novel Noninvasive Approaches to the Treatment of Obesity: From Pharmacotherapy to Gene Therapy. *Endocr Rev.* 2022;43(3):507-557
Fioretto et al Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (CKDstage 3A): The DERIVE Study. Diabetes Obes Metab. 2018;20:2532–2540.
Cherney, DZI, Ferrannini, E, Umpierrez, GE, et al. Efficacy and safety of sotagliflozin in patients with type 2 diabetes and severe renal impairment. *Diabetes Obes Metab.* 2021; 23(12): 2632-2642
Pereira et al. Emerging Role of SGLT-2 Inhibitors for the Treatment of Obesity Drugs (2019) 79:219–230

Combined SGLT2-is and GLP1-RAs and obesity in CKD

Weight reduction
3.8– 4.5 Kg vs placebo
in non CKD patients

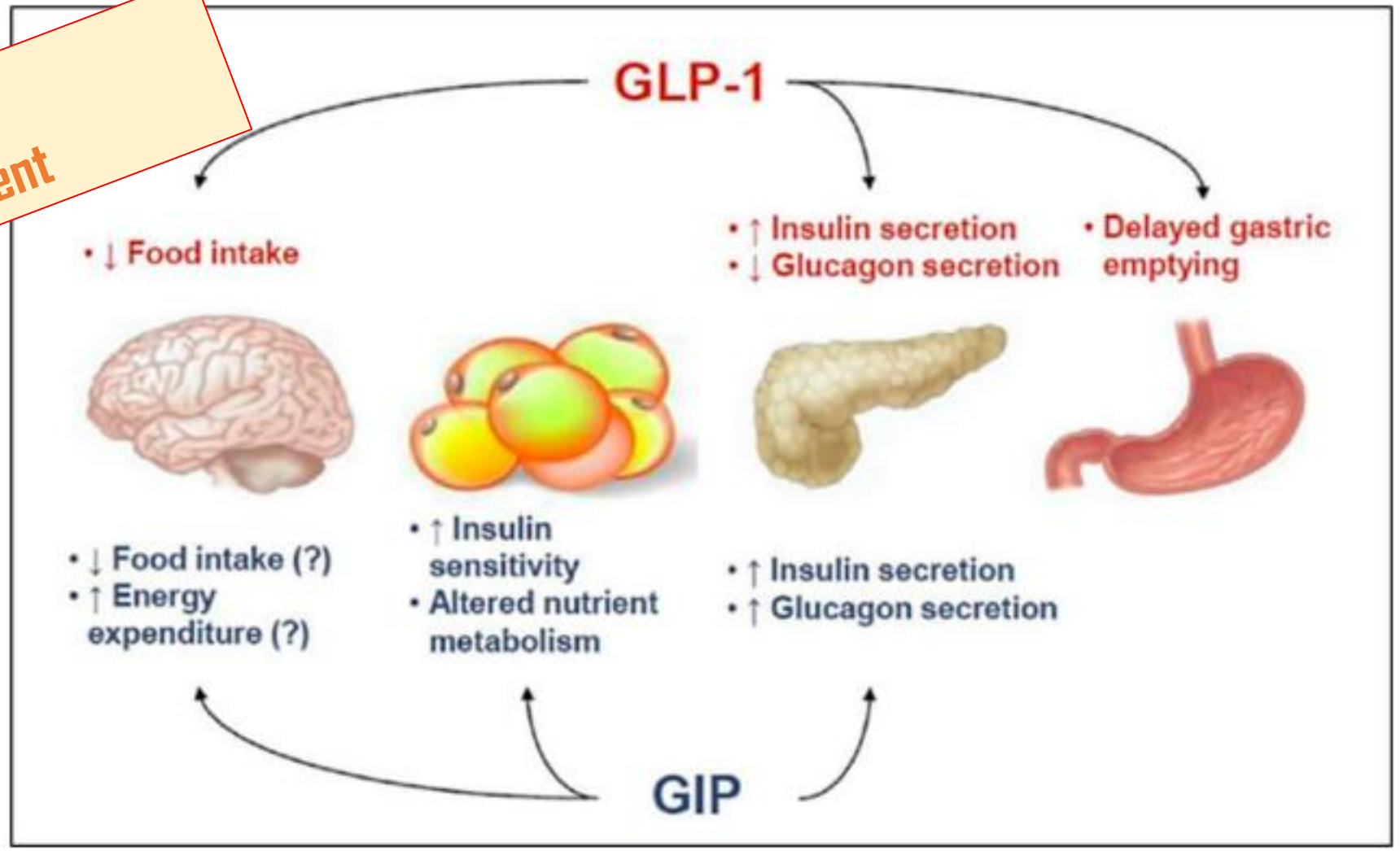


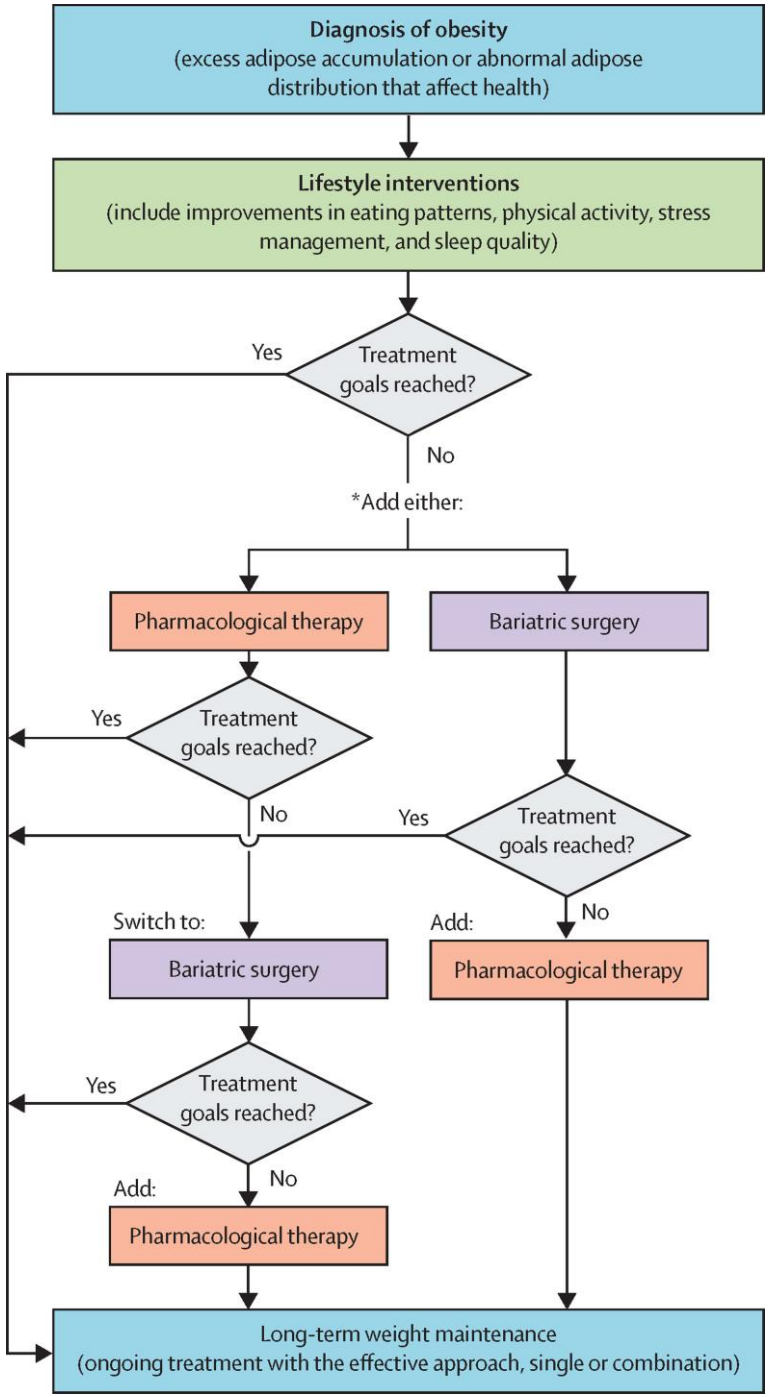
Benefits of this drug combination on weight reduction in CKD are not well established and warrant further attention

Gourdy et al. Combining glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) in patients with type 2 diabetes mellitus (T2DM)
Cardiovascular Diabetology (2023) 22:79

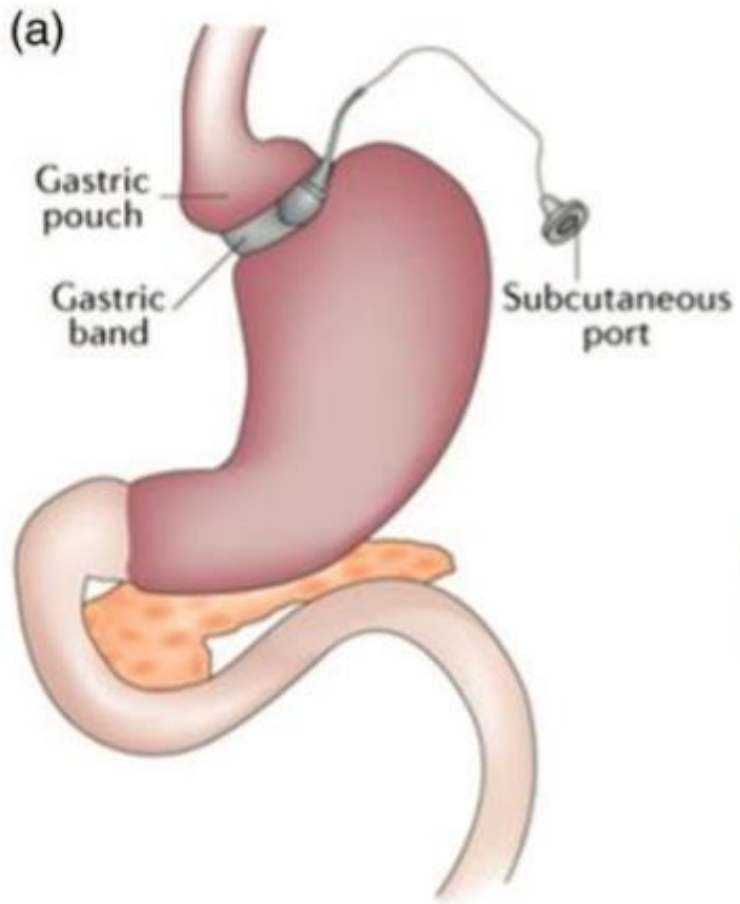
Tirzepatide GIP/GLP-1 dual agonist

2023 FDA approved for obesity treatment

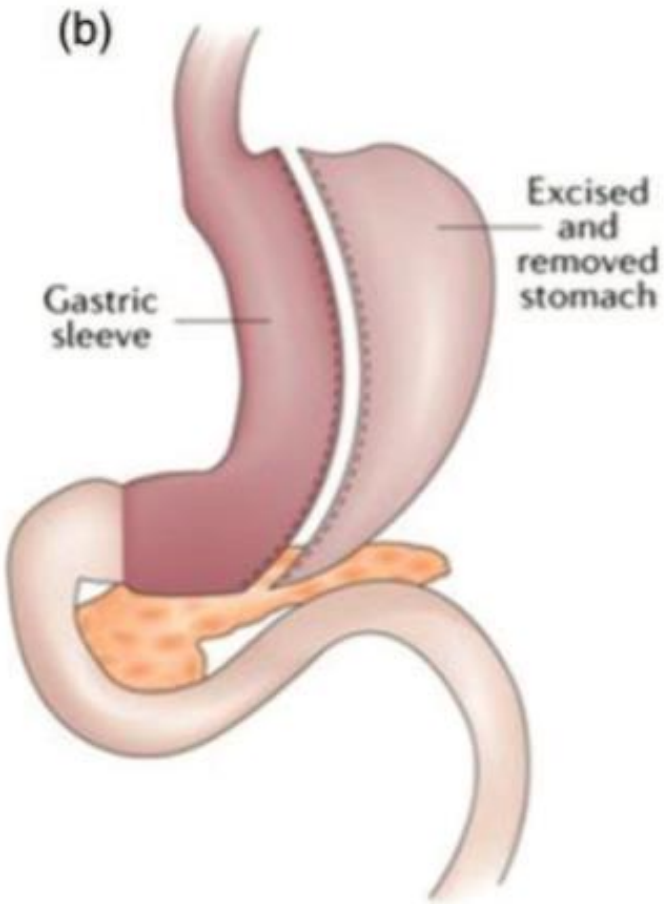



Diagnosis of obesity
(excess adipose accumulation or abnormal adipose distribution that affect health)
Lifestyle interventions
(include improvements in eating patterns, physical activity, stress management, and sleep quality)
Yes
Treatment goals reached?
No
*Add either:
Pharmacological therapy
Bariatric surgery
Yes
Treatment goals reached?
No
Yes
Treatment goals reached?
No
Switch to:
Bariatric surgery
Add:
Pharmacological therapy
Yes
Treatment goals reached?
No
Add:
Pharmacological therapy
Long-term weight maintenance
(ongoing treatment with the effective approach, single or combination)

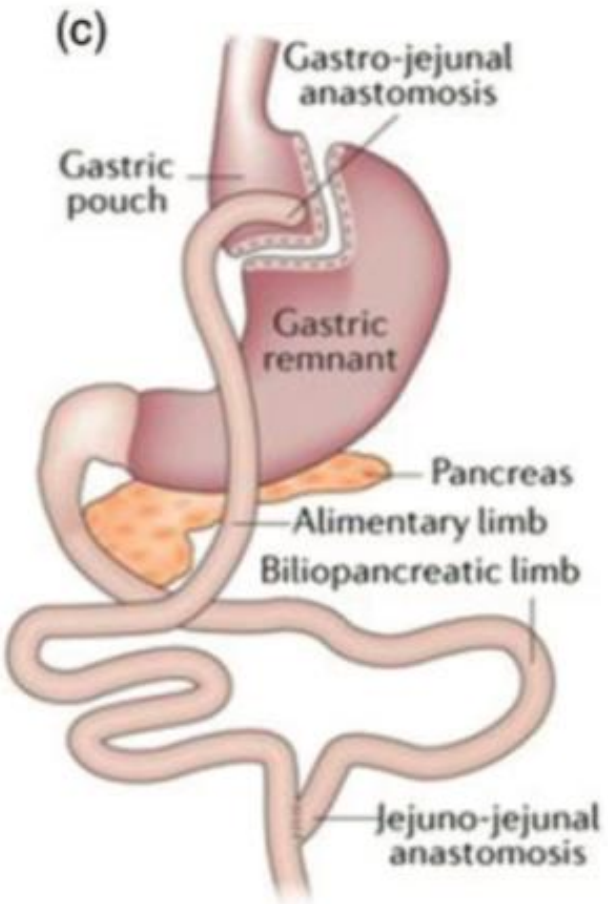
Bariatric surgery



Adjustable gastric banding



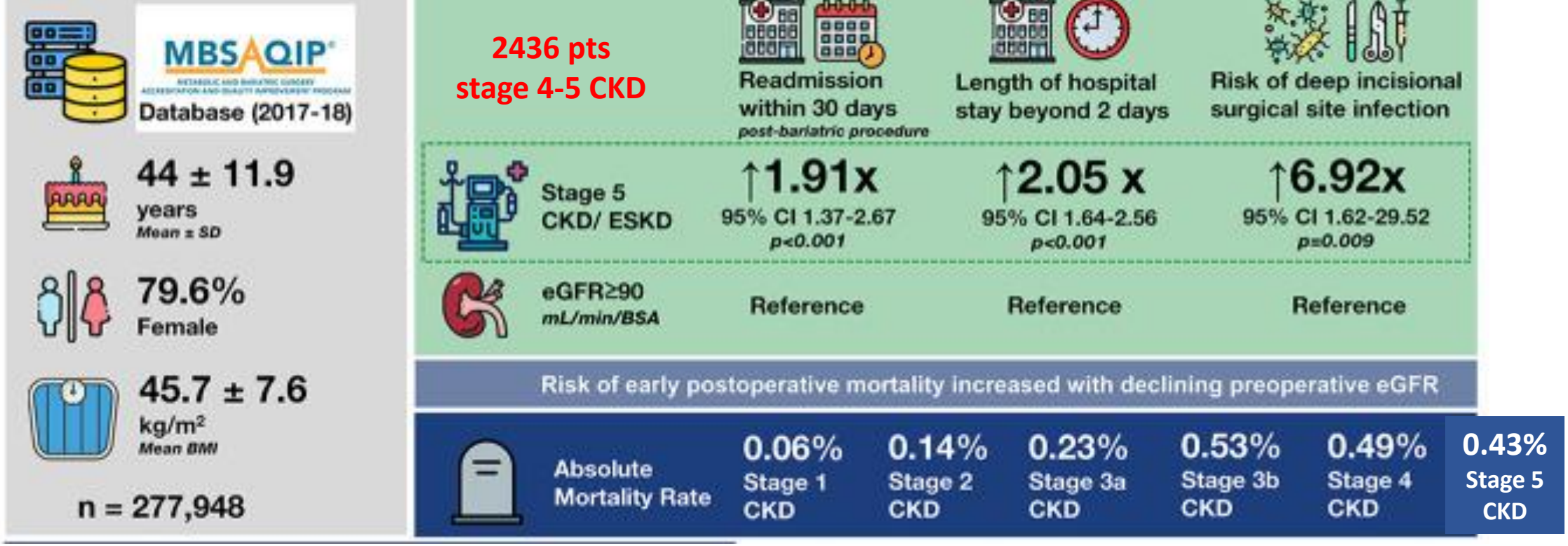
Laparoscopic sleeve gastrectomy



Roux-en-Y gastric bypass

Risks of perioperative complications in patients with CKD who underwent bariatric surgery

Kidney360



Conclusion: Increased severity of kidney disease was associated with increased complications after bariatric surgery. However, even for the population with advanced CKD, the absolute rates of postoperative complications were low (2.5-6.4%). Bariatric surgery should be considered a safe and effective option for patients with CKD

Carvalho Silveira F, et al. The impact of CKD on perioperative risk and mortality after bariatric surgery. KIDNEY360 2: 236–244, 2021

Which bariatric surgery for KTx candidates?

- Most studies in KTx candidates are small, single centre and retrospective without a control group
- No directly comparative data for the different surgical procedures
- The two most commonly used are laparoscopic sleeve gastrectomy and (LSG) and Roux-en-Y Gastric Bypass (RYGB)
- Although RYGB achieves greater weight loss in the general population, **a few reasons exist for preferring LSG over other types of bariatric procedures**
- Compared with RYGB, LSG does not seem to impair **immunosuppressive drug absorption** and does not affect **oxalate absorption** since it does not modify intestinal absorption

Kassam et al. Long-term outcomes in patients with obesity and renal disease after sleeve gastrectomy. Am J Transplant. 2020;20(2):422–9

Kim, Y, et al. Laparoscopic sleeve gastrectomy improves renal transplant candidacy and posttransplant outcomes in morbidly obese patients. *Am J Transplant*. 2018;18 410–16

Sarno, G .The Impact and Effectiveness of Weight Loss on Kidney Transplant Outcomes:A Narrative Review. *Nutrients* 2023, *15*,2508.

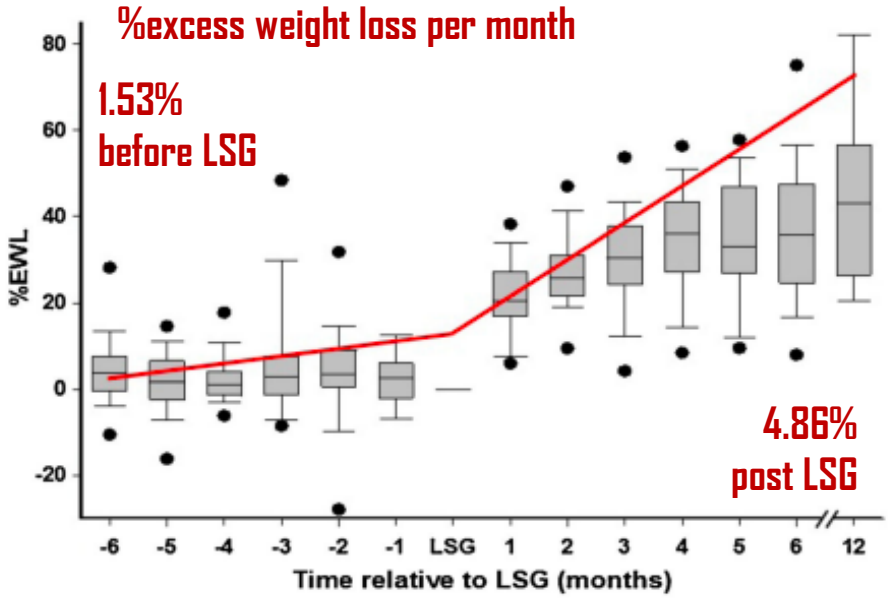
Addressing Morbid Obesity as a Barrier to Renal Transplantation With Laparoscopic Sleeve Gastrectomy

Prospective evaluation of laparoscopic sleeve gastrectomy (LSG) for 52 obese renal transplant candidates patients failing to achieve significant weight loss with 6 months medical therapy

Table 3a: Comparison of endpoints before and after LSG (n = 52)

	Pre LSG mean ± SD (range), n(%)	Post LSG mean ± SD (range), n(%)	p-Value
Weight (kg)	127.1 ± 21.7 (96.0–192.0)	107.7 ± 21.0 (57.4–157.4)	<0.001
BMI (kg/m^2)	43.0 ± 5.4 (35.8–67.7)	36.3 ± 5.3 (29.2–49.8)	<0.001
Hypertension incidence	48 (92.3%)	29 (55.8%)	<0.001
# of Anti-hypertensive medications	2.3 (0–7)	1.4 (0–5)	<0.001
Diabetes mellitus incidence	28(53.8%)	15 (28.8%)	<0.001
Hemoglobin A1c (%)[1]	6.8 ± 1.6	5.8 ± 1.6	<0.05

Follow-up after LSG 220±152 days (range 26–733 days)



55.8% patients achieved goal BMI of < 35 Kg/m^2 to be eligible for Ktx

No perioperative deaths

LSG is a safe and effective means for addressing obesity in kidney transplant candidates in the context of a multidisciplinary approach

Freeman et al. American Journal of Transplantation 2015; 15: 1360–1368

Original Investigation

Kidney360

Kukla A et al. KIDNEY360 3: 1411–1416, 2022

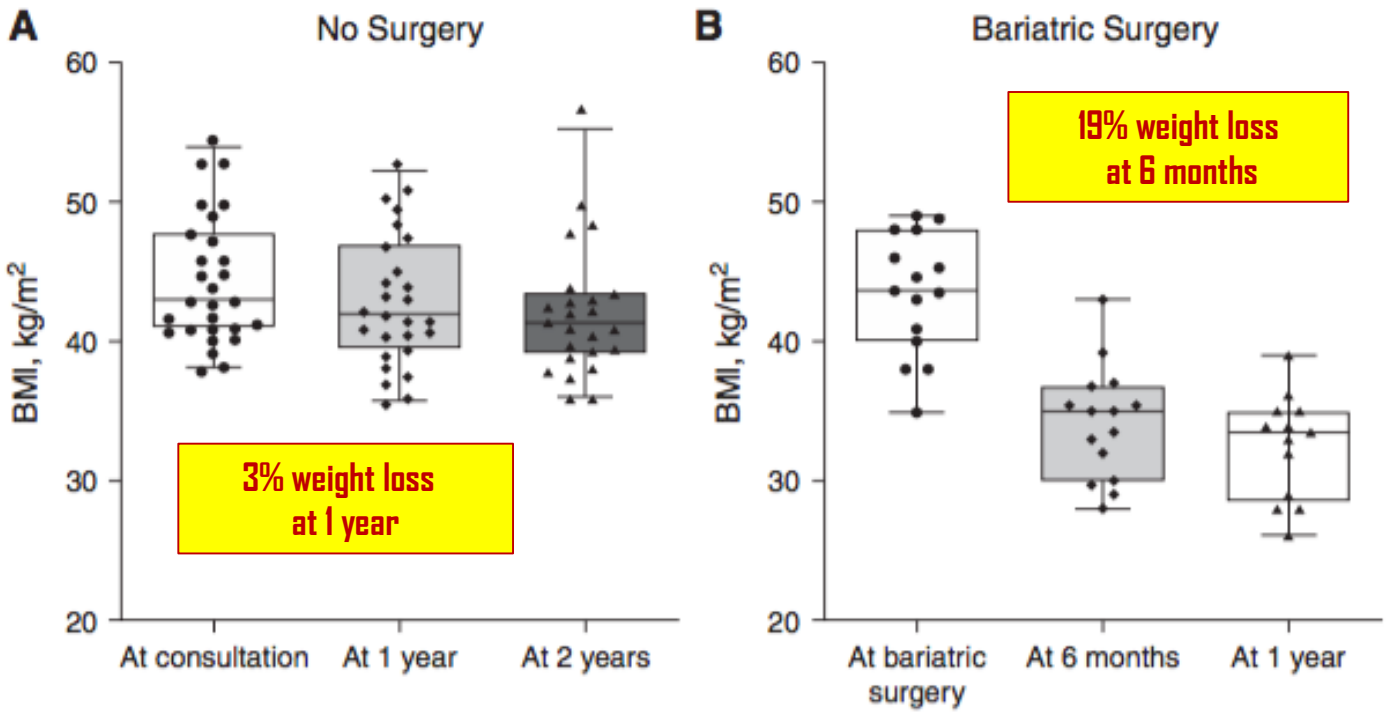
Guiding Kidney Transplantation Candidates for Effective Weight Loss: A Clinical Cohort Study

Retrospective

43 Ktx candidates - 52% on dialysis

15 pts: Bariatric Surgery within 1 year of weight management consultation

(14 SG and 1 RXGB) - no major surgical complications



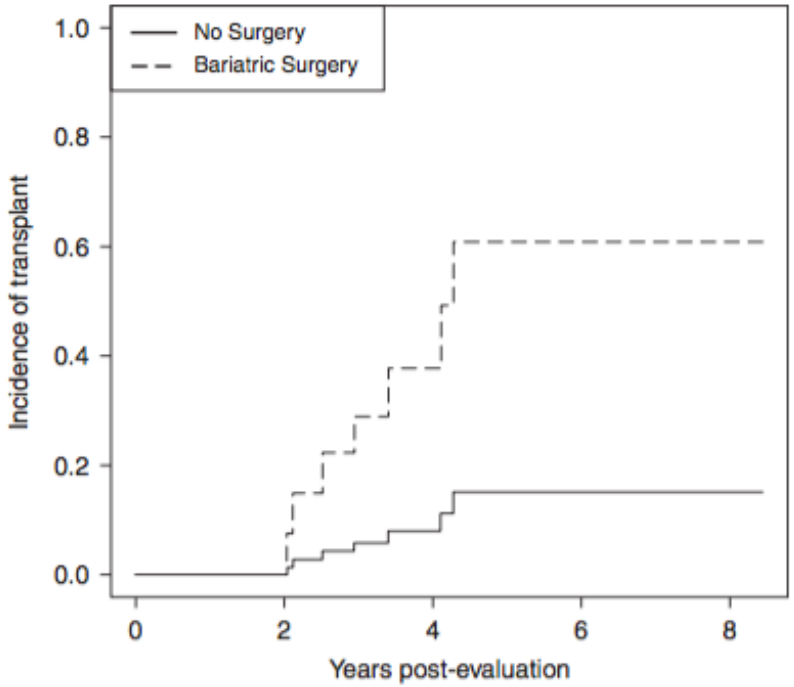


Figure 2. | Comparison of rates of kidney transplantation based on surgical and nonsurgical weight-loss management.

Bariatric surgery was strongly associated with receiving a kidney transplant

HR: 8.39 [95% CI 1.71 to 41.19]; p=0.009

Management of obesity in kidney transplant candidates and recipients: A clinical practice guideline by the DESCARTES Working Group of ERA

Nephrol Dial Transplant (2022) 37: i1–i15

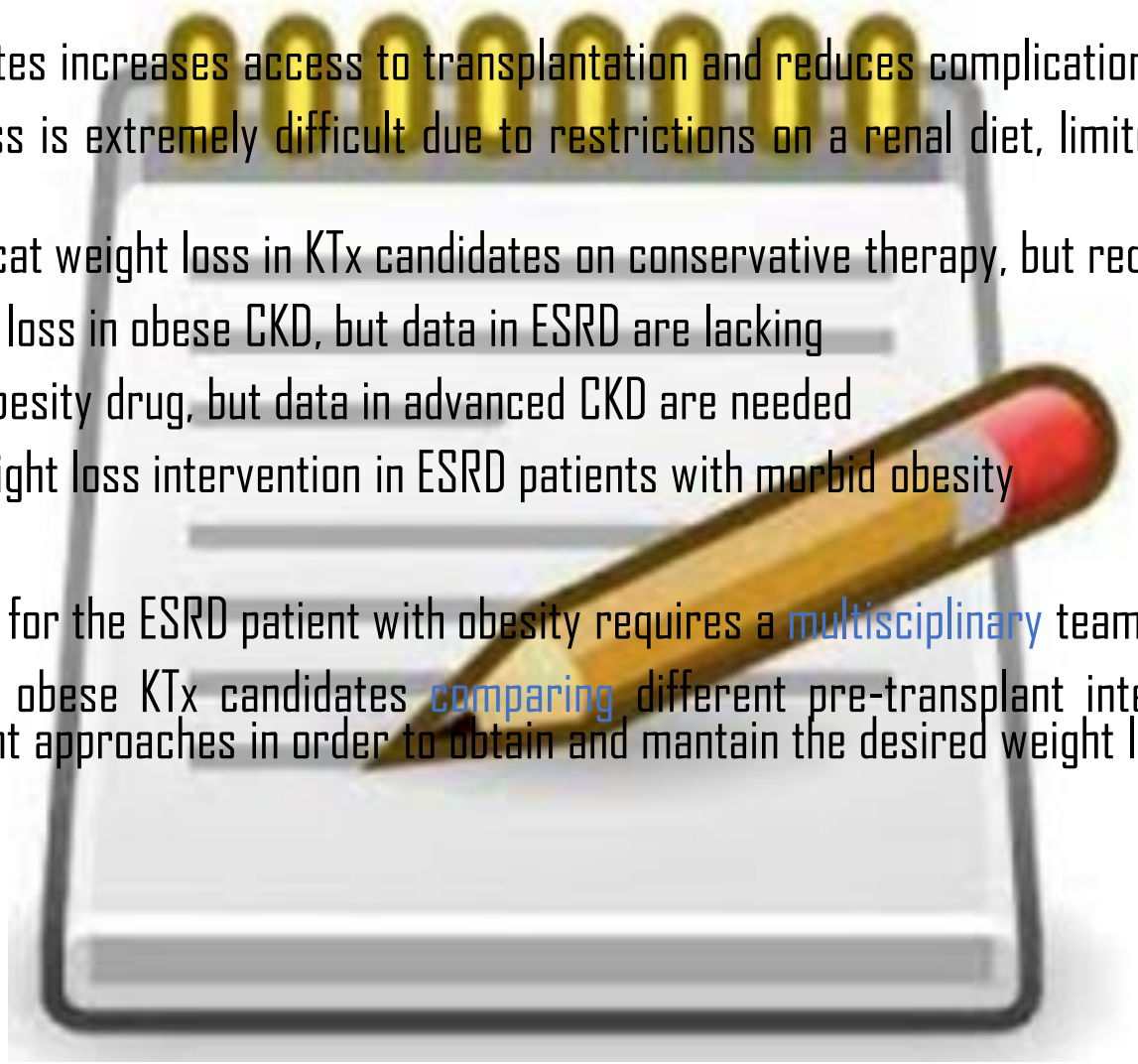
We recommend encouraging kidney transplant candidates living with obesity to lose weight and having their nutritional status supervised by a **multidisciplinary weight-management team** (1D)

We suggest considering bariatric surgery in kidney transplant candidates with a **BMI ≥40 kg/m2** (2C)

We suggest considering bariatric surgery in kidney transplant candidates with a **BMI ≥35 kg/m2** with at least one major obesity-related condition that can be improved by weight loss (2D)

We suggest **laparoscopic sleeve gastrectomy** over other forms of bariatric surgery in kidney transplant candidates (2D)

Take home messages

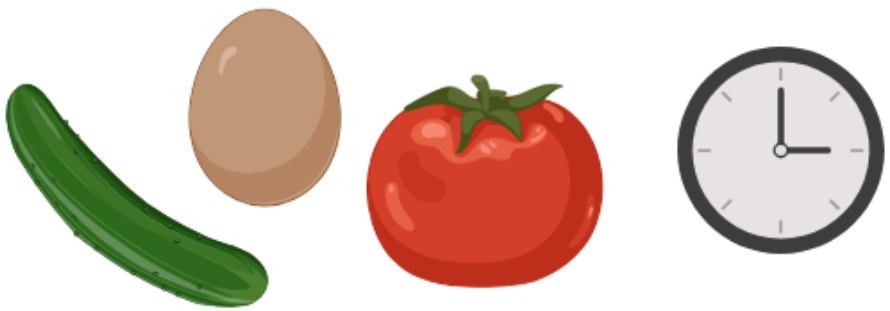


- ✓ Weight loss in obese KTx candidates increases access to transplantation and reduces complications
- ✓ In patients in dialysis: weight loss is extremely difficult due to restrictions on a renal diet, limited exercise tolerance and dialysis-related fatigue
- ✓ Ketogenic diet may obtain significat weight loss in KTx candidates on conservative therapy, but requires a strict medical supervison
- ✓ GLP-1 RAs are effective in weight loss in obese CKD, but data in ESRD are lacking
- ✓ Terzipatide is a promising anti-obesity drug, but data in advanced CKD are needed
- ✓ Bariatric surgery is effective weight loss intervention in ESRD patients with morbid obesity

- ✓ The added complexities of caring for the ESRD patient with obesity requires a multisciplinary team approach
- ✓ Randomized controlled trials in obese KTx candidates comparing different pre-transplant interventions and evaluating possible benefit of integrating the different approaches in order to obtain and mantain the desired weight loss the are needed

Types of Fasting

Prolonged Fasting (PF): no food, only water lasting more than 2 days combined with a week of normal diet

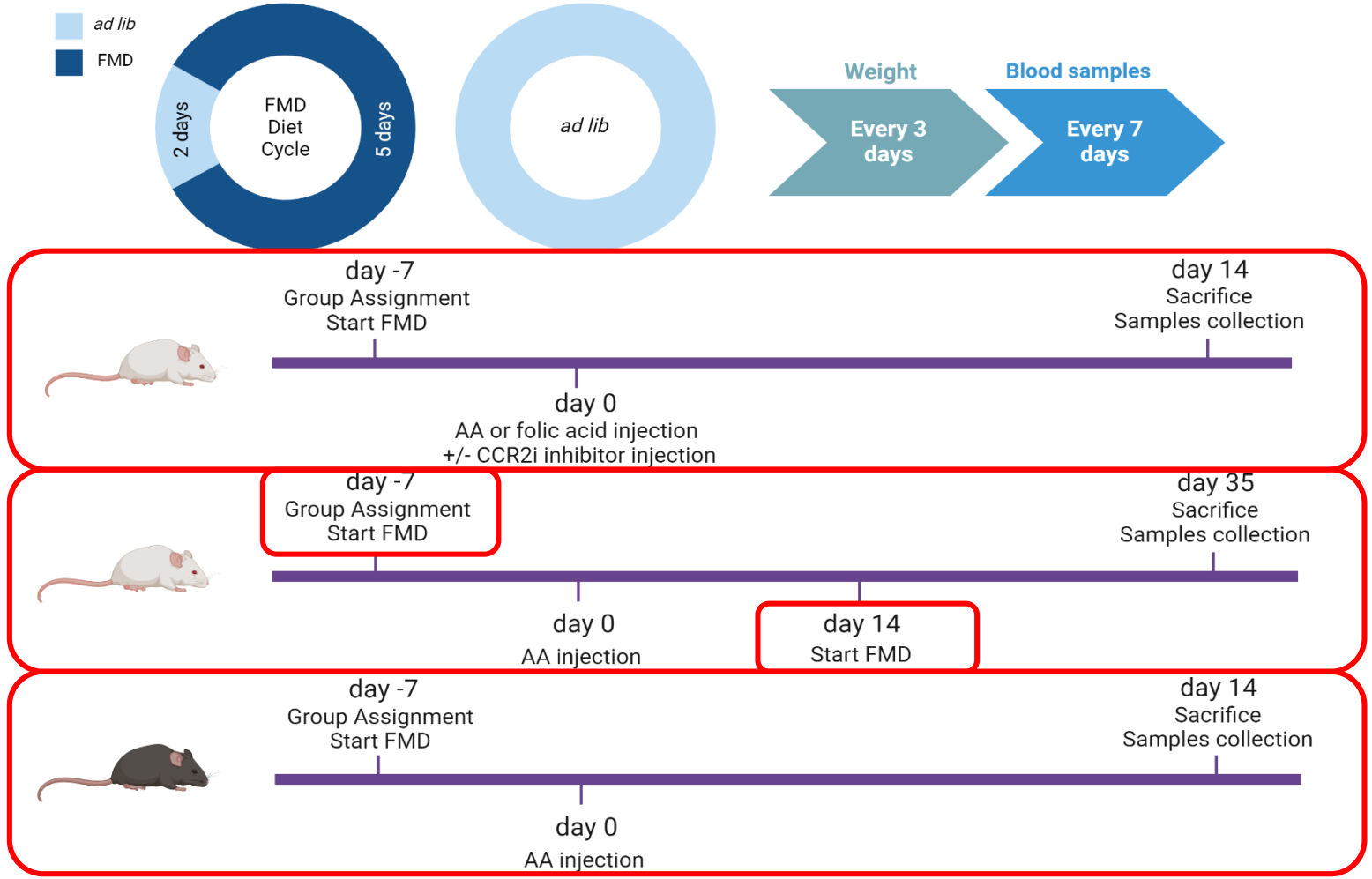


Intermittent Fasting (IF): consuming food during a specific period of time in the day and fasting for the remainder of the day

Fasting Mimicking Diet (FMD): consumption of small amounts of food 5 days a month

Under review, Paolo Molinari et al

Study design



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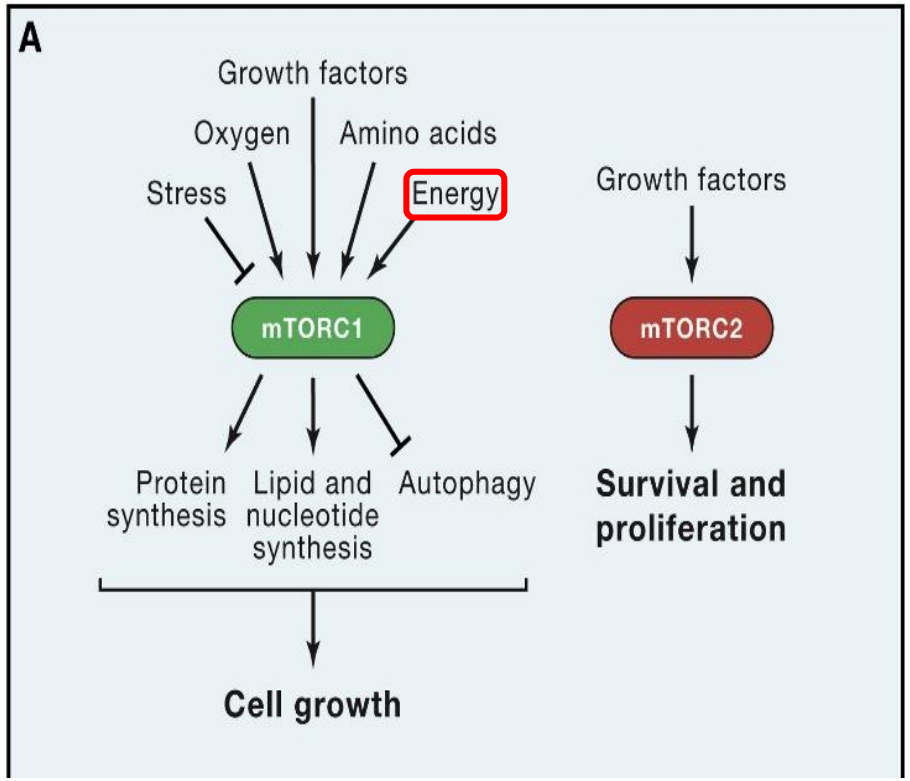
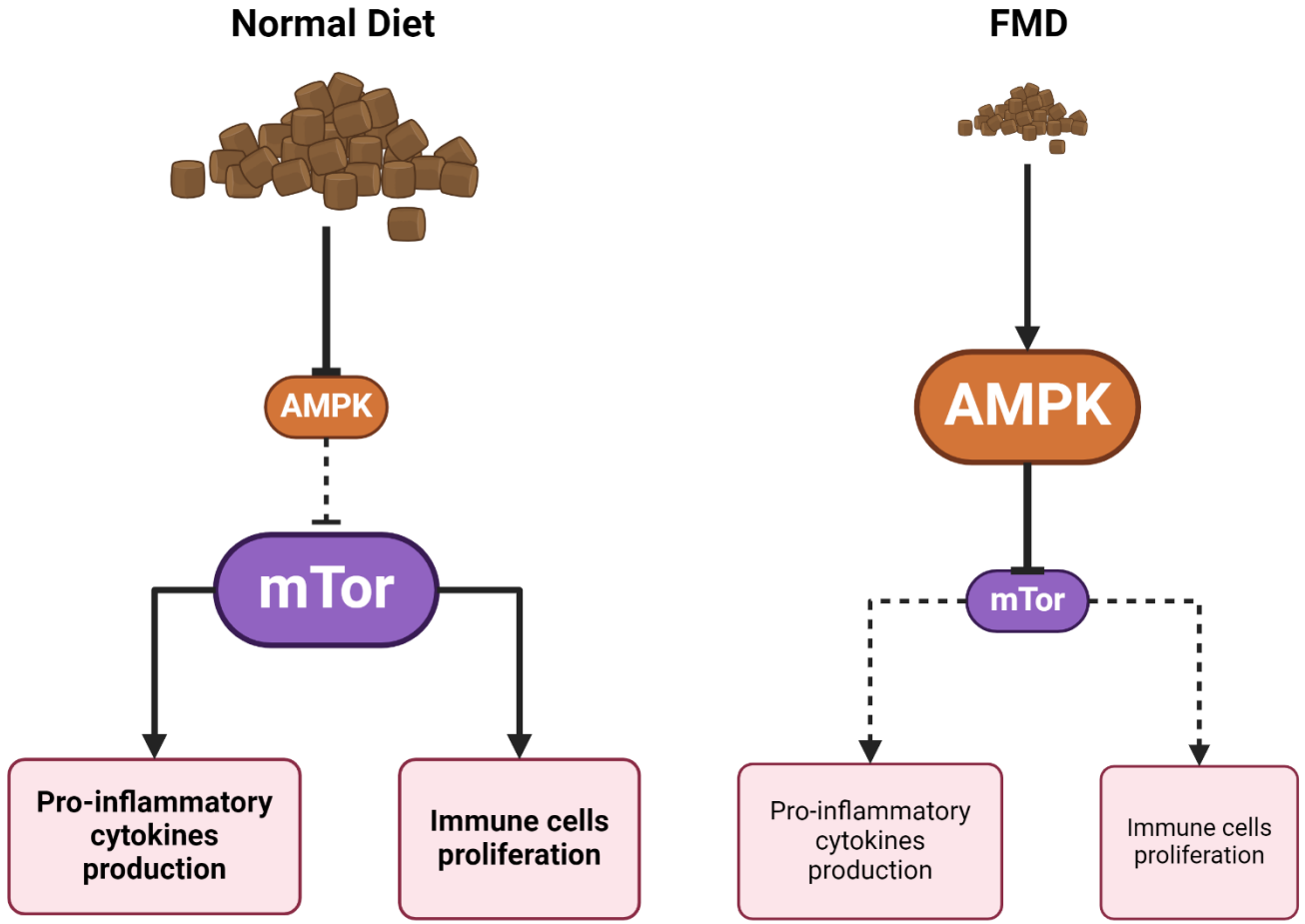
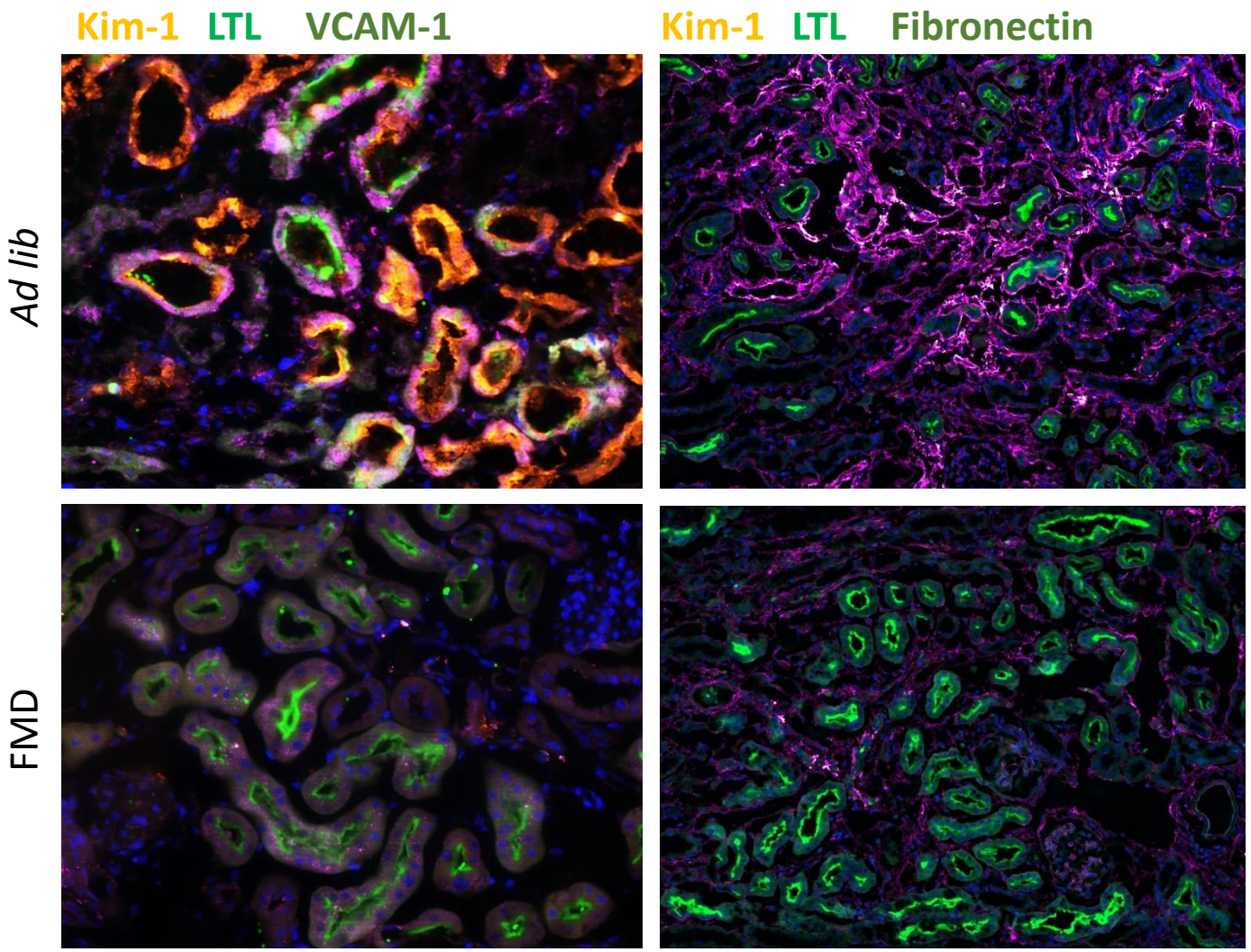
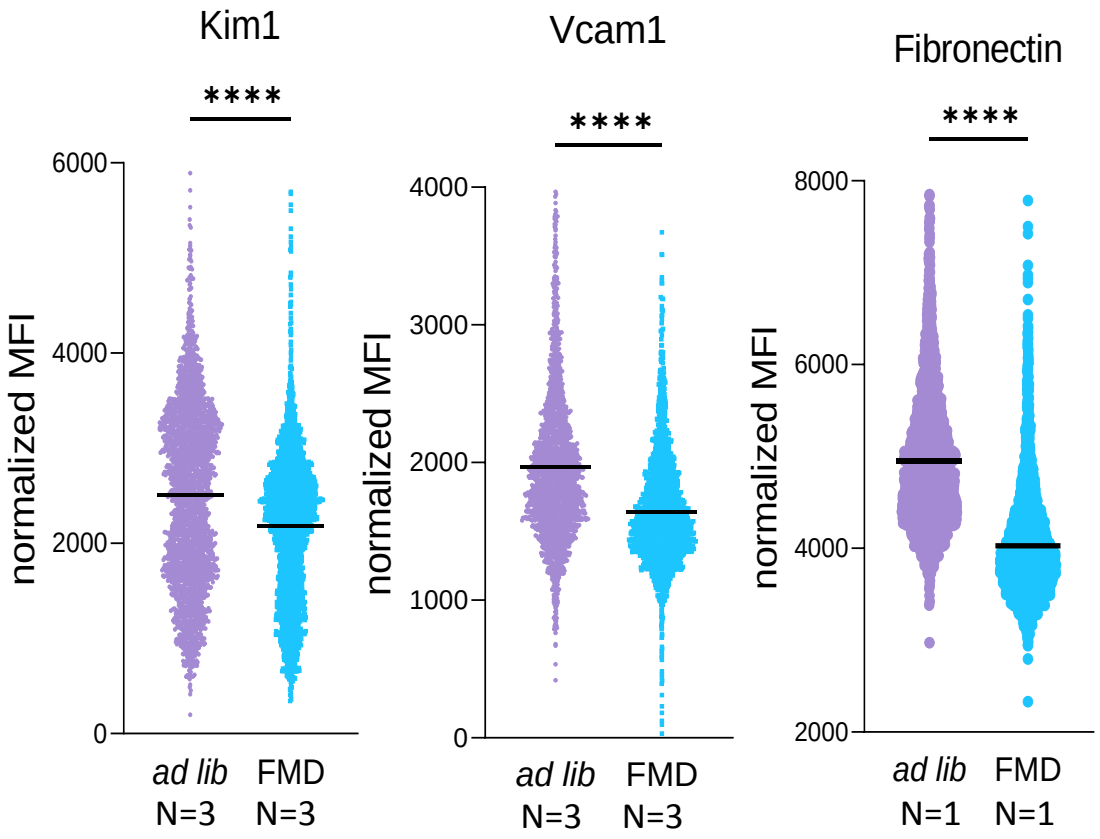
Fasting and caloric restriction – mechanism of action





FMD protects from acute and chronic kidney injury after AA injection – maladaptive repair





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Thank you!