ECHO Diabetes

Diabetes Management in Patients with Renal Disease

January 9th , 2020

SGLT2 inhibitor site & mechanism of Action

Updated Guidelines

- After metformin and lifestyle changes, the 2019 American Diabetes Association (ADA) guidelines recommend the second-line agent be chosen based on the presence or absence of established ASCVD or CKD.

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)

Use principles in Figure 1

Use metformin unless contraindicated or not tolerated

If not at HbA_{1c} target:

- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP-1 RA with proven cardiovascular benefit[1] (see below)

If at HbA_{1c} target:

- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit[1] (see below)

OR reconsider/lower individualized target and introduce SGLT2i or GLP-1 RA

OR reassess HbA_{1c} at 3-month intervals and add SGLT2i or GLP-1 RA if HbA_{1c} goes above target

ASCVD predominates

GLP-1 RA with proven CVD benefit[1]

EITHER/ OR

SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

HF or CKD predominates

PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

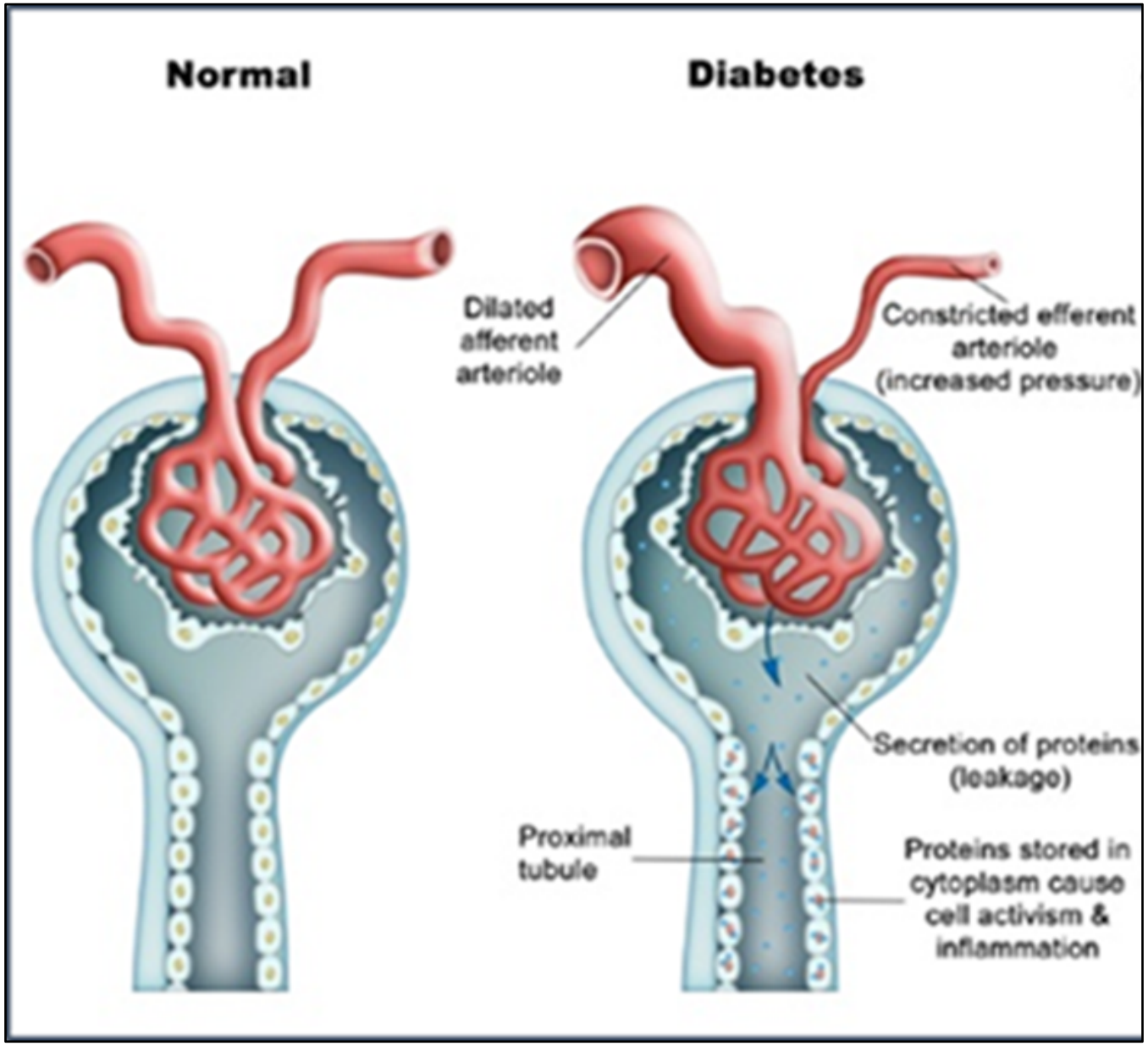
OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1,4]

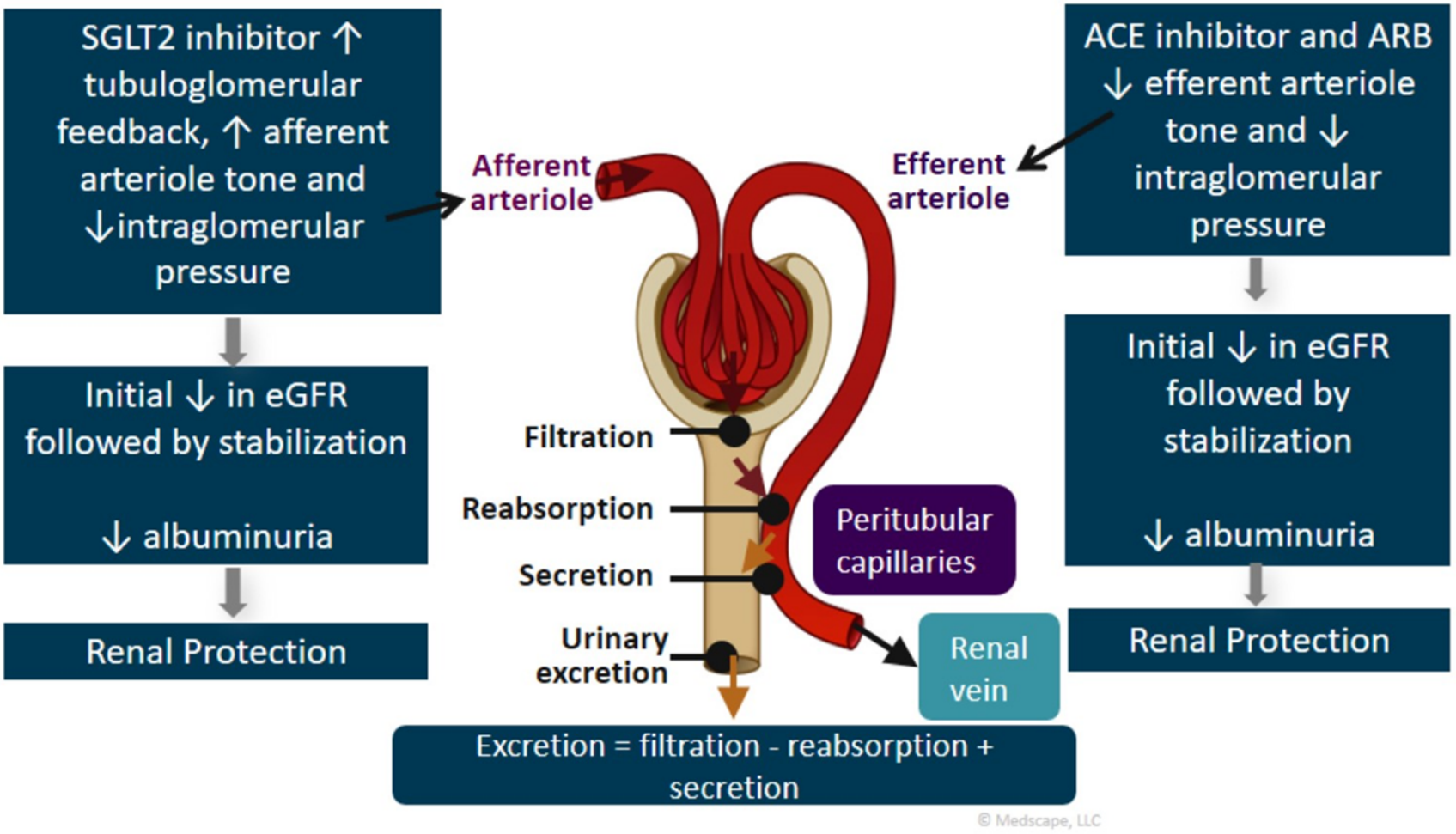
ADA - Updated Renal Management Guidelines

- 11.3 For patients with ***type 2 diabetes and diabetic kidney disease***, consider use of an **SGLT2 inhibitor in patients with an eGFR ≥ 30 mL**/min and **particularly in those with > 300 mg/g albuminuria** to ***reduce risk of CKD progression, cardiovascular events, or both***. Grade of evidence: A

- FDA label indicates for
  - Canagliflozin (Invokana) – use 100 mg/d (avoid 300 mg dose) if
    - eGFR 45 – 60 mL/min
    - eGFR 30-45 mL/min & albuminuria > 300 mg/day
      - *In Credence trial Invokana was continued at eGFR < 30 - unless dialysis started*
  - Empagliflozin (Jardiance) and Dapagliflozin (Farxiga) – label still indicates not to use if eGFR <45 mL/min
    - *Due to limited glycemic response at lower GFR*

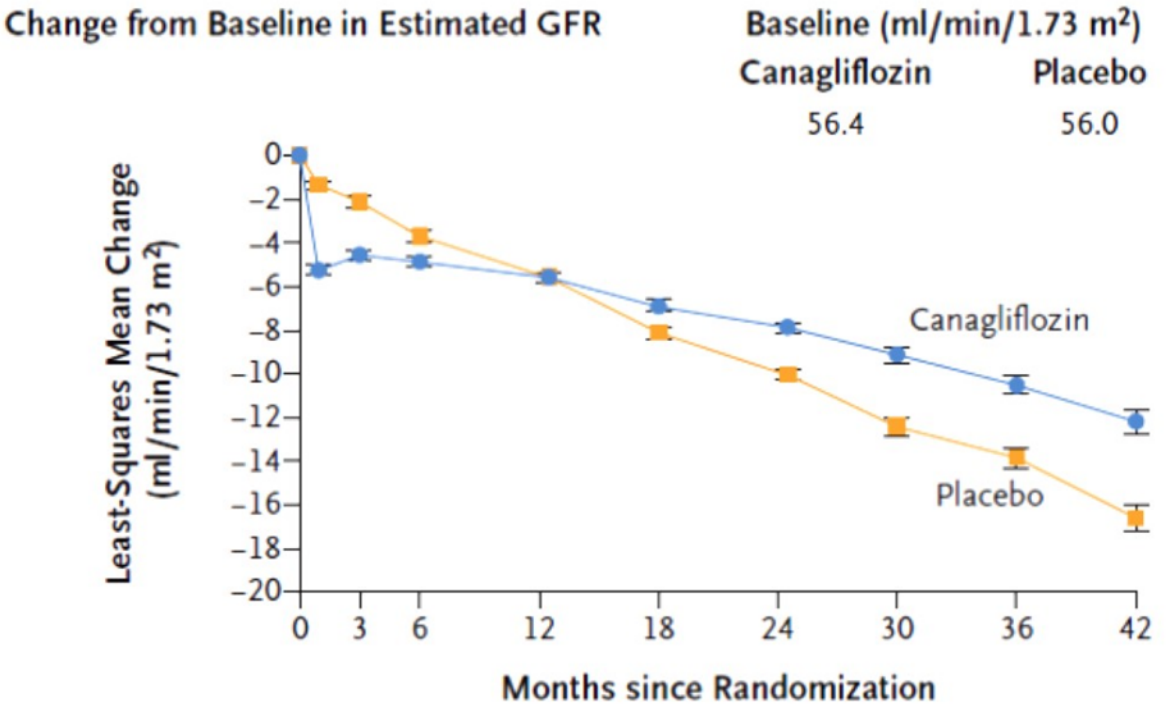

Normal
Diabetes
Dilated afferent arteriole
Constricted efferent arteriole (increased pressure)
Secretion of proteins (leakage)
Proximal tubule
Proteins stored in cytoplasm cause cell activism & inflammation

SGLT2 Inhibition and ACE Inhibition/ARBs Reduce Intraglomerular Pressure



Cherney DZ, et al. *Circulation*. 2014;129:587-597; Perkovic V, et al. *Curr Med Res Opin*. 2015;31:2219-2231.

Effects of Canagliflozin on eGFR



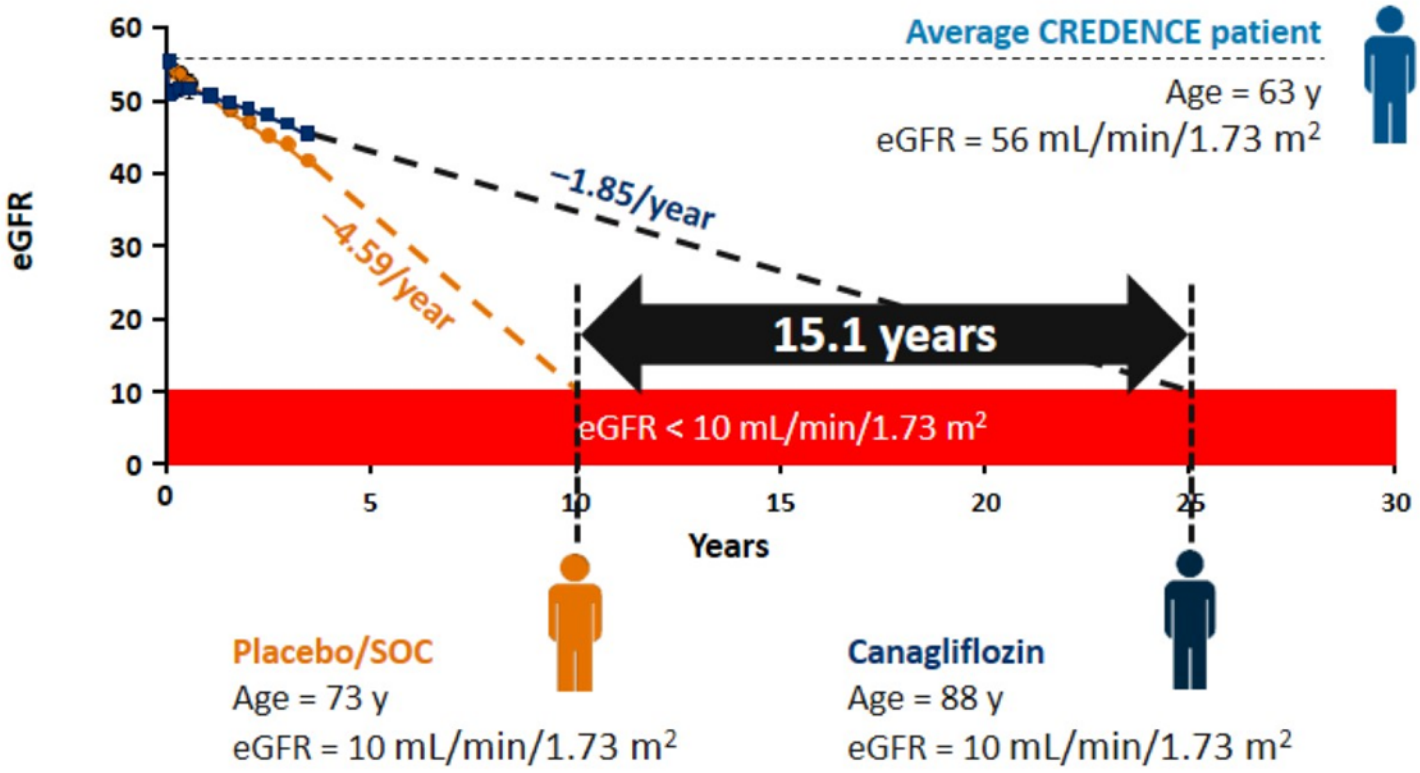
No. of Patients								
Placebo	2178	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2005	1919	1782	1648	1116	652	241

Acute eGFR slope (3 weeks)
Difference: −3.17 (95% CI: −3.87, −2.47)

Chronic eGFR slope
Difference: 2.74/year (95% CI: 2.37–3.11)

Perkovic V, et al. *N Engl J Med*. 2019;380:2295-2306.

Projected Effects of Canagliflozin on eGFR



Perkovic V, et al. *N Engl J Med*. 2019;380:2295-2306.

How to manage Diabetes in patients with ESRD/ESKD and Dialysis

Multiple different factors contribute to individual variation in what is required

CKD KDOQI Classification

- The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) CKD classification:
  - normal eGFR ≥ 90 mL/min (***stage 1 CKD if albuminuria is increased***);
  - mildly reduced eGFR 60–89 mL/min (***stage 2 CKD if albuminuria is increased***);
  - moderately reduced eGFR 30–59 mL/min (***stage 3 CKD***);
  - severely reduced eGFR > 15–29 mL/min (sta***ge 4 CKD***);
  - ***end stage renal failure*** or ***stage 5 CKD*** if eGFR < 15 mL/min

Updates on the Management of Diabetes in Dialysis Patients

Connie M. Rhee et al Semin Dial. 2014 Mar; 27(2): 135–145.

- The treatment of diabetes in ESRD patients is challenging given
  - the *changes in glucose homeostasis*
  - the ***unclear accuracy of glycemic control metrics***
  - the *altered pharmacokinetics* of glucose-lowering drugs by kidney dysfunction
  - the *uremic* milieu
  - *dialysis* therapy

the unclear accuracy of glycemic control metrics

- ***Spuriously elevated HbA1c*** levels may be observed in the context of elevated blood urea nitrogen (BUN) levels and metabolic acidosis.
  - Exposure to high urea concentrations promotes formation of **carbamylated hemoglobin**, which cannot be distinguished from glycated hemoglobin in certain assays (e.g., electric charge-based assays).
- Conversely, ***both spuriously (falsely) and truly low HbA1c levels*** may be observed in the context of **anemia**, blood transfusions, and conditions associated with **shortened erythrocyte life span** (e.g. *erythrocyte fragility due to uremia, erythrocyte lysis due to the dialysis procedure*), which may consequently lead to ***underestimation*** of long-term glucose control and undertreatment of hyperglycemia
- The frequent utilization of ***erythropoietin-stimulating agents*** in dialysis patients also f**alsely lower HbA1c** levels by accelerating erythropoiesis and increasing the proportion of young circulating erythrocytes that have limited time for hemoglobin glycosylation
- [Recommend more **use of CGM and time in range** to monitor patients with CKD due to ***unreliable A1c measurements***]

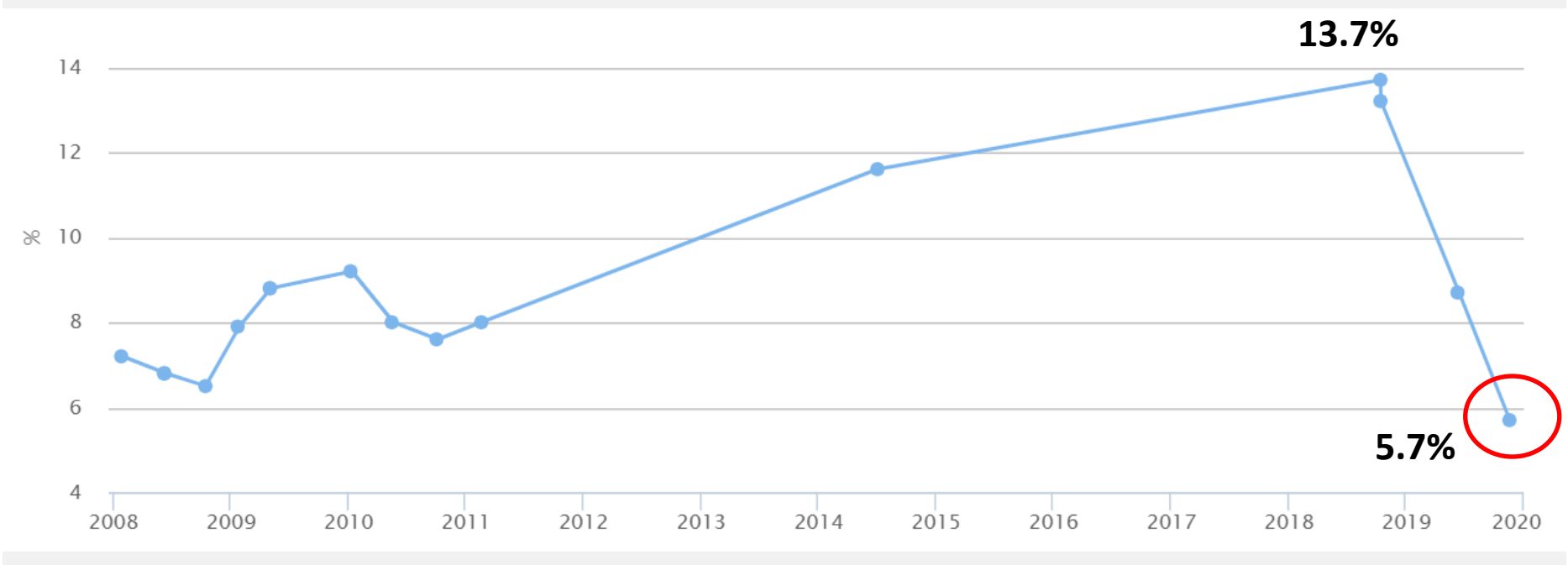
Updates on the Management of Diabetes in Dialysis Patients

Connie M. Rhee et al Semin Dial. 2014 Mar; 27(2): 135–145.

- **Truly low A1c from ESKD -** ***Up to one-third of diabetic [ESRD &] dialysis patients may experience spontaneous resolution of hyperglycemia with hemoglobin A1c (HbA1c) levels <6%, a phenomenon known as "Burnt-Out Diabetes,"*** -- Multiple factors may contribute to this condition.
  - First, **malnutrition, protein-energy wasting, and diabetic gastroparesis** are frequently observed complications in dialysis patients, which heighten the risk of hypoglycemia.
  - Second, the clearance and degradation of exogenous insulin is reduced in kidney dysfunction, which results in **prolongation of insulin half-life**.
  - Third, there is a **decline in the hepatic clearance of insulin** in kidney dysfunction, which may improve after initiation of dialysis.
  - Fourth, decreased nephron mass and kidney function also lead to **a reduction in renal gluconeogenesis.**
  - Finally, the accumulation of some **uremic toxins, such as guanidino compounds, may act similar to biguanide agents** used for the treatment of type 2 diabetes, thus mitigating or even "curing" diabetes.

Patient with ESRD – A1c graph

showing “burn-out diabetes”



Disturbances in Insulin–Glucose Metabolism in Patients With Advanced Renal Disease With and Without Diabetes

Marie-Noel Rahhal et al; JCEM, Vol 104, Issue 11, Nov 2019, Pages 4949–4966

- ***Great variability in adjustments needed in Rx* among individuals with advanced DKD**
  - depending on the magnitude of change in multiple factors – these vary between individuals with the same degree of CKD
    - **decreased insulin clearance by kidneys** as well as by **liver & other tissues** leading to prolongation of its plasma half-life, elevated blood insulin concentration, and hypoglycemia.
    - **decreases in food intake**
    - **decrease in insulin secretion**
    - **deceased renal gluconeogenesis**
    - **heightened resistance to insulin** due to metabolic acidosis, uremic toxins, inflammatory state, and vitamin D deficiency.
  - Adjustments in insulin daily dose
    - In most patients the dose needs to be significantly **reduced**, but with a *high degree of variability*;
    - in some the dose remains **unchanged**
    - rarely it is **increased**

Role of the Kidney in INSULIN CLEARANCE

- In ***healthy nondiabetic*** people:
  - Insulin is ***secreted into the portal system***, passes through the **liver, where about 75%** is metabolized
  - the remaining **25% is metabolized by the kidneys**.
- For diabetic patients receiving ***exogenous insulin***, ***renal metabolism plays a more significant role*** *since there is* ***no first-pass metabolism in the liver*****.**
  - **As renal function significantly declines, insulin clearance by the kidney is reduced**
  - Thus, despite the ***increase in insulin resistance caused by renal failure,*** the net effect is often a ***reduced requirement for exogenous insulin*** in ESRD

- Multiple disturbances in glucose and insulin metabolism that *vary greatly between individuals*
  - Tissue **insensitivity to insulin (insulin resistance)** is a common feature of advanced CKD.
    - Multiple factors underlie the **insulin-resistant state in CKD,** including *metabolic acidosis*, uremia with *accumulation of uremic toxins, the heightened* ***inflammatory state****, vitamin D deficiency, altered intestinal flora, and decreased adiponectin.*
  - **Insulin secretion** is often moderately **suppressed in CKD** due to several factors, including metabolic acidosis.
    - Treatment of *metabolic acidosis* with sodium bicarbonate in patients with ESRD on HD increases both insulin sensitivity and insulin secretion.
    - *Secondary hyperparathyroidism* is known to interfere with the ability of the β-cells to augment insulin secretion in response to hyperglycemia.

altered pharmacokinetics of glucose-lowering drugs by kidney dysfunction

- Many *glucose-lowering drugs and their active metabolites* are renally metabolized and excreted, and hence, require dose adjustment or avoidance in dialysis patients.

Insulin

- Whereas endogenously secreted insulin is degraded by the liver, **exogenous insulin** is primarily excreted by the kidneys.
  - While there are no absolute guidelines regarding dose adjustments for insulin based on estimated glomerular filtration rate (eGFR), experts recommend an insulin dose reduction of 50% when eGFR is <10ml/min/1.73m
  - *Upon initiation of dialysis, peripheral insulin resistance may improve, further reducing insulin requirements*

Day-to-Day Variation of Insulin Requirements of Patients With Type 2 Diabetes and End-Stage Renal Disease Undergoing Maintenance Hemodialysis

Eugene Sobngwi, MD, PHD et al Diabetes Care 2010 Jul; 33(7): 1409-1412.

- Hemodialysis improves *insulin sensitivity* and also *insulin clearance*, making it more difficult to determine insulin requirements for patients with ESRD undergoing maintenance hemodialysis and therefore exposing them to acute metabolic incidents
  - In a population with an average 2 years of maintenance hemodialysis - **on the day after hemodialysis, there is a significant 25% decrease in basal insulin requirements of diabetic patients with ESRD**, the day *post-hemodialysis* compared with the day pre-hemodialysis for comparable food consumption, **but no significant change in bolus premeal insulin.**
- These results therefore **support a systematic reduction of basal exogenous insulin administration by 25% in type 2 diabetic patients undergoing hemodialysis the day after dialysis.**
  - *[basal insulin has long half-life which is further prolonged by ESRD – so accomplishing this may be challenging without CSII (pump) therapy]*

Other Medications

- **Metformin** - recommended maintenance even in the face of CKD has been advocated, though its dose should be
  - reduced for eGFR < 45 mL/min/1.73 m2
  - withdrawn for eGFR < 30 mL/min/1.73 m2

- **Alpha-glucosidase inhibitors** are not recommended mainly because of lack of safety data.

Sulfonylureas & Meglitinides

- Among the newer, second generation SUs, ***short-acting glipizide*** is the preferred agent in dialysis patients, as
  - it is largely metabolized by the liver, has inactive or weakly active metabolites that are excreted in the urine, and has a lower risk of hypoglycemia compared to other SUs (e.g., glyburide, glimepiride).
  - *Most clinicians, however,* ***avoid the use of SUs*** *in the elderly and in dialysis patients, due to the hypoglycemia risk.*
- **Meglitinides** include repaglinide and nateglinide, which are structurally different that SUs but similarly stimulate insulin secretion by regulating ATP-dependent potassium channels on pancreatic beta cells.
  - ***Repaglinide (Prandin)*** is the preferred agent ***in dialysis patients*****,** as it is completely metabolized by the liver, has inactive or weakly active metabolites that are excreted in the urine, and has lower risk of hypoglycemia compared with other agents.
  - Nateglinide (Starlix), while also hepatically metabolized, *has renally-excreted active metabolites* that may result in hypoglycemia in dialysis patients.

Use of conventional antidiabetic drugs in type 2 diabetic patients with chronic kidney disease

	eGFR >60 mL/min	eGFR 30–59 mL/min	eGFR <30 mL/min	Dialysis
Insulin	✓	✓	✓ dose reduction	✓ dose reduction
Metformin	✓	✓ caution	⊘	⊘
Sulfonylureas	✓	caution	caution	⊘
Metiglinides	✓	✓ caution	caution	⊘
Thiazolidinediones	✓	✓ caution	✓ caution	✓ caution
Alpha-glucosidase inhibitors	✓	✓	⊘	⊘

DPP-4 inhibitors

- ***Dose reductions*** are required for vildagliptin and other DPP-4 inhibitors***, except linagliptin***, in T2DM patients with moderate-to-severe CKD.

GLP1 –RA agents

- Exenatide and lixisenatide have renal dosing recommendations; however, semaglutide, liraglutide, and dulaglutide do not have specific recommendations.
  - Caution is recommended for **exenatide and exenatide ER** with a creatinine clearance (CrCl) less than 50 mL/min
  - Use not recommended when CrCl is less than 30 mL/min
  - The LIRARENAL study demonstrated efficacy and safety of the use of **liraglutide** in patients with T2DM and stage 3 CKD (eGFR 45-59 mL/min)
- *Limited data* exist regarding the use of GLP-1 RA in patients with stage 4 or 5 CKD.
  - Dulaglutide (Trulicity) - no renal dose adjustments recommended for this agent. However, because of the *lack of patients in the phase 2 and 3 trials with stage 4 and 5 CKD*, caution should be used in this population.
  - Semaglutide - no renal dose adjustments are recommended based on pharmacokinetic study that included patients with ESRD

DPP-4 inhibitors and GLP-1 receptor agonists treatments in type 2 diabetic patients with chronic kidney disease

	Renal excretion	eGFR >60 mL/min	eGFR 30–59 mL/min	eGFR <30 mL/min	Dialysis
Sitagliptin	Predominant	100 mg	50 mg	25 mg	25 mg
Vildagliptin	Intermediate	100 mg	50 mg	50 mg	50 mg caution
Saxagliptin	Predominant	5 mg	2.5 mg	2.5 mg caution	2.5 mg caution
Linagliptin	Low	5 mg	5 mg	5 mg	?
Alogliptin	Predominant	12.5–25.0 mg	?	?	?
Exenatide	Predominant	5–10 µg/day	Caution	∅	∅
Liraglutide	No	0.6–1.8 mg/day	0.6–1.8 mg/day (caution)	∅	∅

TZDs

- Thiazolidinediones (TZDs) bind to the peroxisome proliferator-activated receptor-gamma (PPAR-γ) receptor and improves peripheral insulin sensitivity and suppresses hepatic gluconeogenesis.
- TZDs are wholly *metabolized in the liver*, and neither the parent drug nor its major metabolites are renally excreted.
- TZDs may ***promote edema and congestive heart failure*** via PPAR-γ-mediated stimulation of distal tubular sodium channels and sodium reabsorption,
  - but this risk may be irrelevant in oliguric and anuric dialysis patients.
- TZDs may also ***decrease bone formation and increase bone loss and fracture*** risk,
  - which may bear consequence in patients with underlying CKD-mineral bone disease.
- However, TZDs may also favorably impact health by **improving** lipid (e.g. HDL, triglyceride) and **adiponectin levels**; reducing visceral adiposity; ***decreasing inflammation*****; and *reducing muscle catabolism*** and protein-energy wasting.
- In the general population, observational data and meta-analyses suggest that TZD safety and effectiveness may be dependent on the specific agent used.
  - Studies of rosiglitazone have shown an increased risk of cardiovascular events,
  - Studies of pioglitazone have demonstrated a reduced risk of CVD morbidity and mortality

Usually dc TZD with Insulin Rx

October 9, 2019 - JCEM

Pioglitazone May Reduce Overall Mortality Risk in Patients With Type 2 Diabetes

- ***Pioglitazone in combination with insulin* therapy *reduces*** the **risk for mortality and non-cardiovascular death** in patients with type 2 diabetes,
  - The adjusted hazard ratio of hospitalized coronary artery disease, hospitalized stroke, and incident heart failure were not significantly different between pioglitazone users and nonusers.
  - Patient information was collected from the Longitudinal Health Insurance Database 2000
- The **all-cause mortality rate among pioglitazone users** was **15.02 per 1000** person-years. This was significantly lower than the **mortality rate among nonusers**, which was **30.26 per 1000** person years
  - This was primarily driven by ***differences in the rates of non-cardiovascular death*** for users and nonusers, which were 9.11 and 19.74 per 1000 person-years, respectively***. There was no significant difference in the rates of and risk for cardiovascular death or events between pioglitazone users and nonusers.***
- "Our study demonstrated that the combination of insulin and pioglitazone lowered the all-cause mortality risk," the researchers concluded. "Pioglitazone *might be* a beneficial complementary agent for insulin treatment. ***Additional studies are needed to establish its optimal application in real-world practice."***

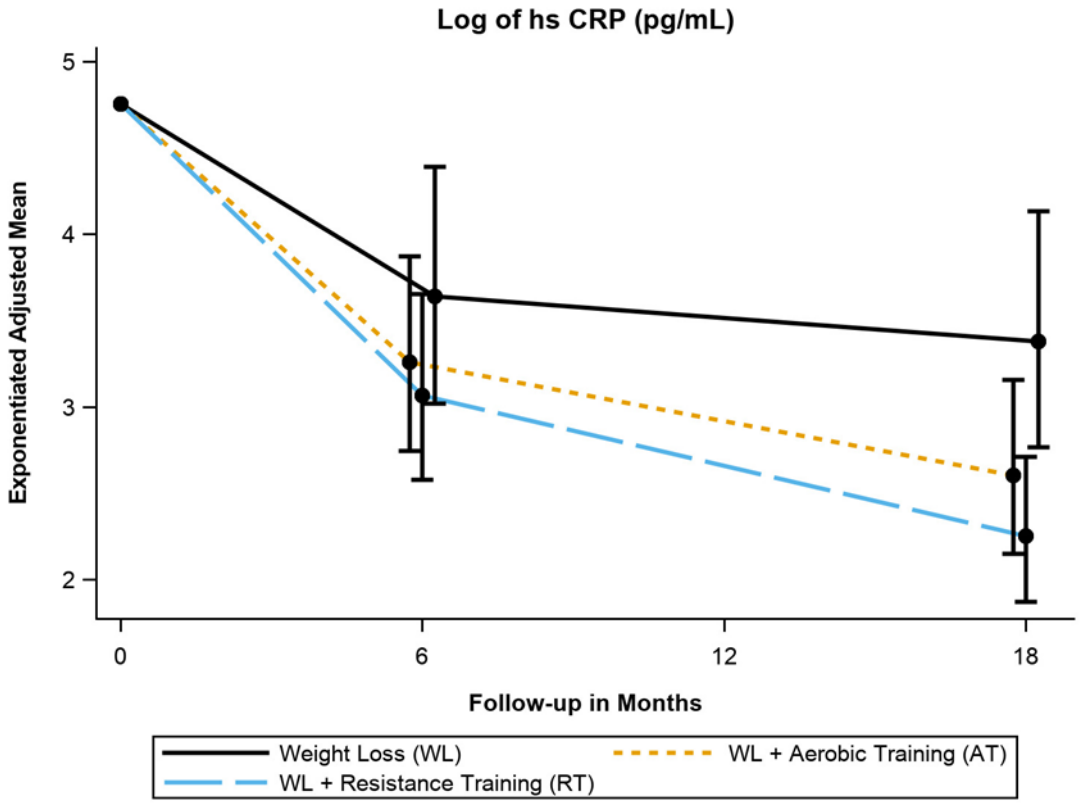
Muscle Matters

Dietary Weight Loss, Exercise, and Inflammation in Older Adults with Overweight or Obesity and Cardiometabolic Disease

W. Jack Rejeski et al Obesity: 05 November 2019

- *Chronic low-grade inflammation* is a consequence of aging and is associated with the *risk of developing* several age-associated chronic health conditions, such as ***ischemic heart disease***, ***diabetes, kidney disease, and Alzheimer disease***.
  - Welty et al. posited chronic inflammation **as a central mechanism underlying the pathophysiology of the metabolic syndrome (MetS),**
- **Body fat** is an active endocrine organ, and ***obesity is associated with increased levels of inflammation***,
  - Supported by the efficacy of weight loss in lowering biomarkers of inflammation
  - Chronic inflammation leads to anemia, fatigue, and muscle wasting, all of which encourage physical inactivity, contributing to a vicious cycle that feeds functional decline and chronic disease
- Not only does ***physical activity*** improve the magnitude of lost weight, but it ***also improves the inflammatory profile, particularly for CRP, especially for resistance training***

Dietary Weight Loss, Exercise, and Inflammation in Older Adults with Overweight or Obesity and Cardiometabolic Disease

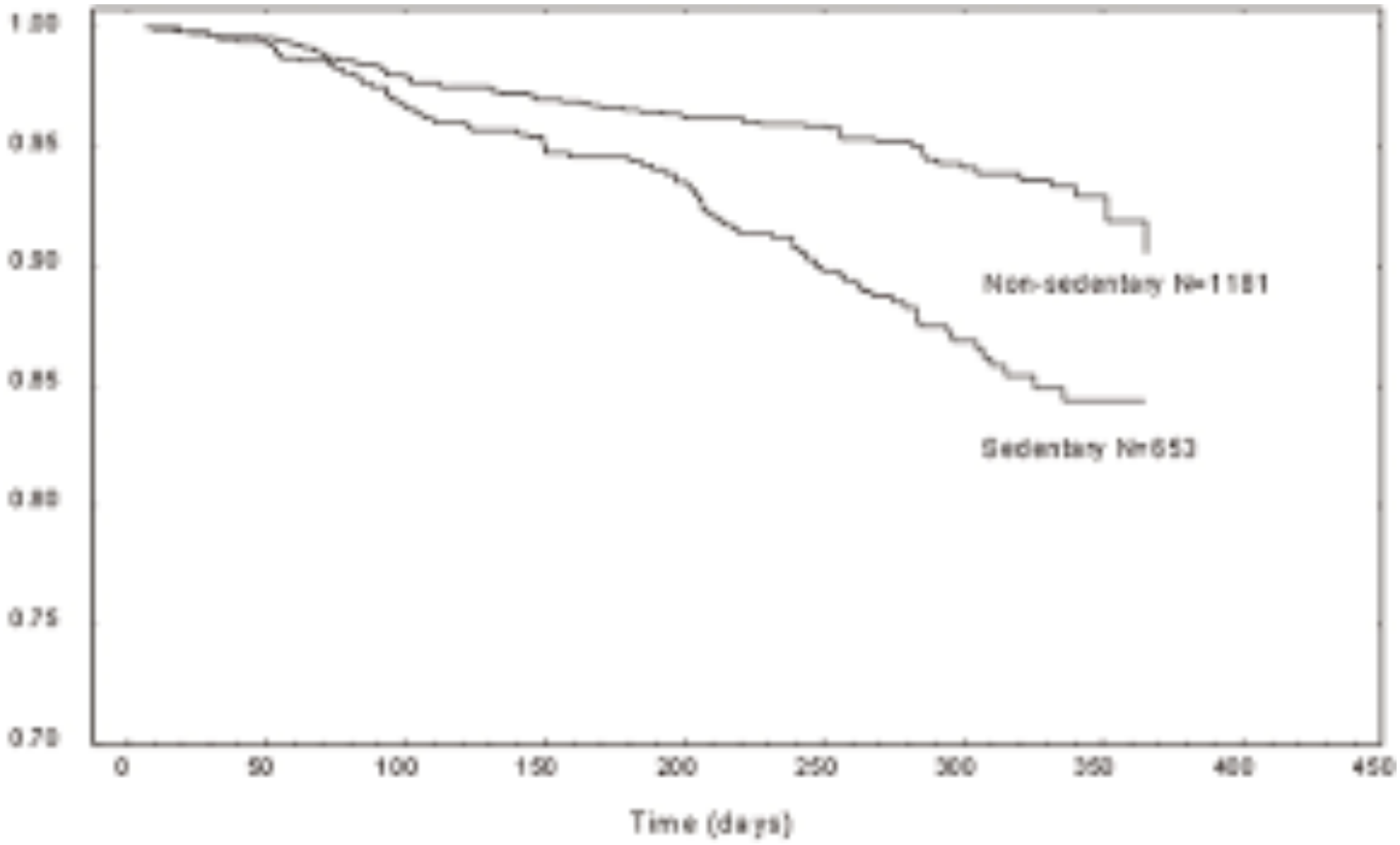


Obesity, Volume: 27, Issue: 11, Pages: 1805-1811, First published: 05 November 2019, DOI: (10.1002/oby.22600)

Dietary Weight Loss, Exercise, and Inflammation continued

- …increases **in IL-6 released by muscle** during contraction have an ***anti-inflammatory effect*** in *opposition to the* ***IL-6 released by visceral adiposity****, which is* ***proinflammatory***.
- Specifically, ***IL-6 from muscle*** increases *IL-10 and IL-1ra, both of which are anti-inflammatory*, and does so in the absence of increasing the proinflammatory cytokines tumor necrosis factor-α and IL-1β.
- IL-15, which increases with ***muscle hypertrophy,*** is known to play a role in the *lipolysis of liver fat*, and greater muscle mass is *protective against the accumulation of visceral fat*
- This latter point is particularly important given the role that ***increasing visceral fat and decreasing muscle mass play in chronic elevated inflammation with aging.***

Survival in Dialysis Patients: Sedentary vs Non-sedentary



END

Effect of Vitamin D and Omega-3 Fatty Acid Supplementation on Kidney Function in Patients With Type 2 Diabetes
JAMA: The Journal of the American Medical Association

- TAKE-HOME MESSAGE
- Adults with type 2 diabetes were randomized to receive vitamin D3 and omega-3 fatty acids, vitamin D3 and placebo, placebo and omega-3 fatty acids, or two placebos for 5 years to evaluate the association between vitamin D3 and omega-3 fatty acid supplementation and the development and progression of chronic kidney disease (CKD). There was no significant difference in the change in eGFR between those taking vitamin D3 and placebo and between those taking omega-3 fatty acids and placebo.
- CONCLUSIONS AND RELEVANCE
- Among adults with type 2 diabetes, supplementation with vitamin D3 or omega-3 fatty acids, compared with placebo, resulted in no significant difference in change in eGFR at 5 years. The findings do not support the use of vitamin D or omega-3 fatty acid supplementation for preserving kidney function in patients with type 2 diabetes.
    - The use of vitamin D or omega-3 fatty acid supplementation cannot be recommended for the preservation of kidney function among adults with type 2 diabetes.

Disturbances in Insulin–Glucose Metabolism in Patients With Advanced Renal Disease With and Without Diabetes

Marie-Noel Rahhal et al; JCEM, Vol 104, Issue 11, Nov 2019, Pages 4949–4966

- Use of insulin in patients with diabetes and advanced chronic kidney disease (CKD; stages 4 to 5) is challenging and shows great variability among individuals. We explored the mechanisms underlying this variability.
- Evidence Synthesis
- The evidence shows that in most patients the daily dose of insulin needs to be significantly reduced with a high degree of variability; in some the dose remains unchanged, and rarely it is increased.
- The premise that the marked reduction in insulin requirement is essentially attributable to decreased insulin clearance by kidneys leading to prolongation of its plasma half-life, elevated blood insulin concentration, and hypoglycemia is not entirely correct. Other factors including decreases in food intake, insulin secretion, insulin clearance by peripheral tissues, and renal gluconeogenesis play important roles. There is also heightened resistance to insulin due to metabolic acidosis, uremic toxins, inflammatory state, and vitamin D deficiency. Importantly, the magnitude of changes in each of these factors varies between individuals with the same degree of CKD.

- Conclusions
- In the presence of diabetes with advanced CKD, the insulin regimen should be individualized based on knowledge of the daily glucose patterns. The use of CGM is promising for safer glycemic control in patients with advanced CKD and diabetes and helps prevent extremes of hypoglycemia and hyperglycemia.