Vitamin D & PTH

Vitamin D & Type 2 DM

- Enhances insulion secretion
- Increases insulin release
- Promotes β-cell survival
- Reduces PTH
- Enhances insulin sensitivity
- RAS blockade
- Antiinflammatory

Harinarayan Hormones 13:163 2014

Vitamin D and β cell function/insulin secretion

Direct Actions

$1,25(OH)_2D_3$ + VDR

↓ RXR

VDR + RXR

↓

Vitamin D response elements (VDRE)

↓

Enhances transcriptional activation of insulin gene

↓

↑ Insulin Synthesis

Indirect Actions

1. Calcium flux through the β-cells and intracellular calcium Ca^+
2. Regulates calbindin
3. "Calcium Paradox"

Other Actions

Anti-apoptotic effect by

1. Modulating the generation and effects of cytokine
2. Down-regulating Fas-related pathways
3. Via calbindin by its ability to buffer intracellular calcium

Vitamin D and insulin sensitivity

Direct Actions

1. Stimulates expression of INS-R
2. Activation of PPAR – δ (transcription factor) – implicated in fatty acid metabolism in skeletal muscles and adipose tissues

Indirect Actions

1. Regulating extracellular calcium flux though the cells
2. Anti-apoptotic effect (by modulating through interaction of nuclear K-β (NF-κβ) and effects on cytokines
3. Through RAAS

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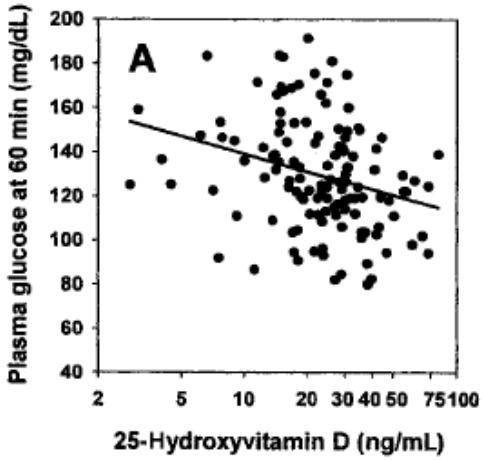
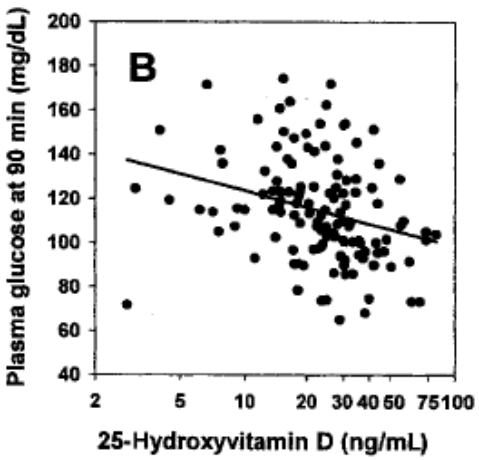
Vit D & T2DM: Trials

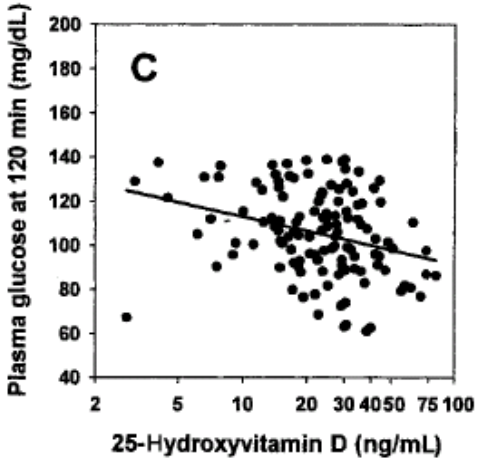
Author	Trial	Pts.	Rx	Time (wks)	No. (A/C)	Results
Gedik 86	C	NonDM	Vit D 50 µg/d	26	4/10	IS↑ II↑
Inomata 86	C	DM	1□ 2 µg/d	3	7/7	IS↑
Boucher 95	NC	DM	Vit D 2,500 µg once i.m.	10	22/0	IS↑
Borissova	C	DM	Vit D 35µg/d	4	10/17	IS↑
Von Hurst 10	RCT	IR	Vit D 100µg/d	26	42/39	IS↑ IR↓
Sabherwal 10	NC	DM	Target [25-OHD] >50 nM		52/0	HbA1c↓ -0.7%
Nikoyeh 11	RCT	DM	Vit D 12.5 µg/d	12	60/30	IR↓ IS↑
Mitri	RCT	IR	Vit D 50 µg/d	16	46/45	IS↑ DI↑
Eftekari	RCT	DM	1□ 0.5 µg/d	12	35/35	IS↑

C: controlled. NC: no control. RCT: randomized controlled trial
IR: Insulin resistance. IS: Insulin sensitivity DI: Disposal index
II: insulinogenic index

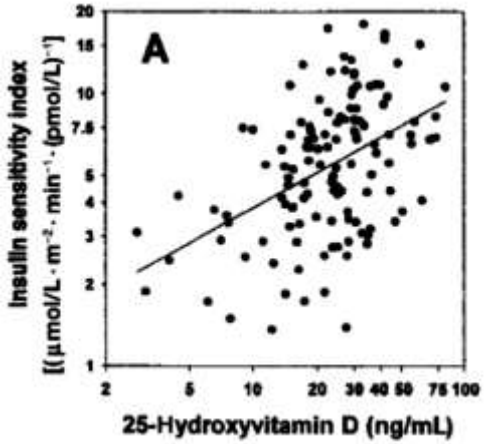
Vitamin D and the Metabolic Syndrome







Oral Glucose Tolerance Test

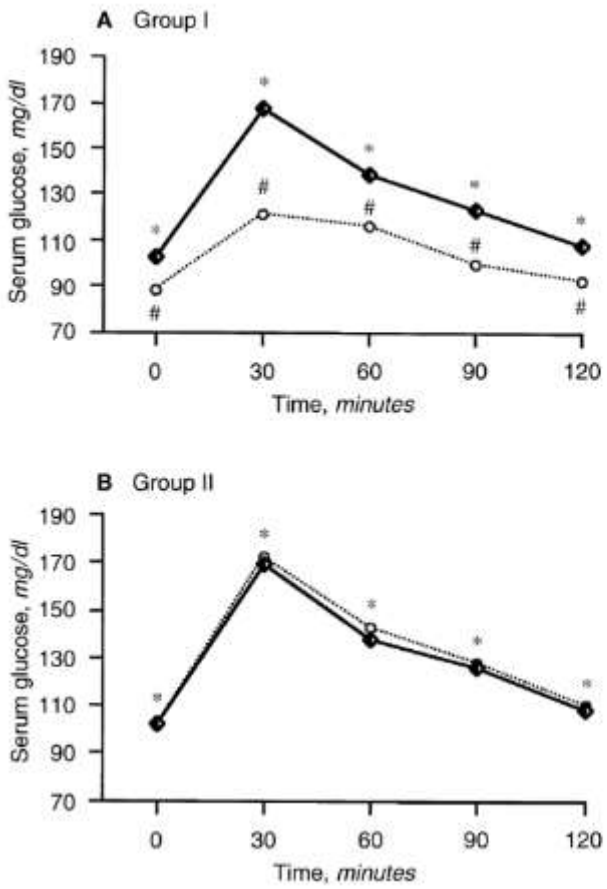


Hyperglycæmic
Insulin clamp

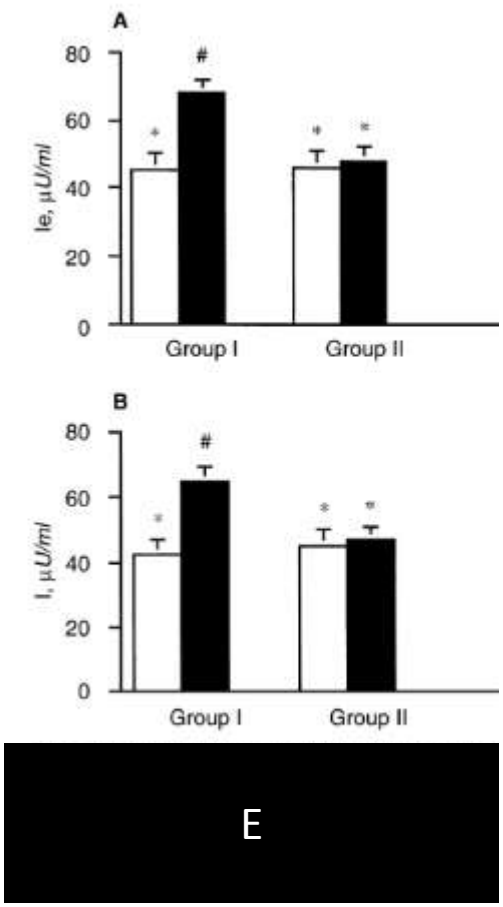
126 healthy individuals with noraml OGTT

Chiu Am J Clin Nutr 79,820 2004

1,25-Vitamin D improves Insulin Sensitivity



Oral glucose tolerance test
Before: ◊ and after: o



16 Insulin resistant
HD patients

PTH 798 pg/ml
did not change during study

RCT
1.8 µg 1,25-vitamin D
X3/week for 4 weeks
vs. Control (group 2)

Triglycerides 198→148 mg/dL

Euglycaemic clamp study
A: Insulin stimulated glucose metabolism
B: Insulin concentration

Mak KI 53,1353 1998

Parathyroidectomy improves insulin secretion in uraemic dogs

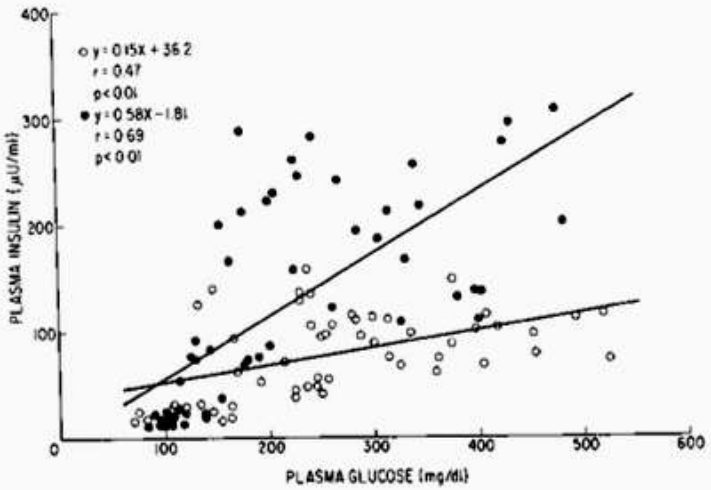


Figure 5. The relationship between plasma insulin and glucose concentrations observed during intravenous glucose tolerance tests performed in NPX (○) and NPX-PTX (●).

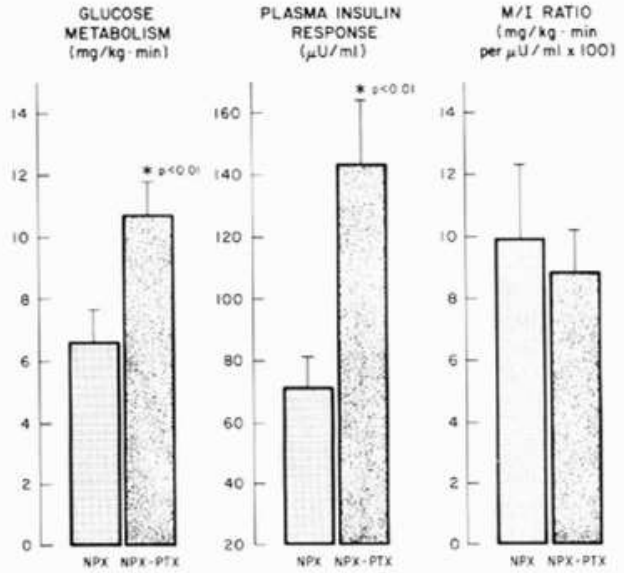
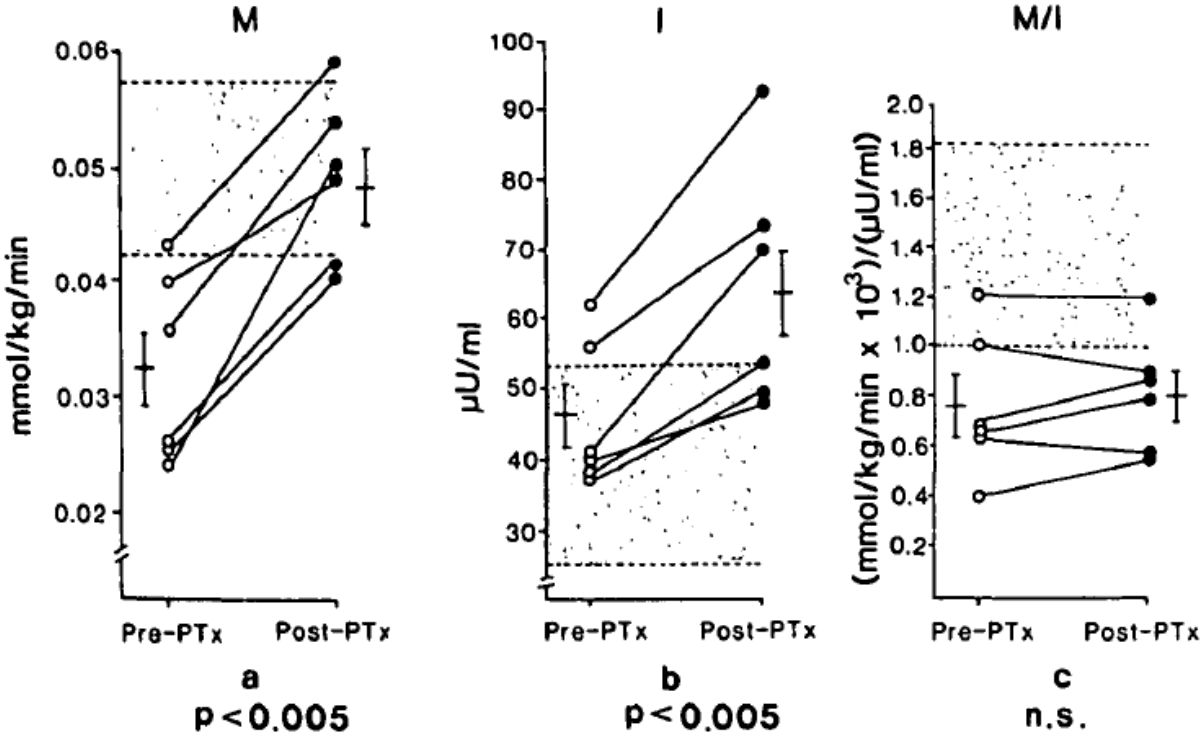


Figure 6. Glucose metabolism, total insulin response, and M/I ratio observed during the hyperglycemic clamp in NPX and NPX-PTX dogs. Each column represents the mean of data from six NPX and seven NPX-PTX dogs. The brackets denote 1 SE. Star indicates significant difference from NPX with $P < 0.01$.

Akmal J Clin Invest 75:1037 1985

Parathyroidectomy improves Insulin Secretion in HD



6 insulin-resistant HD pts.

Hyperglycaemic clamp study

PTH 3500 →210 ng/l

Glucose Metabolic Rate

Insulin levels (β-cell response to glucose↑)

Tissue sensitivity to insulin

Mak J Clin Endocrin Metab 60:229 1985

Type 2 DM Treatment in CKD

- Insulin
- Biguanides
- Sulphonylureas
- Meglitinides (”Glitinides”)
- Thiazolidinediones (TZD) (”Glitazones”)
- GLP-1 Antagonists
- DPP-4 Inhibitors (”Gliptins”)

American Diabetes Association – European Association for the Study of Diabetes (ADA/EASD) Guidelines

ADA/EASD 2012 Position Statement: 2-Drug Combinations

Metformin +	SU*	TZD	DPP-4 Inhibitor	GLP-1 RA	Insulin (usually basal)
Efficacy (↓ HbA1c)	High	High	Intermediate	High	Highest
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	High risk
Weight	Gain	Gain	Neutral	Loss	Gain
Major side effect	Hypoglycemia	Edema, CHF, fractures	Rare	GI	Hypoglycemia
Costs	Low	High	High	High	Variable
If needed to reach individualized HbA1c target after ~ 3 months, proceed to 3-drug combination (order not meant to denote any specific preference)					

Appropriate class selection is based on specific patient requirements.

*Consider glinides as alternative

GI = gastrointestinal; GLP-1RA = glucagon-like peptide-1 receptor agonist

LIPID & METABOLIC

Adapted from Inzucchi SE, et al. *Diabetologia*. 2012;55(6):1577-1596.

Medscape EDUCATION

Inzucchi Diabetologia 55,1577 2012

Anti-Diabetic Drugs

V • T • E	Oral anti-diabetic drugs and Insulin analogs (A10)			
Insulin	Sensitizers	Biguanides		Metformin[#] · Buformin[‡] · Phenformin[‡]
		TZDs/"glitazones" (PPAR)		Pioglitazone · Rivoglitazone[†] · Rosiglitazone · Troglitazone[‡]
		Dual PPAR agonists		Aleglitazar[†] · Muraglitazar[§] · Saroglitazar · Tesaglitazar[§]
	Secretagogues	K+ ATP	Sulfonylureas	*1st generation*: Acetohexamide · Carbutamide · Chlorpropamide · Metahexamide · Tolbutamide · Tolazamide *2nd generation*: Glibenclamide (Glyburide)[#] Glibornuride · Glipizide · Gliquidone · Glisoxepide · Glyclopyramide · Glimepiride · Gliclazide
			Meglitinides/"glinides"	Nateglinide · Repaglinide · Mitiglinide
		GLP-1 agonists		Exenatide · Liraglutide · Taspoglutide[†] · Albiglutide[†] · Lixisenatide
		DPP-4 inhibitors		Alogliptin · Gemigliptin · Linagliptin · Saxagliptin · Sitagliptin · Vildagliptin
		GPR40 Free fatty acid receptor 1		Fasiglifam[†]
	Analogs/other insulins	*fast-acting* (Insulin lispro · Insulin aspart · Insulin glulisine) · *short-acting* (Regular insulin) · *long-acting* (Insulin glargine · Insulin detemir · NPH insulin) · *ultra-long-acting* (Insulin degludec[†]) · *inhalable* Exubera[‡]		
Other	Alpha-glucosidase inhibitors	Acarbose · Miglitol · Voglibose		
	Amylin analog	Pramlintide		
	SGLT2 inhibitors	Canagliflozin · **Dapagliflozin** · Empagliflozin[†] · Remogliflozin[§] · Sergliflozin[§] · Tofogliflozin[†]		
	Other	Benfluorex[‡] · Tolrestat[‡]		
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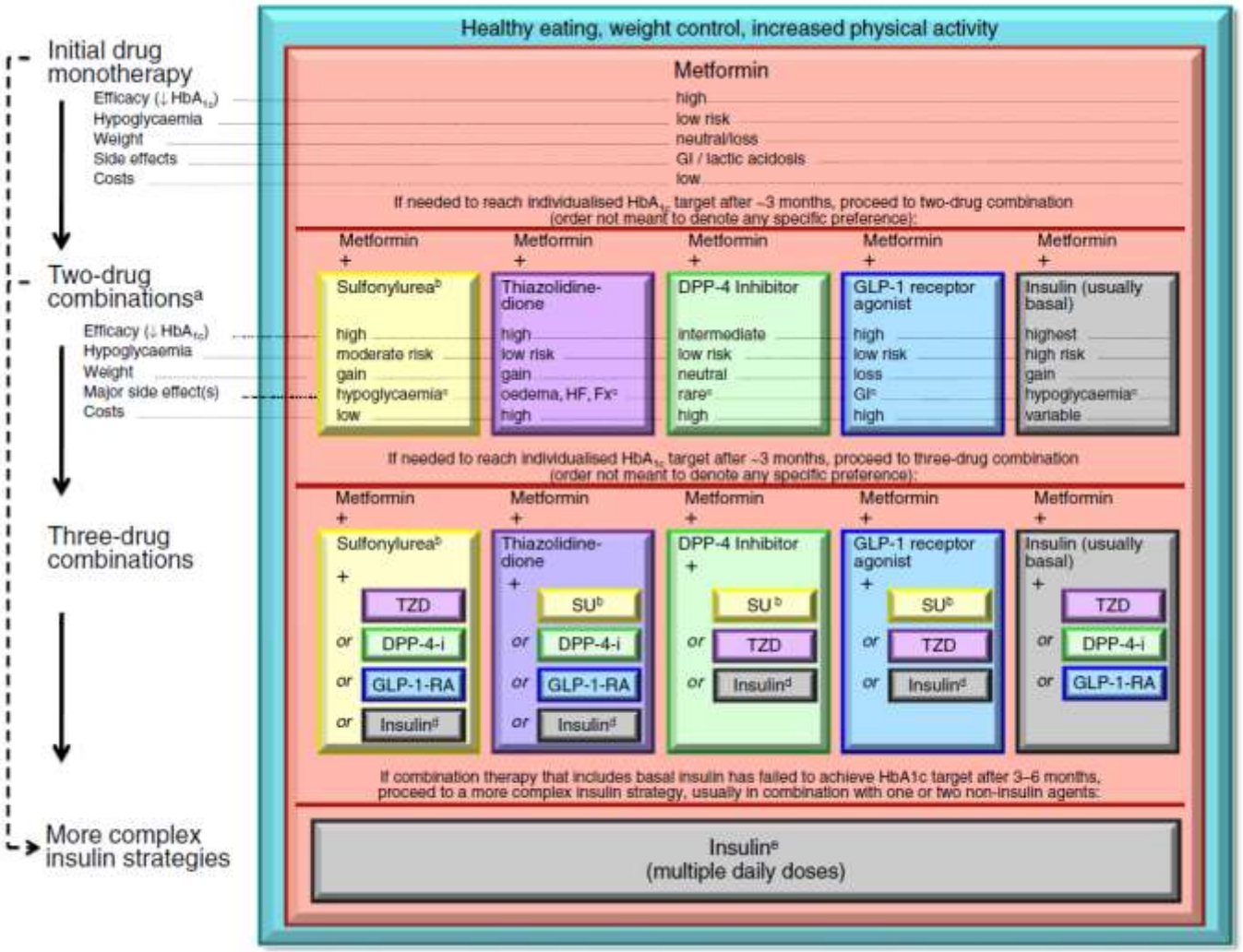
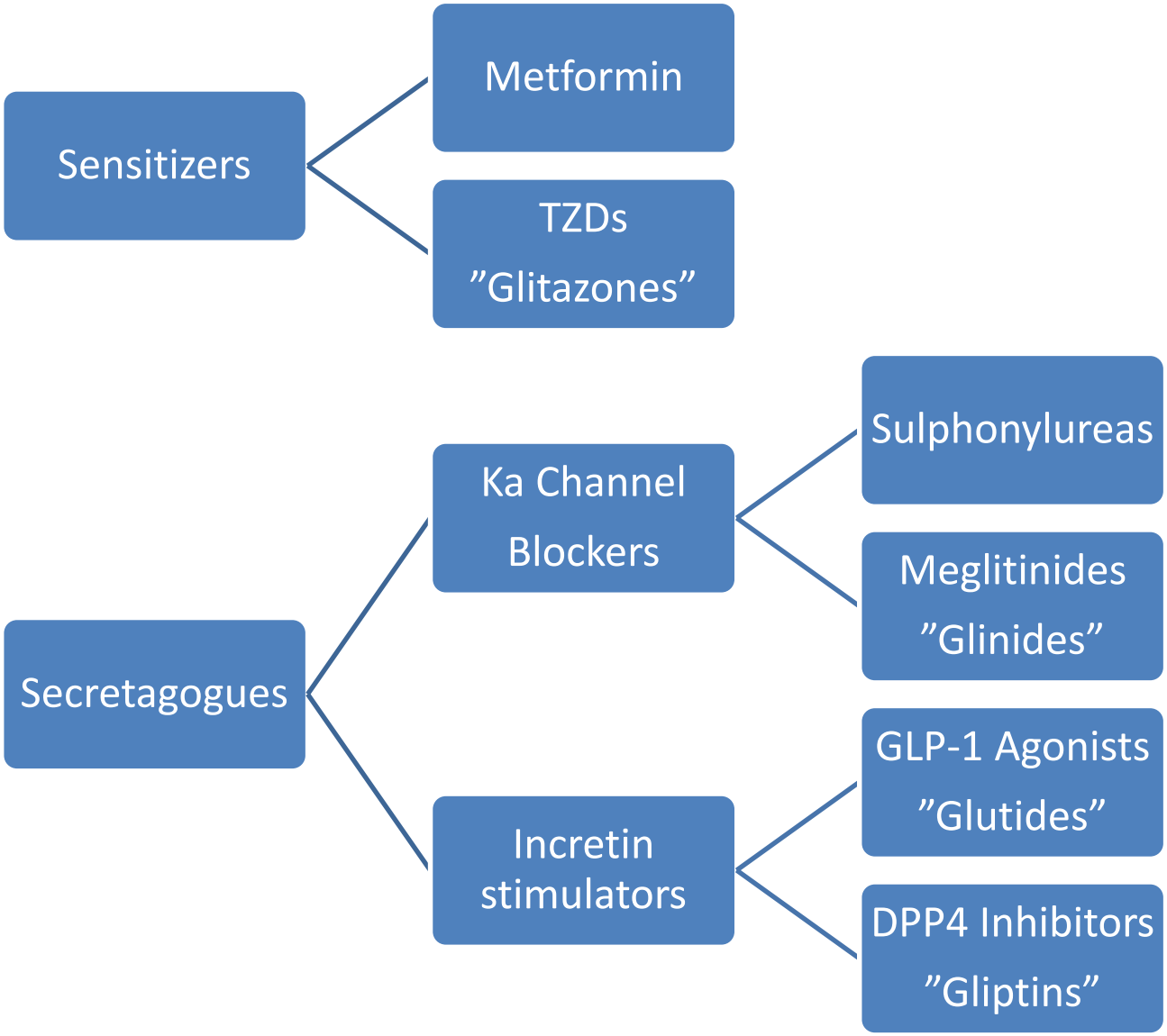
ADA/EASD Guidelines



Inzucchi Diabetologia 55:1577 2012



(SGLT2 Inhibitors → Glucosuria & Dehydration)

Treatment Problems in CKD

Rx Group	Problem
Metformin	Lactic Acidosis?
Sulphonylureas	Hypoglycaemia, weight gain
Meglitinides	Nausea, diarrhea, hypoglycemia
Thiazolidinediones (”Glitazones”) PPARγ agonists	Oedema, Heart Failure
DPP-4 inhibitors and incretin mimetics	Limited experience
Insulin	Hypoglycaemia, weight gain

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Holstein 2010	All	CKD/Normal with Hypoglycaemia	139	Retro-spective	NonCKD	73% of cases had CKD 27% Rx with interacting drugs -Clopidogrel -Phenprocoumon -Diclofenac -Phenytoin -Fluvastatin

CKD: Chronic Kidney Disease
NODAT: New onset diabetes after transploantation
FBG: Fasting blood glucose

Meglitinides

- Ka-channel blockers (different receptor than SUs)
- Repaglinide & Netaglinide
- Lower rate of hypoglycaemia than SUs?
- More expensive than SUs
- Increase insulin secretion $\rightarrow$ Burnout
- Repaglinide: dose reduction in CKD

Meglitinides

- Repaglinide (Novonorm®) & Netaglinide (Stalix®)
- Ka-channel blockers
- Increase insulin secretion
- Drug of choice in NODAT? (new onset diabetes after transplantation)

Davidson Diab Care 27:805 2004

Turk AJ Transpl 6:842 2007

Metiglinides in CKD

	Drug	Patients	No. (A/C)	Type	Control	Result
Türk 2006	Repaglinide	NODAT	23/21	Control	Rosi-glitazone	HbA1c 7.6→5.8% 39% switched to insulin Similar to rosiglitazone 8% nausea/diarrhea
Voytovich 2007	Nateglinide	NODAT	14/0	Prospective	No	2-week Rx 2-hr BG 10.5→7.6 Late insulin response↑
Sun 2009	Glinides	HD	68/34	Control	Insulin	34% risk of hypoglycaemia Compared to insulin
Abe	Mitiglinide	HD	31	Prospective	No	HbA1c 7.0→5.9% FBG 9.4→8.3 mM No side effects

CKD: Chronic Kidney Disease
NODAT: New onset diabetes after transploantation
FBG: Fasting blood glucose
A/C: Active/controls

Thiazolidinediones (TZDs) ”Glitazones”

- Peroxisome proliferator-activated (PPAR) γ receptor activators
- Reduce insulin resistance
- Antiproliferative
- Antiinflammatory
- Leptin ↓→Appetite ↑

- Registration difficulties (heart failure, hepatitis, bladder cancer)

Glitazones in CKD

Author	Pts.	No	Drug	Time (mths)	Factor	Change	Side Effects	Other
Abe 2008	HD	31	Pioglitazone	6	Hb A1c	-1.1***	No	Triglyc↓ BP↓
Luther 2004	RT	10	Pioglitazone	8	Hb A1c	-1.3*	No	
Abe 2010	HD	63	Pioglitazone	21	Hb A1c	-0.6***	No	CRP↓ Adiponectin↓
Luther 2004	RT	10	Pioglitazone	8	Hb A1c	-1.3*	No	
Agarwal 2005	CKD	301	Rosiglitazone	6	Hb A1c	-1.1**	No	
Akcay 2009	PD	24	Rosiglitazone	12	Hb A1c	-0.5***	No	Echocardiography unchanged
Van Hooland 2009	PD	12	Rosiglitazone	1			Oedema	Peritoneal transport↑ BP↓
Chiang 2007	HD	78	Rosiglitazone	15	Hb A1c	-1.5**	No	
Pietruck	RT	21	Rosiglitazone	2	Hb A1c	-0.4?	Oedema	BP↓
Villanueva 2005	RT	8	Rosiglitazone	12	Insulin Rx	-75% pts.	Oedema	
Voytovitch 2005	RT	10	Rosiglitazone	1	Glucose	-0.6 mmol/l**	No	Endothelial function↑
Wong 2005	PD	52	Rosiglitazone	6	Insulin Rx	-6 IU/d***		
Mohideen	HD	12	Troglitazone	6	Insulin Rx	-13 IU/d*	No	
Kurian 2008	RT	46	TZD	16	Hb A1c	-0.5	No	
Manley 2003	HD	40	TZD	3	Hb A1c	-0.6	No	BP↓

*:p<0.05
**:p<0.01
***:p<0.001

Glitazones and Mortality

Author	Pts.	No	Drug	Time (mths)	Factor	Change
Brunelli 2009	CKD	91	TZD	12	Death risk	-Insulin 0.53* +Insulin 0.82
Ramirez 2009	HD	2393	Rosiglitazone	13	CV Death Risk	1.59**
Schneider 2008	CKD	597	Pioglitazone	36	Death + AMI + Stroke	0.60*

DPP4 Inhibitors in CKD
"Gliptins"

Author	Pts.	No	Drug	Time (mths)	Factor	Subsets	Change	Side Effects
Chan 2008	CKD	91	Sitagliptin	12	Hb A1c		-0.8?	No
Lukashevich 2011	CKD	525	Vildagliptin	6	Hb A1c	GFR 30-50 GFR <30	-0.5*** -0.6***	No
Nowicki 2011	CKD/ ESRD	170	Saxagliptin	12	Hb A1c	GFR 30-50 (90 pts.) GFR <30 (41) ESRD (39)	-0.7*** -0.3? -0.1	No
Lane 2011	NODAT	15	Sitagliptin	3	Hb A1c		-0.5**	No

*:p<0.05
**:p<0.01
***:p<0.001

GLP antagonists & CKD

Author	Pts.	No. (A/C)	Drug	Time (mths)	Control	Change	Other Effects
Davidsen 2011	CKD	63/13	Litaguride	6	Placebo & normal renal function	-1.3*	Weight↓ BP↓ Increased risk of nausea (19%) & hypoglycaemia (17%) vs. Normals

*:$p<0.05$

TZDs, GLP-A & DPP4-I

Drug Name	Commercial Name	Typical Side Effects	Dose reduction in CKD
Thiozolidinediones (TZD) (oral) PPARγ Agonists			
Pioglitazone	Actos	Oedema, hypoglycaemia, weight↑, GI, (bladder cancer)	No
(Rosiglitazone)		Withdrawn from many markets (CV toxicity?)	No
GLP Analogues (s.c.)			
Exanatide	Byetta	Hypoglycaemia, Nausea, GI Symptoms, Headache, (pancreatitis, AKI)	No (Caution/ No evidence)
Liraglutide	Victoza		
Lixisenatide	Lyxumia		
DPP4 Inhibitors (oral)			
Sitagliptin	Januvia	Hypoglycaemia, Nausea, GI Symptoms, Oedema, Headache Rash (pancreatitis)	Yes
Vildagliptin	Galvus		Yes
Saxagliptin	Onglyza		Yes
Linagliptin	Trajenta		No
Combination with metformin	Eucreas, Janumet, Jentadueto, Komboglyze		To be avoided

Conclusions

- ESRD is a prediabetic condition
- Hb A1c is problematic in CKD
- Unambitious target in ESRD: <8.5%
- Metformin is not contraindicated in CKD
- Choice of other non-insulin drugs determined mainly by price & side effects

Conclusions

- ESRD is a prediabetic condition
- Unambitious target in ESRD: <8.5%
- Metformin first choice
- Choice of second non-insulin drugs determined mainly by price & side effects
- My personal choices:
  - SUs: Glipizide (Mindiab®), gliquidone (Glurenorm®)
  - Glitazones: Pioglitazone (Actos®)
  - Gliptins: Linagliptin (Trajenta®)
  - GLP-1 Analogues: no
  - SGLT2 Inhibitors: no

Modern Guidelines Methodology

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

randomised controlled trials. The relevance to parachute use is that individuals jumping from aircraft without the help of a parachute are likely to have a high prevalence of pre-existing psychiatric morbidity. Individuals who use parachutes are likely to have less psychiatric morbidity and may also differ in key demographic factors, such as income and cigarette use. It follows, therefore, that the apparent protective effect of parachutes may be merely an example of the "healthy cohort" effect. Observational studies typically use mul-

Results We were unable to identify any randomised controlled trials of parachute intervention.
Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

Contributors: GCSS had the original idea. JPP tried to talk him out of it. JPP did the first literature search but GCSS lost it. GCSS drafted the manuscript but JPP deleted all the best jokes. GCSS is the guarantor, and JPP says it serves him right.

BMJ 327:1459 2003

PICO Studies

P	**P**atient, Population, or Problem	How would I describe a group of patients similar to mine?
I	**I**ntervention, Prognostic Factor, or Exposure	Which main intervention, prognostic factor, or exposure am I considering?
C	**C**omparison or Intervention (if appropriate)	What is the main alternative to compare with the intervention?
O	**O**utcome you would like to measure or achieve	What can I hope to accomplish, measure, improve, or affect?
	What type of question are you asking?	Diagnosis, Etiology/Harm, Therapy, Prognosis, Prevention
	Type of study you want to find	What would be the best study design/methodology?

ERBP DM ”P”:
Patients with CKD 3-5 and Diabetes Mellitus

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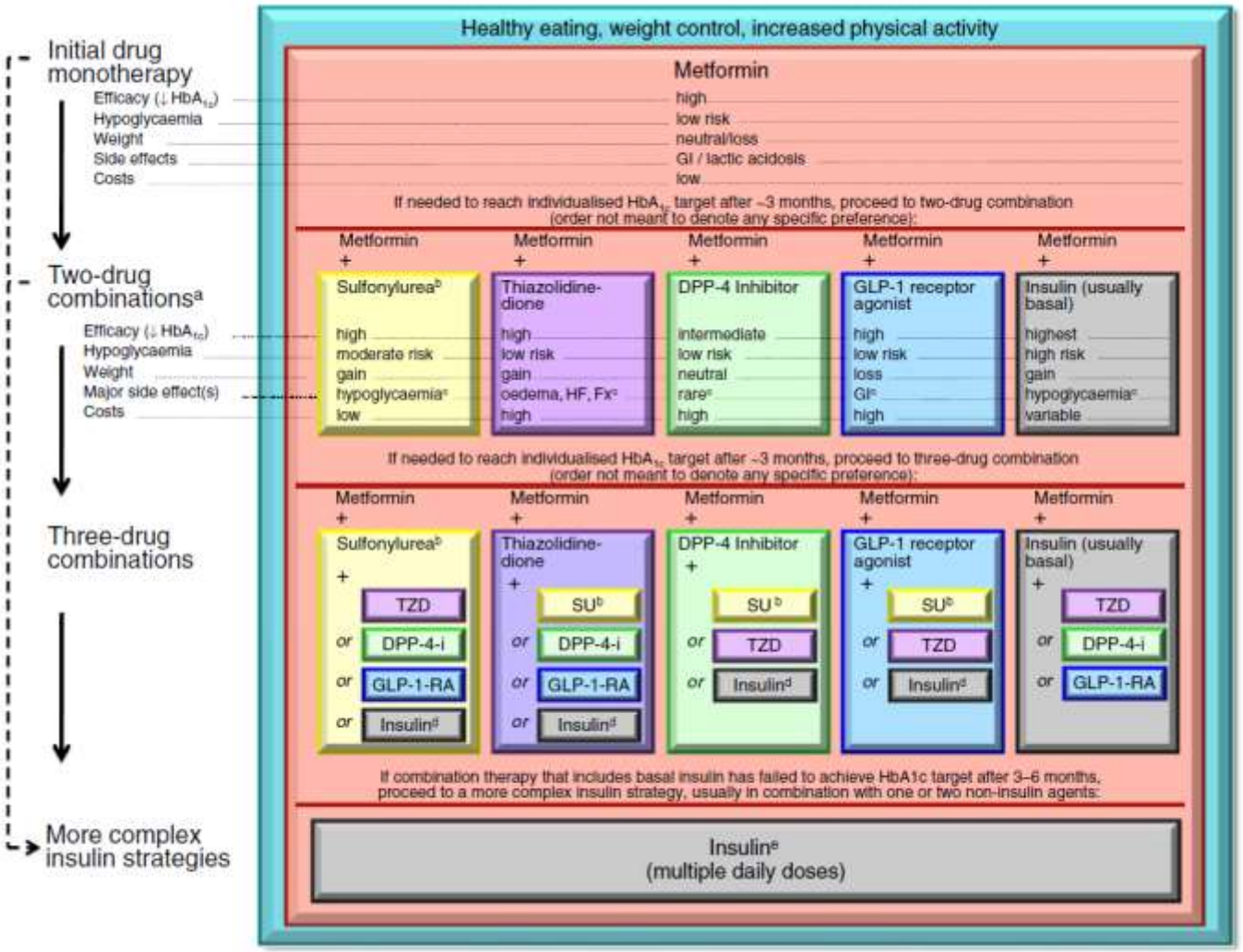
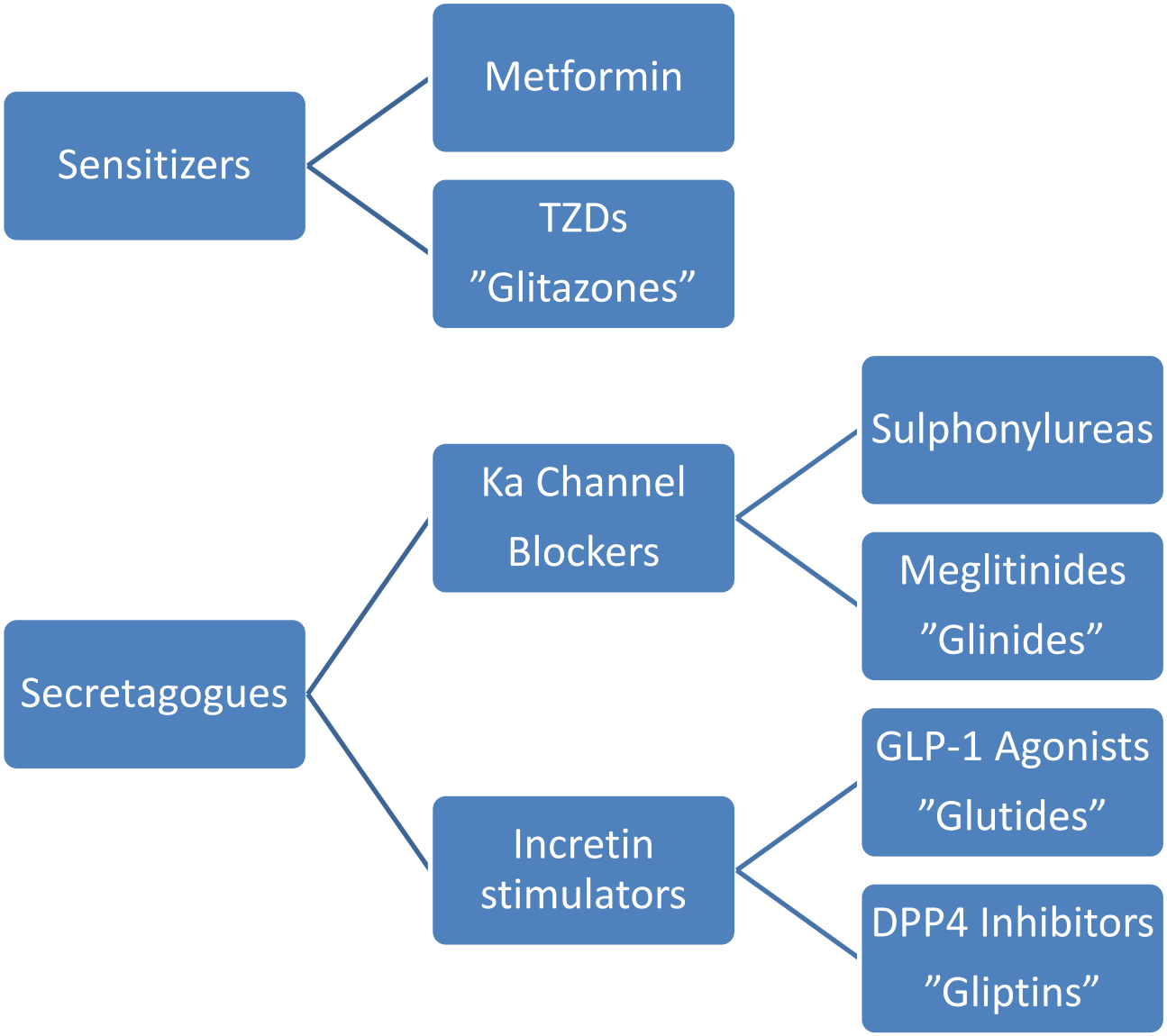


Inzucchi Diabetologia 55:1577 2012



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Abe	Mitiglinide	HD	31	Prospective	No	HbA1c 7.0→5.9% FBG 9.4→8.3 mM No side effects

CKD: Chronic Kidney Disease
NODAT: New onset diabetes after transploantation
FBG: Fasting blood glucose
A/C: Active/controls

Thiazolidinediones (TZDs) ”Glitazones”

- Peroxisome proliferator-activated (PPAR) γ receptor activators
- Reduce insulin resistance
- Antiproliferative
- Antiinflammatory
- Leptin ↓→Appetite ↑

- Registration difficulties (heart failure, hepatitis, bladder cancer)

Glitazones in CKD

Author	Pts.	No	Drug	Time (mths)	Factor	Change	Side Effects	Other
Abe 2008	HD	31	Pioglitazone	6	Hb A1c	-1.1***	No	Triglyc↓ BP↓
Luther 2004	RT	10	Pioglitazone	8	Hb A1c	-1.3*	No	
Abe 2010	HD	63	Pioglitazone	21	Hb A1c	-0.6***	No	CRP↓ Adiponectin↓
Luther 2004	RT	10	Pioglitazone	8	Hb A1c	-1.3*	No	
Agarwal 2005	CKD	301	Rosiglitazone	6	Hb A1c	-1.1**	No	
Akcay 2009	PD	24	Rosiglitazone	12	Hb A1c	-0.5***	No	Echocardiography unchanged
Van Hooland 2009	PD	12	Rosiglitazone	1			Oedema	Peritoneal transport↑ BP↓
Chiang 2007	HD	78	Rosiglitazone	15	Hb A1c	-1.5**	No	
Pietruck	RT	21	Rosiglitazone	2	Hb A1c	-0.4?	Oedema	BP↓
Villanueva 2005	RT	8	Rosiglitazone	12	Insulin Rx	-75% pts.	Oedema	
Voytovitch 2005	RT	10	Rosiglitazone	1	Glucose	-0.6 mmol/l**	No	Endothelial function↑
Wong 2005	PD	52	Rosiglitazone	6	Insulin Rx	-6 IU/d***		
Mohideen	HD	12	Troglitazone	6	Insulin Rx	-13 IU/d*	No	
Kurian 2008	RT	46	TZD	16	Hb A1c	-0.5	No	
Manley 2003	HD	40	TZD	3	Hb A1c	-0.6	No	BP↓

*:p<0.05
**:p<0.01
***:p<0.001

Glitazones and Mortality

Author	Pts.	No	Drug	Time (mths)	Factor	Change
Brunelli 2009	CKD	91	TZD	12	Death risk	-Insulin 0.53* +Insulin 0.82
Ramirez 2009	HD	2393	Rosiglitazone	13	CV Death Risk	1.59**
Schneider 2008	CKD	597	Pioglitazone	36	Death + AMI + Stroke	0.60*

DPP4 Inhibitors in CKD
"Gliptins"

Author	Pts.	No	Drug	Time (mths)	Factor	Subsets	Change	Side Effects
Chan 2008	CKD	91	Sitagliptin	12	Hb A1c		-0.8?	No
Lukashevich 2011	CKD	525	Vildagliptin	6	Hb A1c	GFR 30-50 GFR <30	-0.5*** -0.6***	No
Nowicki 2011	CKD/ ESRD	170	Saxagliptin	12	Hb A1c	GFR 30-50 (90 pts.) GFR <30 (41) ESRD (39)	-0.7*** -0.3? -0.1	No
Lane 2011	NODAT	15	Sitagliptin	3	Hb A1c		-0.5**	No

*:p<0.05
**:p<0.01
***:p<0.001

GLP antagonists & CKD

Author	Pts.	No. (A/C)	Drug	Time (mths)	Control	Change	Other Effects
Davidsen 2011	CKD	63/13	Litaguride	6	Placebo & normal renal function	-1.3*	Weight↓ BP↓ Increased risk of nausea (19%) & hypoglycaemia (17%) vs. Normals

*:$p<0.05$

TZDs, GLP-A & DPP4-I

Drug Name	Commercial Name	Typical Side Effects	Dose reduction in CKD
Thiozolidinediones (TZD) (oral) PPARγ Agonists			
Pioglitazone	Actos	Oedema, hypoglycaemia, weight↑, GI, (bladder cancer)	No
(Rosiglitazone)		Withdrawn from many markets (CV toxicity?)	No
GLP Analogues (s.c.)			
Exanatide	Byetta	Hypoglycaemia, Nausea, GI Symptoms, Headache, (pancreatitis, AKI)	No (Caution/ No evidence)
Liraglutide	Victoza		
Lixisenatide	Lyxumia		
DPP4 Inhibitors (oral)			
Sitagliptin	Januvia	Hypoglycaemia, Nausea, GI Symptoms, Oedema, Headache Rash (pancreatitis)	Yes
Vildagliptin	Galvus		Yes
Saxagliptin	Onglyza		Yes
Linagliptin	Trajenta		No
Combination with metformin	Eucreas, Janumet, Jentadueto, Komboglyze		To be avoided

Conclusions

- ESRD is a prediabetic condition
- Hb A1c is problematic in CKD
- Unambitious target in ESRD: <8.5%
- Metformin is not contraindicated in CKD
- Choice of other non-insulin drugs determined mainly by price & side effects

Conclusions

- ESRD is a prediabetic condition
- Unambitious target in ESRD: <8.5%
- Metformin first choice
- Choice of second non-insulin drugs determined mainly by price & side effects
- My personal choices:
  - SUs: Glipizide (Mindiab®), gliquidone (Glurenorm®)
  - Glitazones: Pioglitazone (Actos®)
  - Gliptins: Linagliptin (Trajenta®)
  - GLP-1 Analogues: no
  - SGLT2 Inhibitors: no