The pathophysiology of the dysglycaemia of diabetes: A personalised journey from insulin and glucose sensitivities and beta cell function to the incretins – familial vs acquired?

Frank P Alford

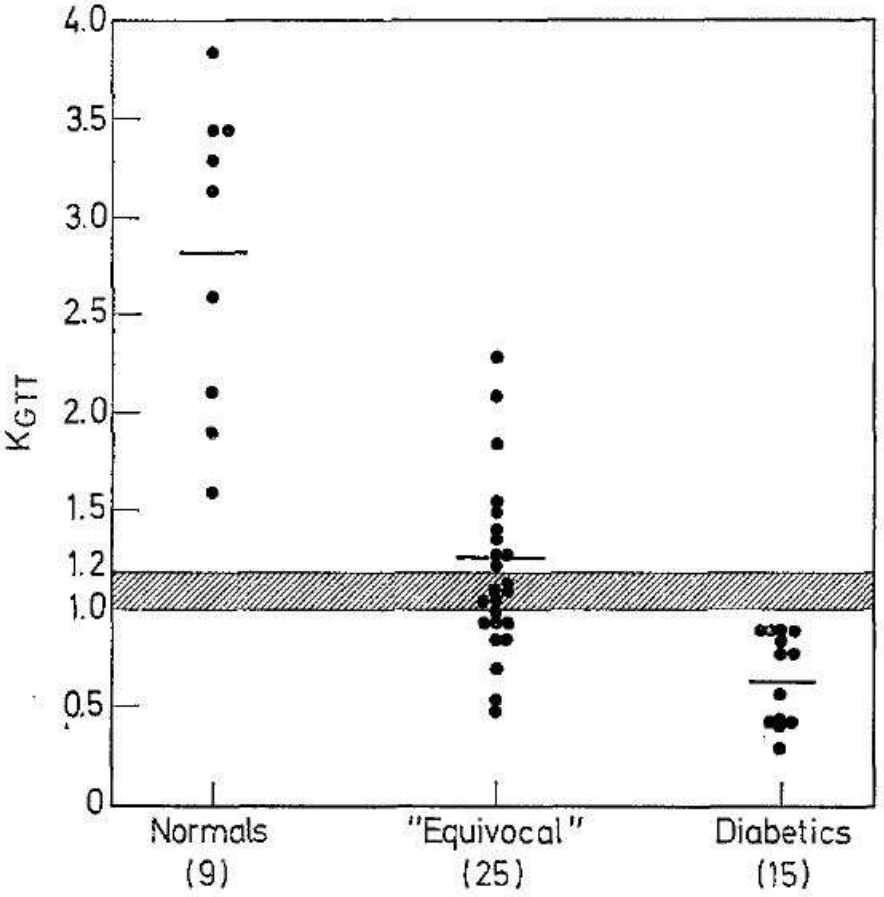
Outline of Talk

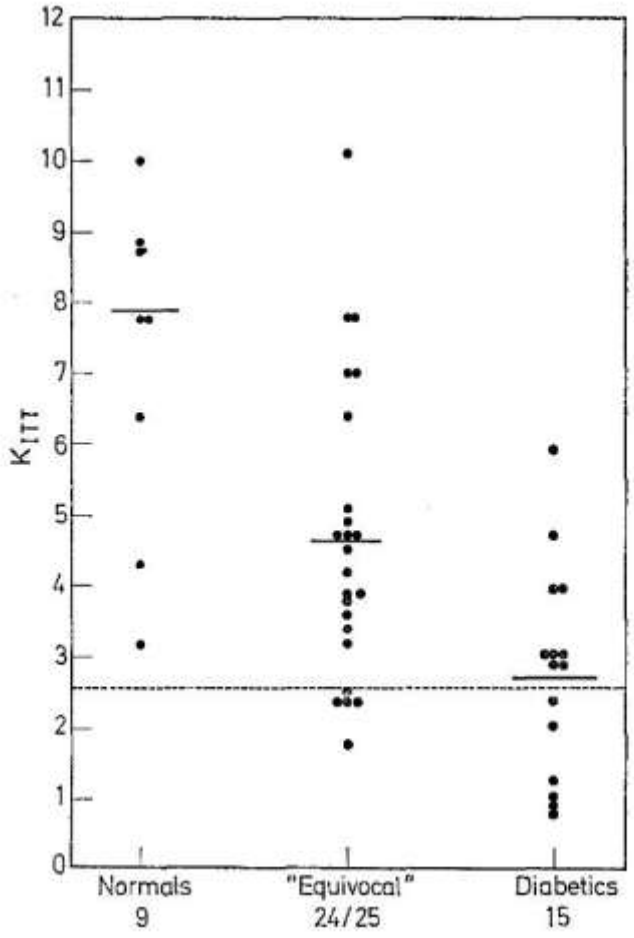
- The beginning
  - Insulin sensitivity
  - Beta cell function
  - Glucose-mediated glucose disposal
  - Alpha cell function
  - Hepatic "insulin resistance"
- Insulin sensitivity + glucose sensitivity
  - Metabolic pathways

Outline of talk

- Regulation of HGP
  - Primary vs peripheral (SkM)
- Metabolic impact of AMP-K activation
- Non-diabetic relative and twin studies
  - A glimpse of the future?
- Incretin hormone actions and the beta cell
  - Primary or secondary?
- Conclusions

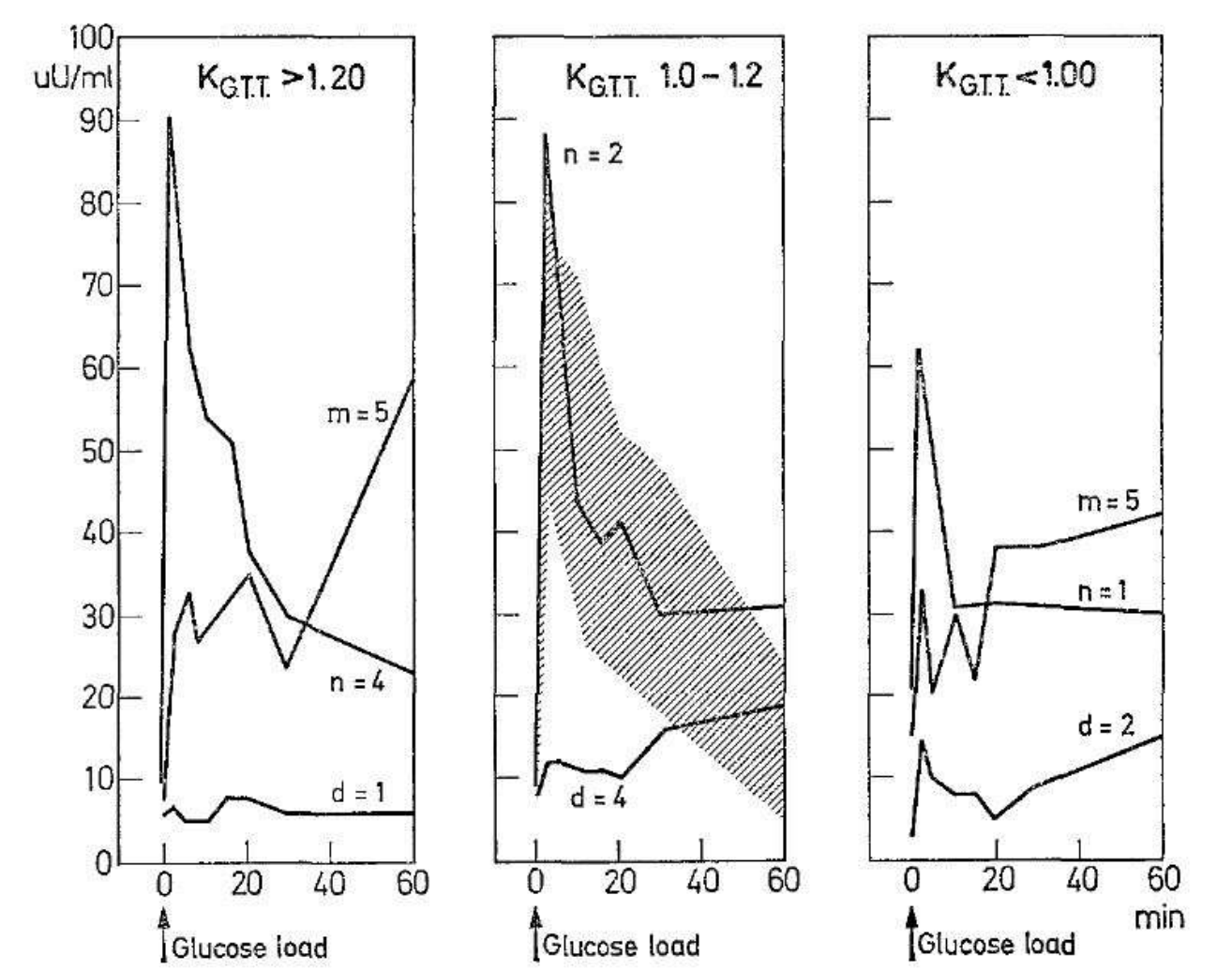
"Equivocal" glucose tolerance, insulin sensitivity and β cell function





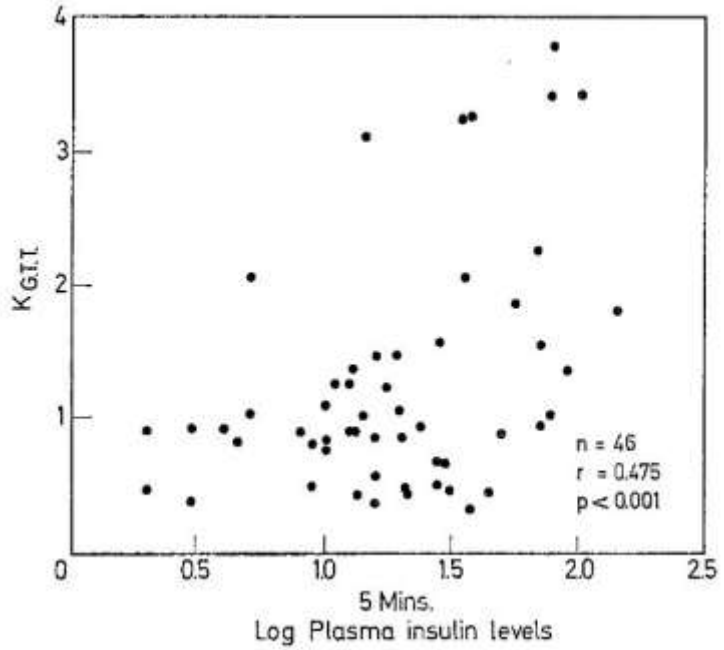
Alford F et al Diabetologia 7:173, 1971

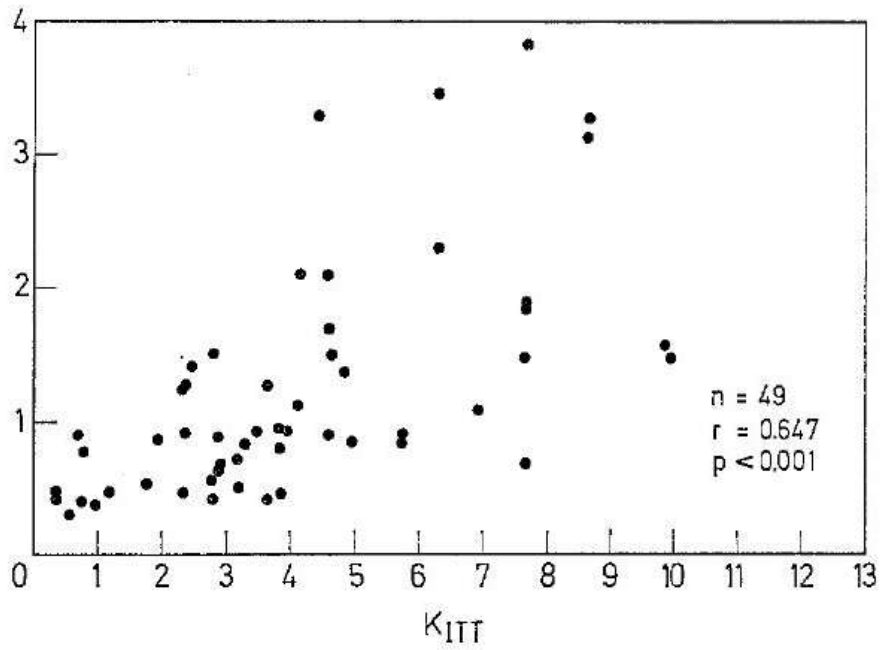
Insulin Secretion in "equivocal" GT



Alford F et al Diabetologia 7:173, 1971

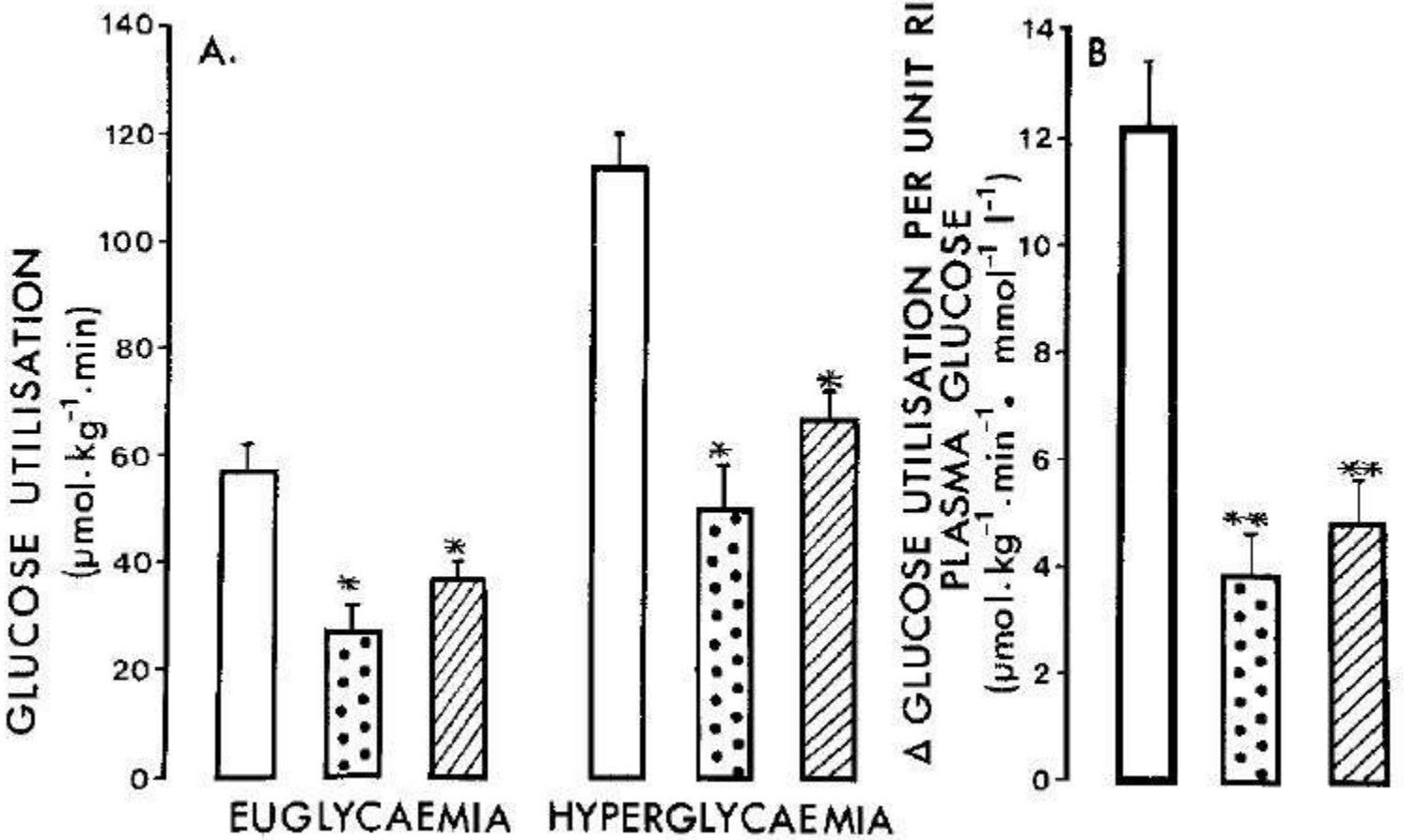
Kg vs. Acute insulin secretion or K_{ITT}





Alford F et al Diabetologia 7:173, 1971

Eu vs Hyperglycaemia in Diabetes



Control IRI 50mU/l)

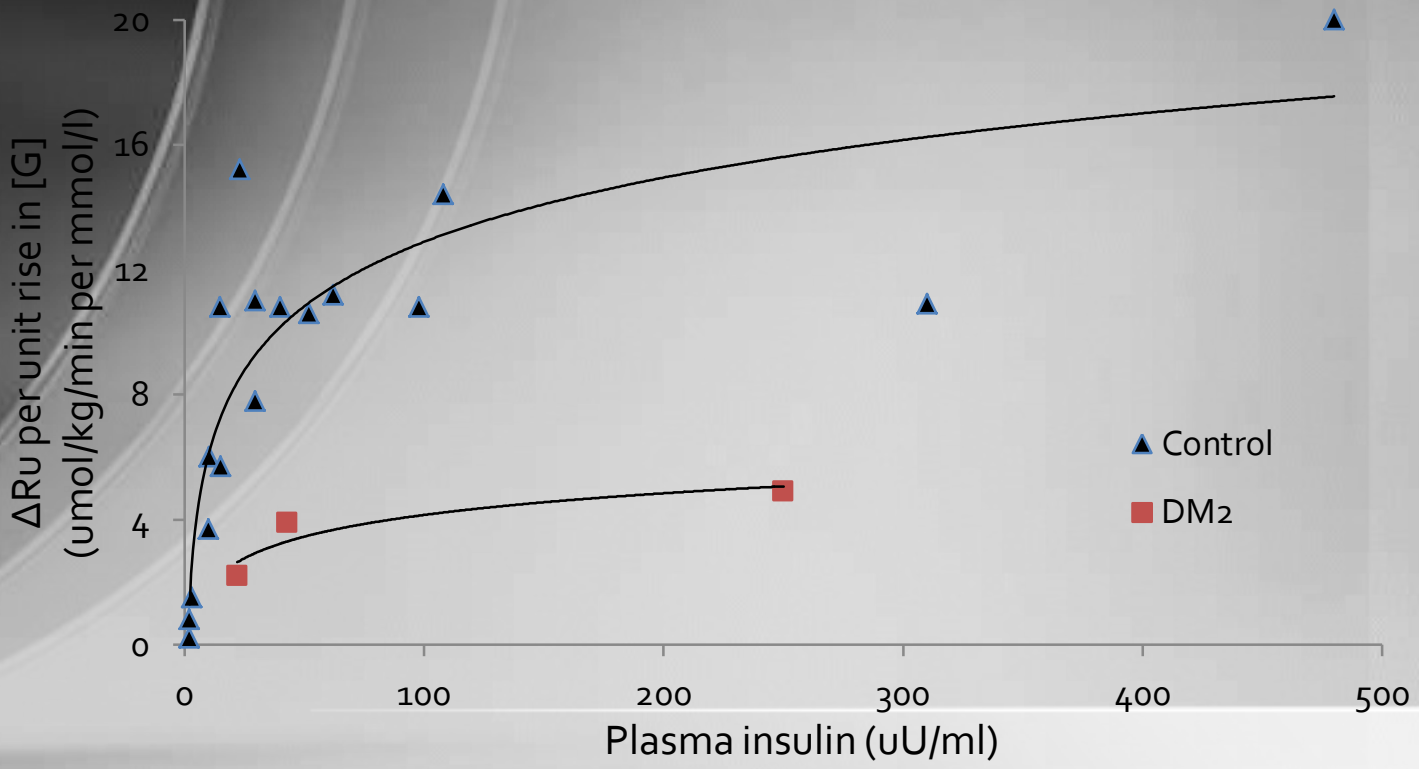
Diabetic 50mU/l)

Diabetic 250mU/l)

* - ** p<0.005 - <0.001

Proietto J et al Diabetologia 25: 331, 1983

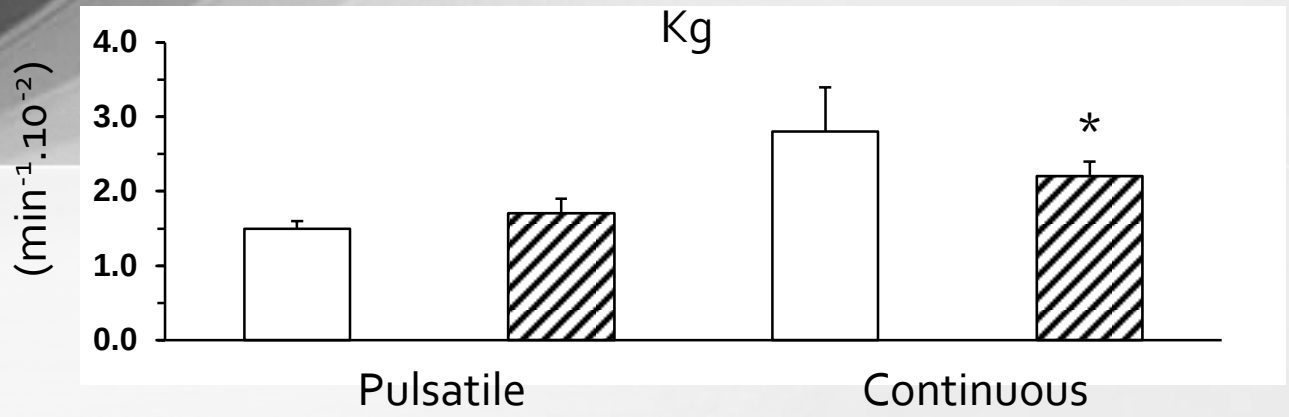
Changes in Glucose uptake per unit change in plasma glucose in CON and DM subjects

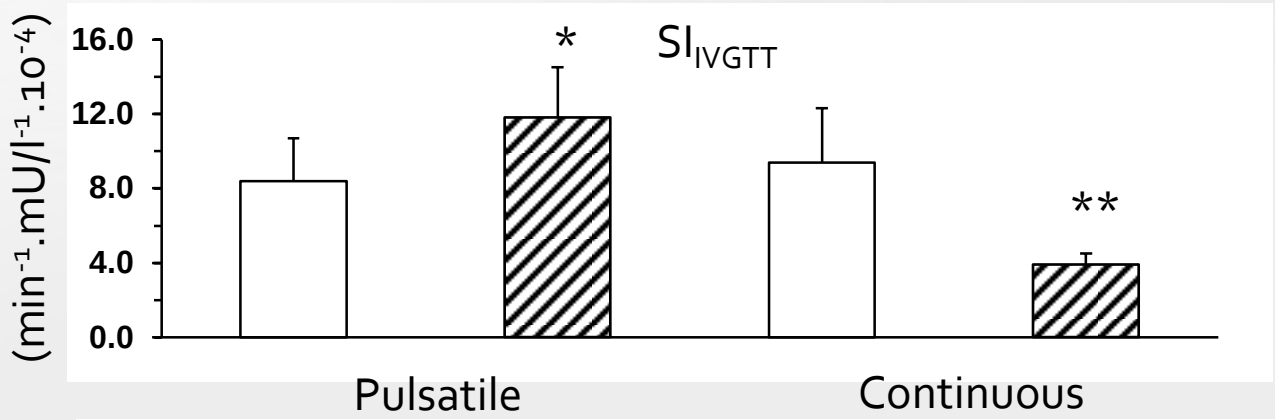


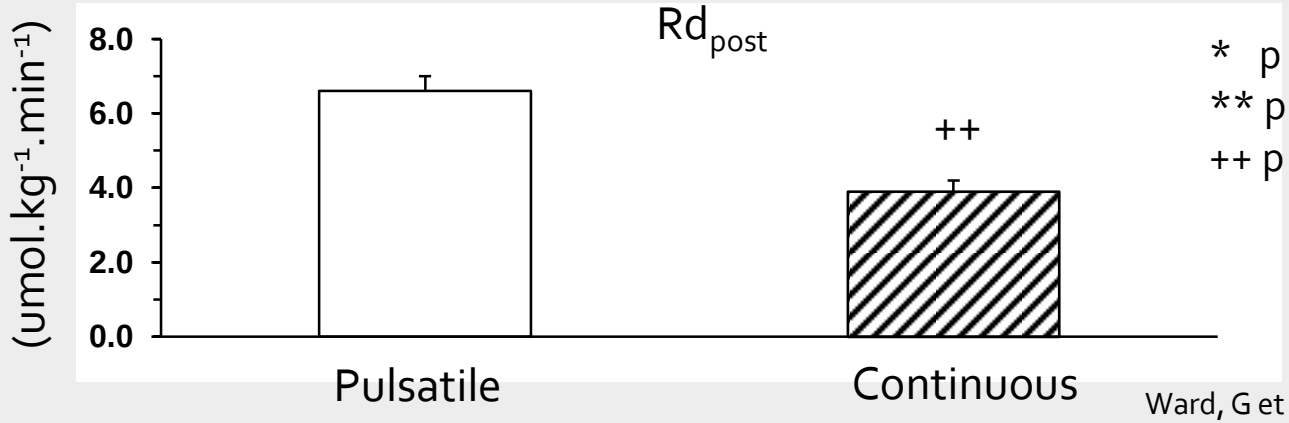
Proietto et al; Metabolism, 32(11): 1022 (1983)

What are the metabolic consequences of hyperinsulinaemia?

2ohr Pulsatile vs Continuous Insulin infusion



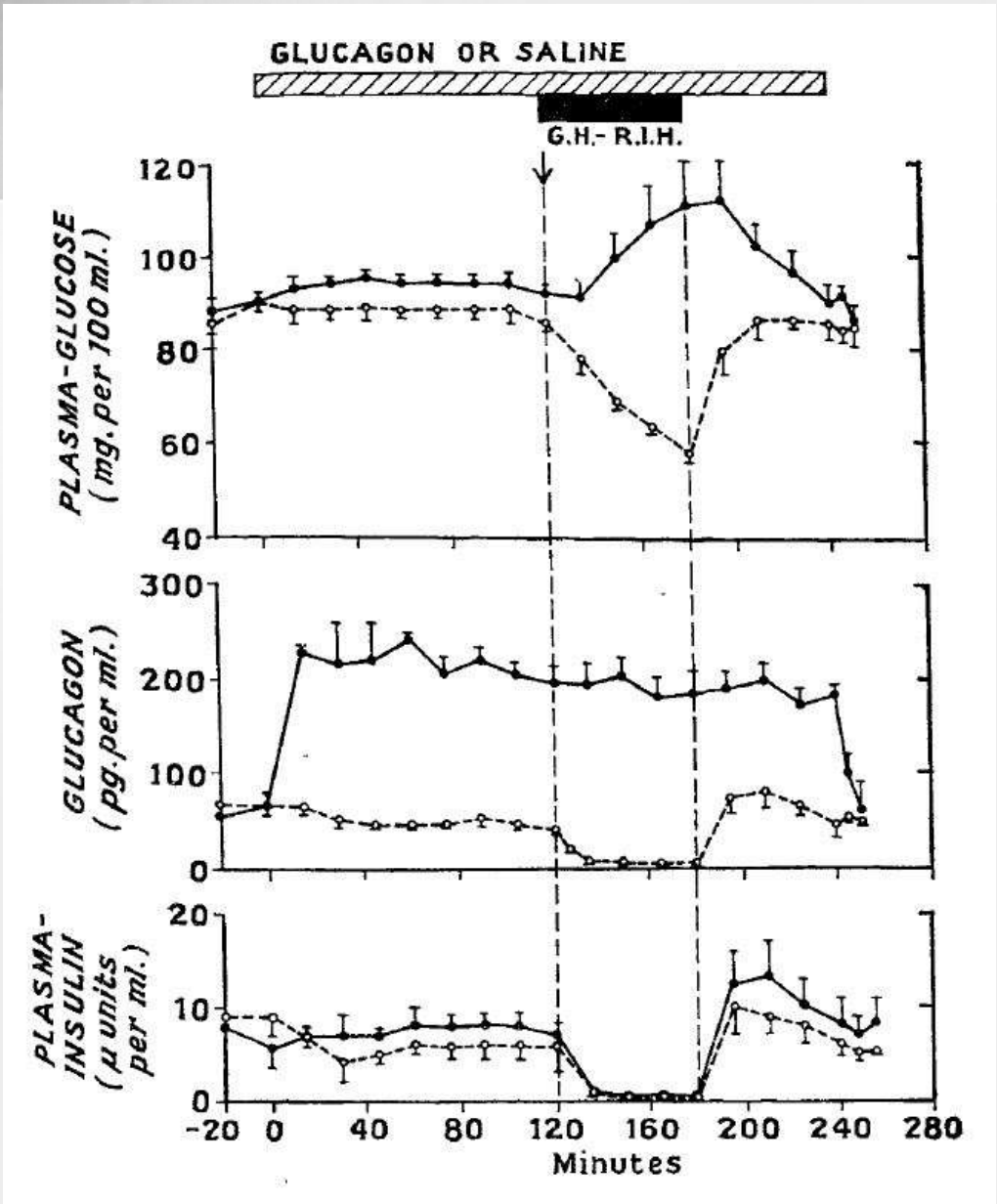




* p < 0.05 vs pre test
** p < 0.01 vs pre test
++ p < 0.01 vs pulsatile

Ward, G et al Diabetes 39: 501 (1990)
Marangau, A et al Diabetes 35:1383 (1986)

What is the role of glucagon (alpha cell function) in glucose metabolism?



Alford F et al Lancet Oct: 974, 1974

What is the Metabolic Role of Chronic Hyperglucagonaemia?

In **cirrhosis**:

IRG X 4 fold higher and IRI 2X higher vs Controls

HGP_{BASAL} is decreased ($p<0.003$) and is suppresses by insulin normally

Rd is decreased ($p<0.005$) and correlates with FG ($r=-0.87$)

Hepatic response to glucagon bolus is normal

Glucose tolerance: NGT, iIGT/DM2

Alford F et al, Clin Endocrin 11:413 ,1979
Proietto J et al, J Clin Endocr Metab 51: 1030, 1980

In **glucagonoma subject**:

IRG X 100 fold higher and IRI equal vs Controls

HGP_{BASAL} not raised

Rd is decreased

Hepatic response to glucagon bolus is absent (no cAMP rise)

Glucose tolerance: iIGT

Nankervis A et al, Clin Endocrin 15:325 ,1981

Glucose Processing During and IVGTT vs Clamp and Minimal Model Analysis

	IVGTT	Clamp 1	Clamp 2
Mean Insulin Level	~ 25	~ 25	~ 60
Glucose Disposal	↑	↑	↑↑↑
Glucose Oxidation	↑	↑	↑↑
Glucose Storage	↔	↔	↑↑
Glycogen Synthase Activation	↔	↔	↑
Lipid Oxidation	↓	↓	↓

Henriksen J et al, Metabolism 45:598, 1996; Mandarino l et al, J Clin Invest 80: 655, 1987

Note

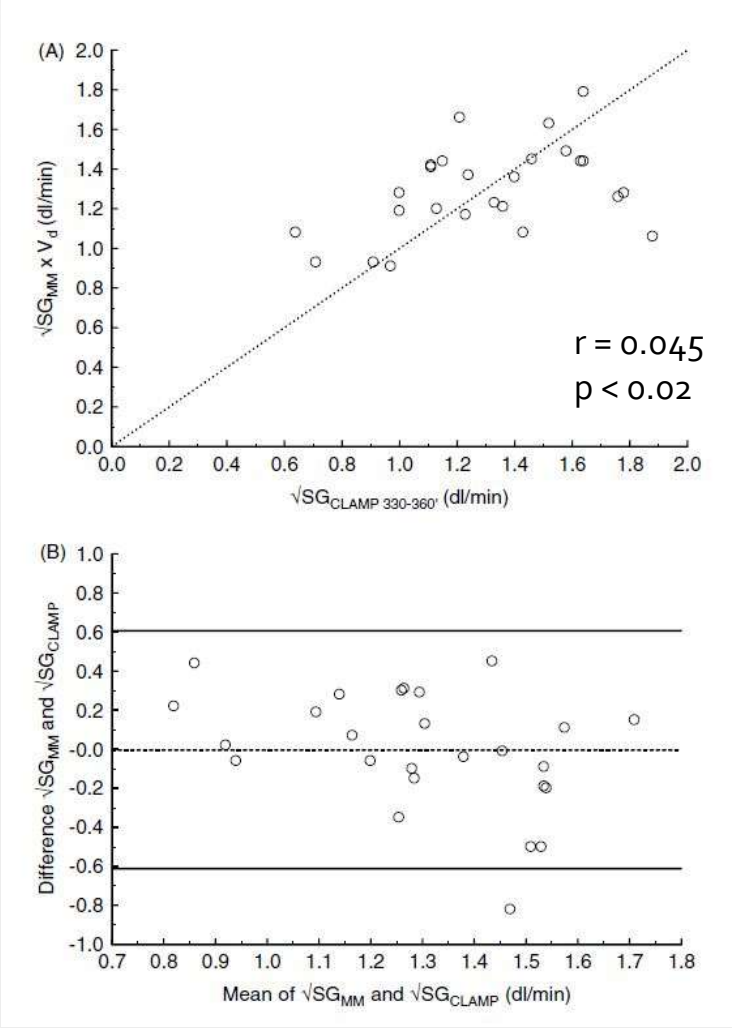
SI_{IVGTT} = Transmembrane glucose transport + Glucose phosphorylation (IRI 10 – 100 mU/l)

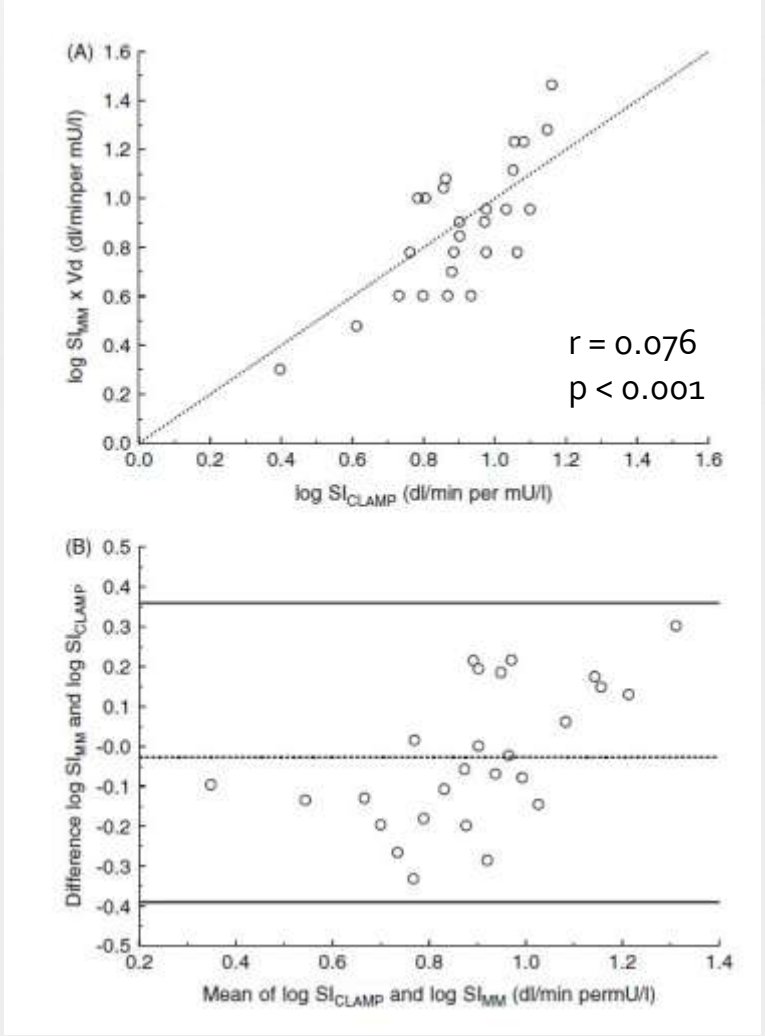
$SI_{CLAMP\ 1}$ = Transmembrane glucose transport + Glucose phosphorylation (IRI 10 – 100 mU/l)

$SI_{CLAMP\ 2}$ = Transmembrane glucose transport + Glucose phosphorylation + Glycogen synthase activation (IRI >30 mU/l)

$SI_{CLAMP\ 1}$ glucose processing matches SI_{IVGTT} glucose processing

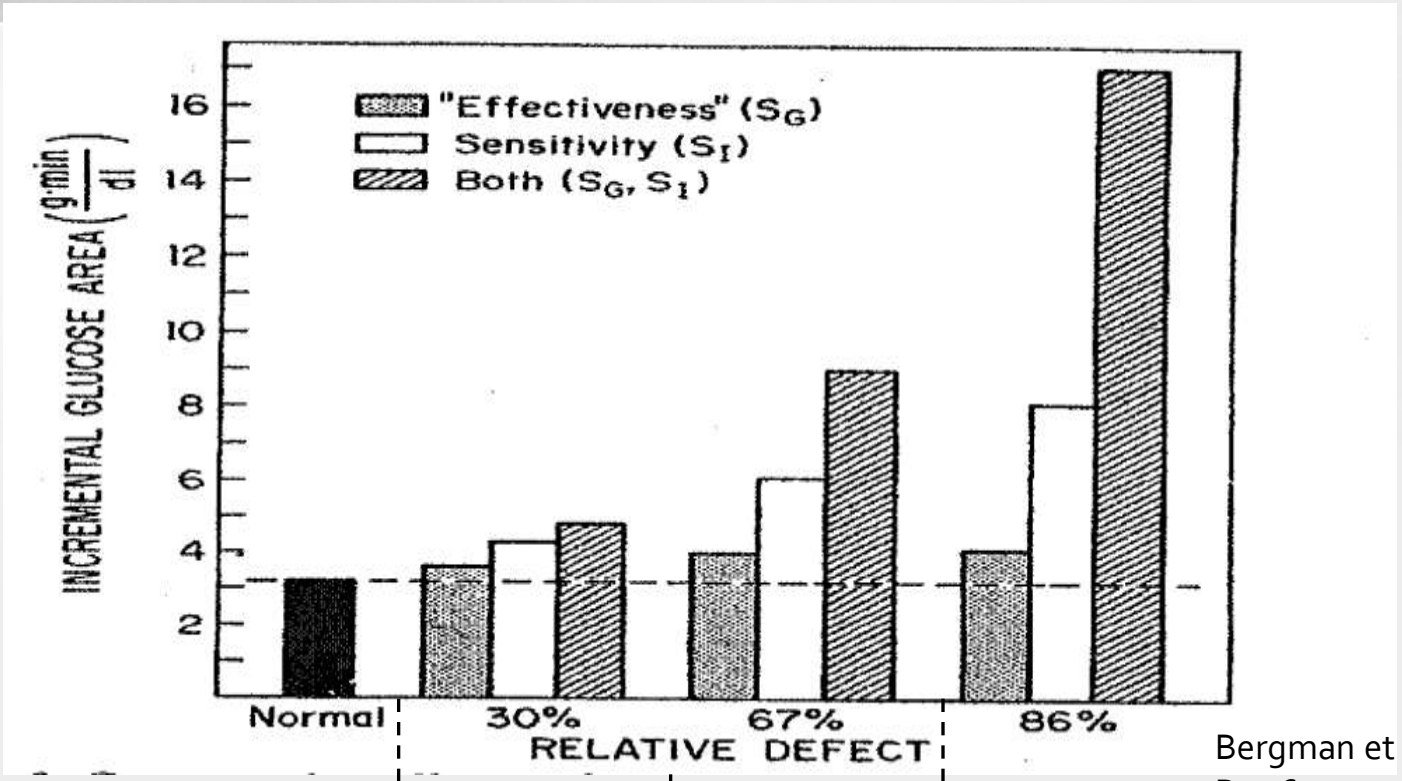
Comparisons of Sg and Si by Clamp and Minimal Model Analyses





Henriksen J et al Diabetes Metab Res Rev 26: 569, 2010

Compounding effect of the defect in glucose sensitivity (Sg) on glucose tolerance in insulin resistant subjects.



Bergman et al, Endocrinol Rev 6: 45 ,1985

FG	<5.5		<6.0		<6.5		≤8
2h OGTT G	<8.0		<10.0		>11.0		>>11.0
↓ Ins Secr.	0		↑↑		25 %		>50 %
Gluc Toler.	NGT		IGT		DM		DM++

Reaven et al, Diabetes:

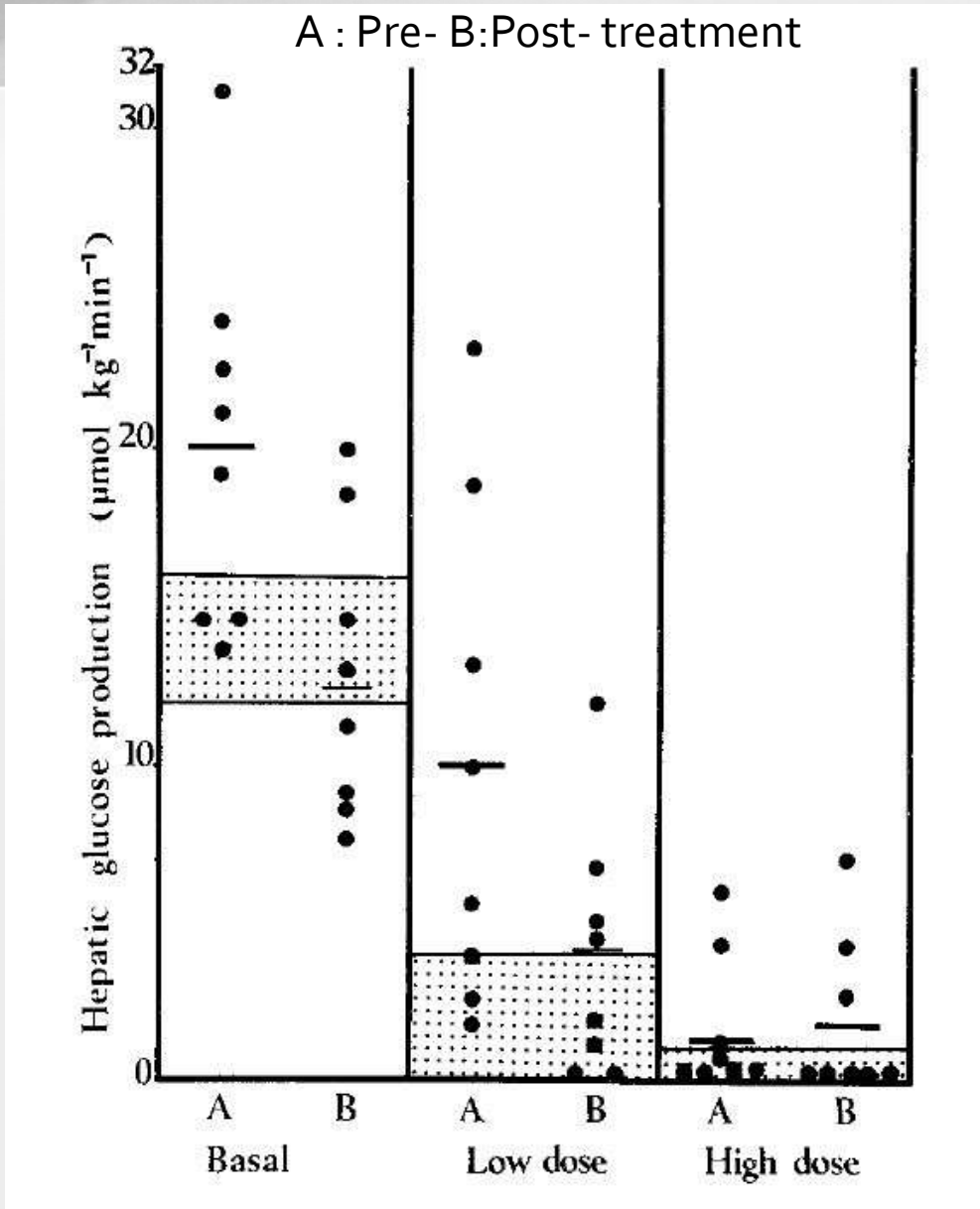
Glucose Metabolic Partitioning Pathways for Sg and SI

- Parallel increases in GF and GS occur during matched normo-hyperinsulaemic clamps, with euglycaemica and hyperglycaemia, but greater ΔGS is reflected in SkM by matched increases of glycogen and glycogen synthase activation at higher insulin.
- At matched Rd values (i.e. high glucose/low insulin vs. normal glucose/raised insulin): GS and GS are similar i.e. hyperglycaemia alone can stimulate both GS and GF pathways in SkM.
- At normo-physiologic hyperinsulinaemia (<25mU/l): GS contributes ~15% and GF ~85% to Sg.
- HGP is supressed more with combined hyperglycaemia/ normoinsulinaemia vs. euglycaemia/normoinsulinaemia, and is therefore a major contributor to Sg.

Christopher M et al, Amer J Physiol 266:E62, 1994; 268: E410, 1995

HGP in Type 2 DM and Control Subjects – What Regulates HGP?

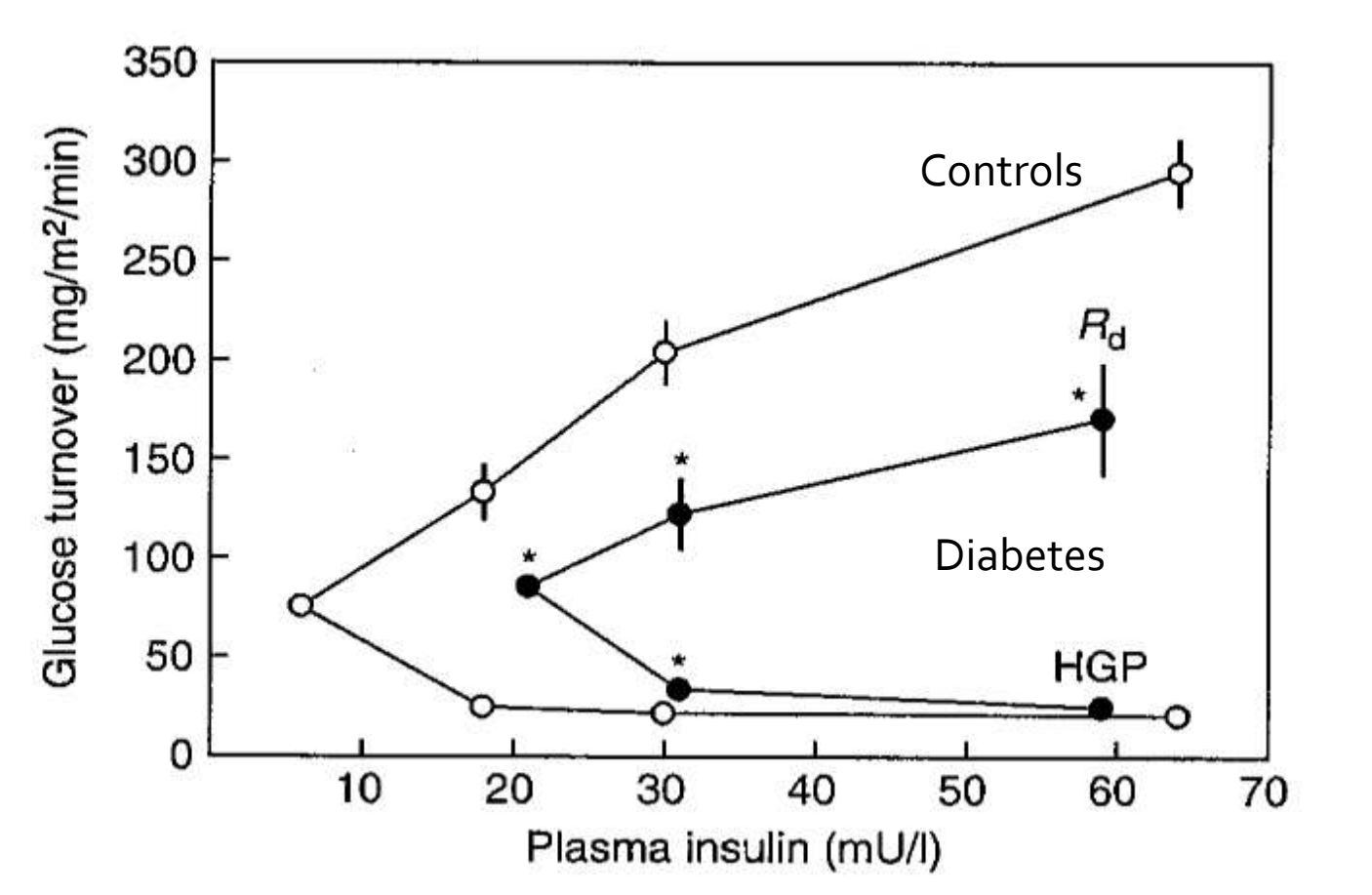
Hepatic "Insulin Resistance" in Diabetes



A = Pre-treatment
B = Post-treatment

Nankervis A et al,
Diabetologia 23:320, 1982

DR Curves for Rd and HGP in Con vs DM2:
Hepatic Resistance vs. Hepatic Sensitivity



Staehr P et al, Diabetes 50:1363 , 2001

Regulation of HGP – Autonomy of the Liver VS Peripheral metabolic needs?

Metabolic Responses to :

Normal Dog

- Prolonged 20h fast
- Low (30% of HGP) GINF vs High dose GINF (at basal Insulinaemia)
- Exercise

Alloxan Diabetic Dog

- Hyperglycaemia (at basal insulinaemia)
  vs
  Phlorizin-induced "Normoglycaemia"
- Exercise

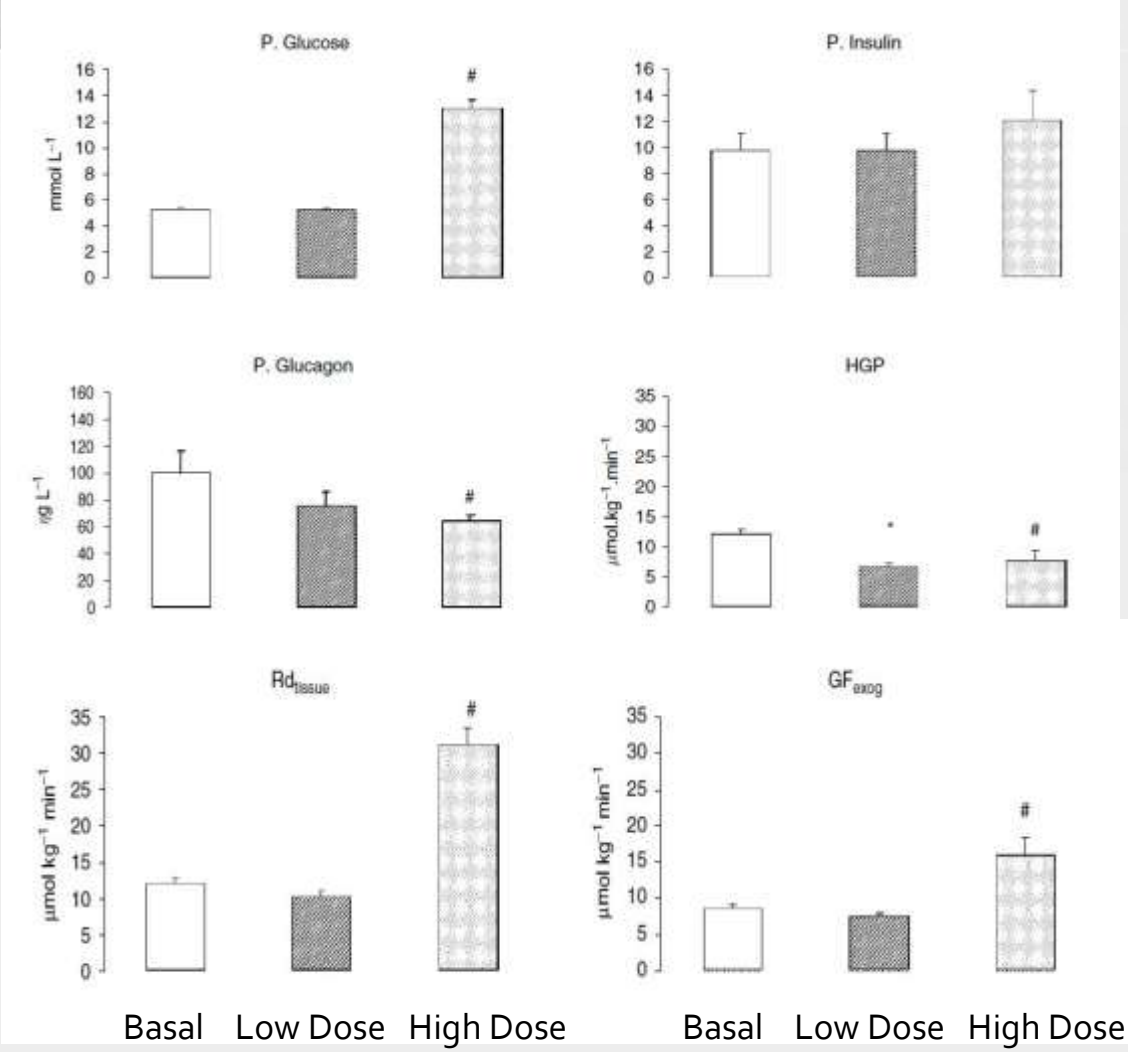
Prolonged 20hr fast – Normal Dog
[Glucose Deprivation]

	15h	**20h**
HGP ($umol.kg^{-1}.min^{-1}$)	13.6 ± 1.2	12.3 ± 1.1 *
Rd ($umol.kg^{-1}.min^{-1}$)	13.6 ± 1.2	12.3 ± 1.1 *
MCRg ($ml.min^{-1}$)	2.6 ± 0.3	2.4 ± 0.2 **
GF ($umol.kg^{-1}.min^{-1}$)	11.4 ± 1.6	9.3 ± 0.8 **

* $p < 0.05$; ** $p < 0.01$

Note: matching of HGP to MCRg and GF

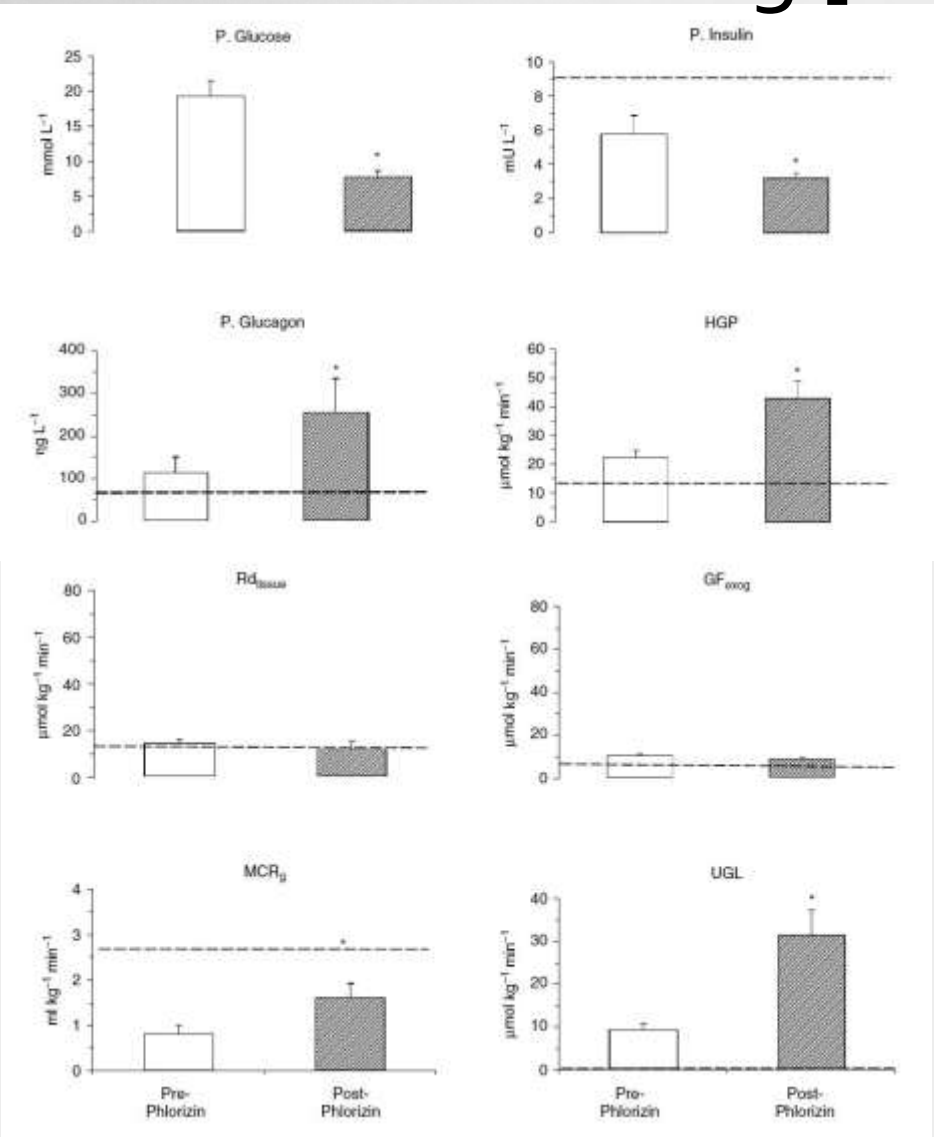
Impact of GINF on Glucose Metabolism in Dog: [Glucose sufficiency]



# p < 0.05 vs Con

Christopher M et al Diabetes Metab Res Rev 22: 155, 2006

Impact of Phlorizin Infusion on Glucose Metabolism in Diabetic Dog [Glucopaenia]



* $p < 0.05$ vs Prephlorizin

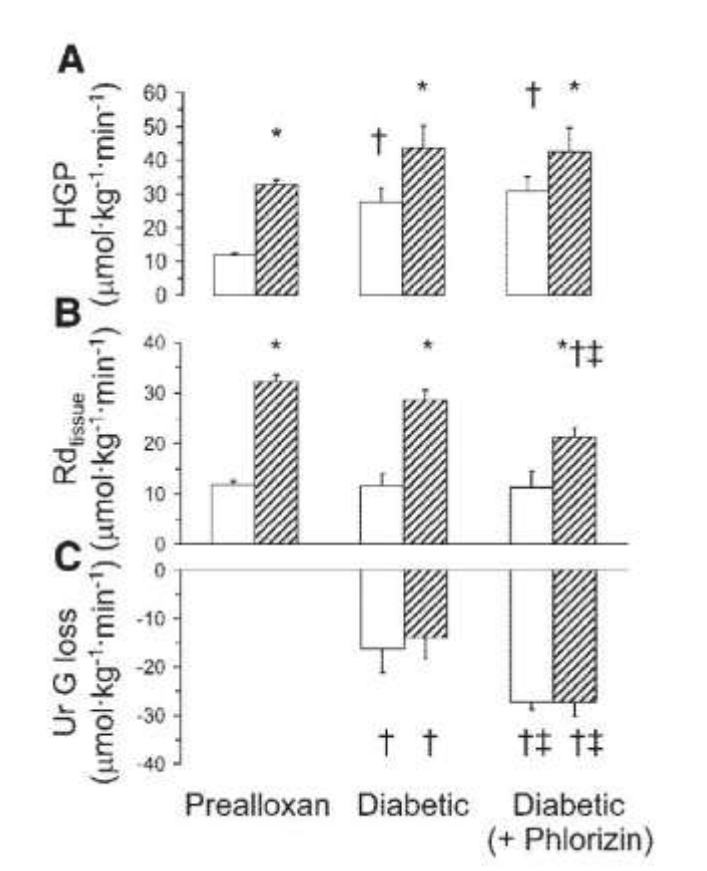
Note:
SkM intracellular [G] ↓

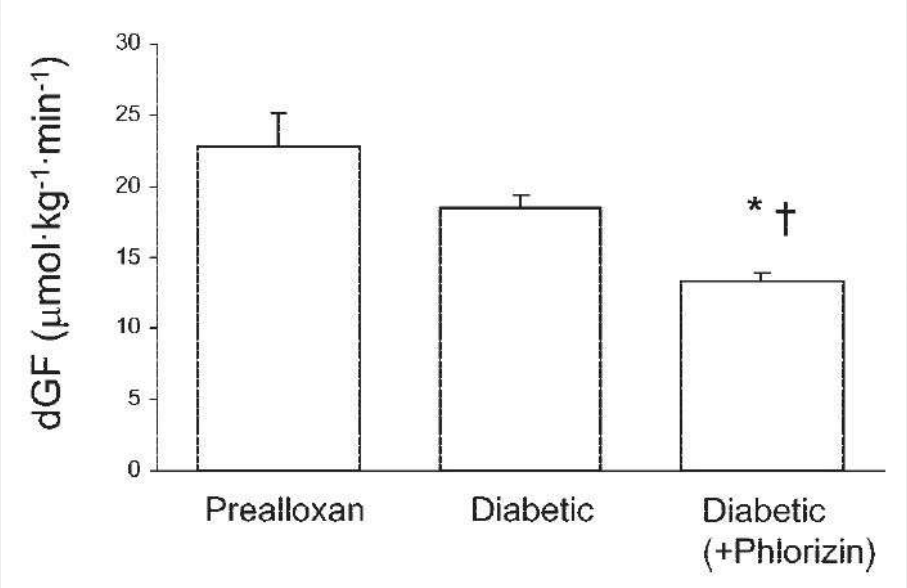
Christopher M et al
Diabetes Metab Res Rev
22: 155, 2006

Note: HGP vs UGL; $r = 0.89$ $p < 0.001$; $\Delta HGP_{Phlor} = \Delta UGL_{Phlor}$

Impact of Phlorizin and Exercise on Glucose Metabolism in Diabetic Dog

[Glucopaenia-Exercise]





Stepwise regression analysis:

$Rd_{EXER} \alpha p[G]_B + GF_{EXER}$

$r^2_{adj} = 0.88$

Christopher M et al J Appl Physiol 98: 930, 2005

Conclusions

- HGP appears to be set by the peripheral tissues' metabolic needs
- During exercise in diabetes, an adequate supply of glucose through hyperglycaemia is critical for the maintenance of normal muscle glucose metabolism (Rd_{TISSUE} and GF) in working muscle.
- HPG response to phlorizin during exercise is finite and fails to meet peripheral metabolic needs (Rd_{TISSUE} and GF).

What metabolic role does the Intracellular "emergency energy" pathway – AMP activated protein kinases – play in glucose metabolism of diabetes.

Metabolic Actions of AMPK Activation

Metabolic Responses to:

AMPK SkM Activation (by AICAR)

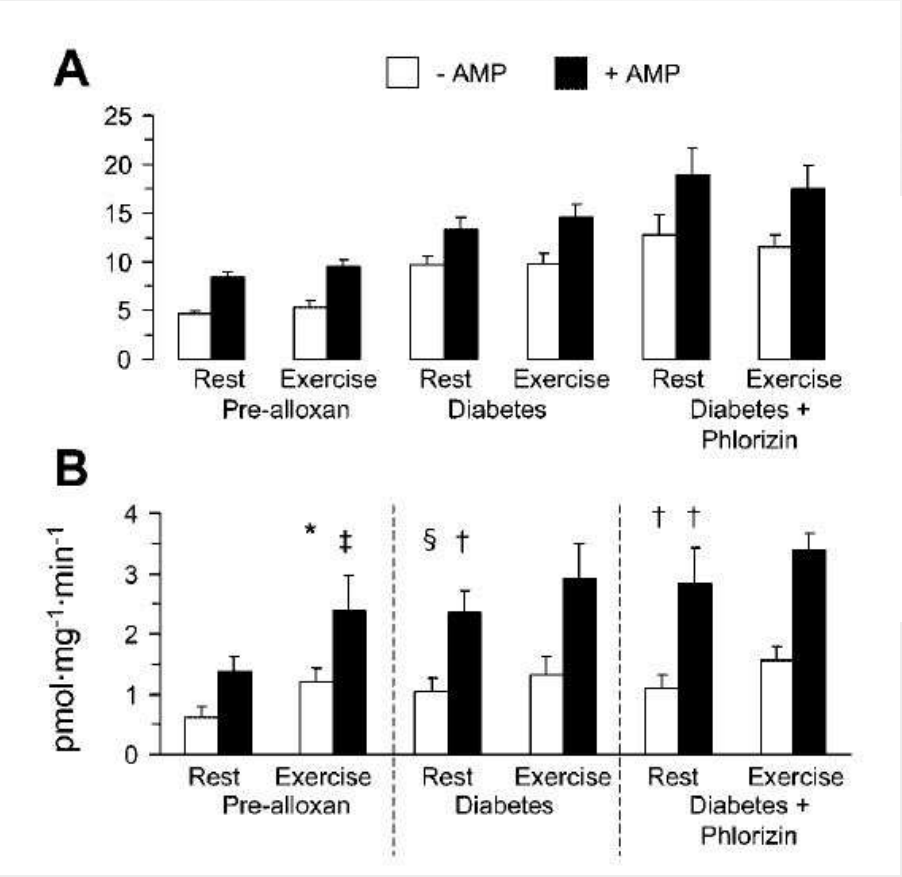
- Glucose uptake and oxidation ↑
- Fatty acid oxidation ↑
- Glycogenolysis ↑
- Glycogen synthase activation ↓

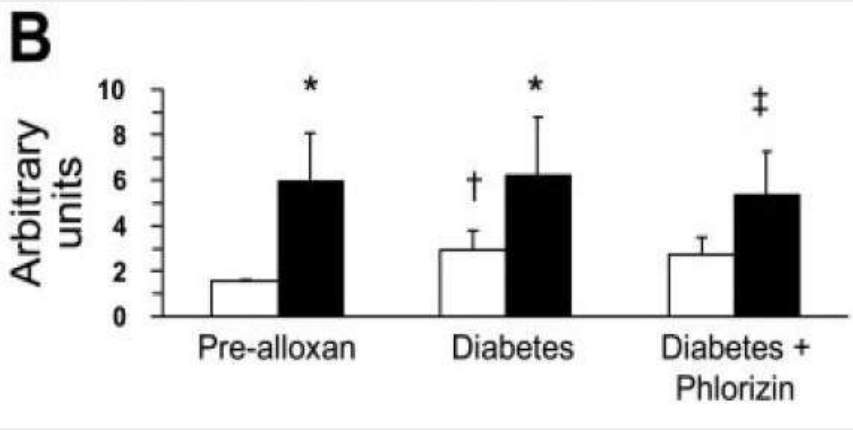
AMPK Liver Activation

- Glycogenolysis ↑↑
- Gluconeogenesis ↓
- Lypogensis ↓ and FA oxidation ↑
- Insulin action on HGP ↓

Note: AICAR's metabolic impact in vivo on the liver is due to the direct allosteric effect of ZMP (Camacho R et al, Amer J Physiol 89: 289, E1039, 2005)

$AMPK_{\alpha 1+2}$ and ACCβ Activation in Dog with Exercise





Christopher M et al, J Appl Physiol 95(4): 1523, 2003

In Vivo Effects of AICAR Activation on AMPK in Normal Dog

In normal dogs infused with AICAR infusion for 3h:	
Glucose response	↓** transient
Insulin response	↑** transient
FFA response	↓** transient
Lactate response	↑↑***
HGP	↑**
Rd_{TISSUE}	↑**
GF_{EXOG}	↑**
SkM AMPKα1+2	↑
SkM ACC-β	↑**

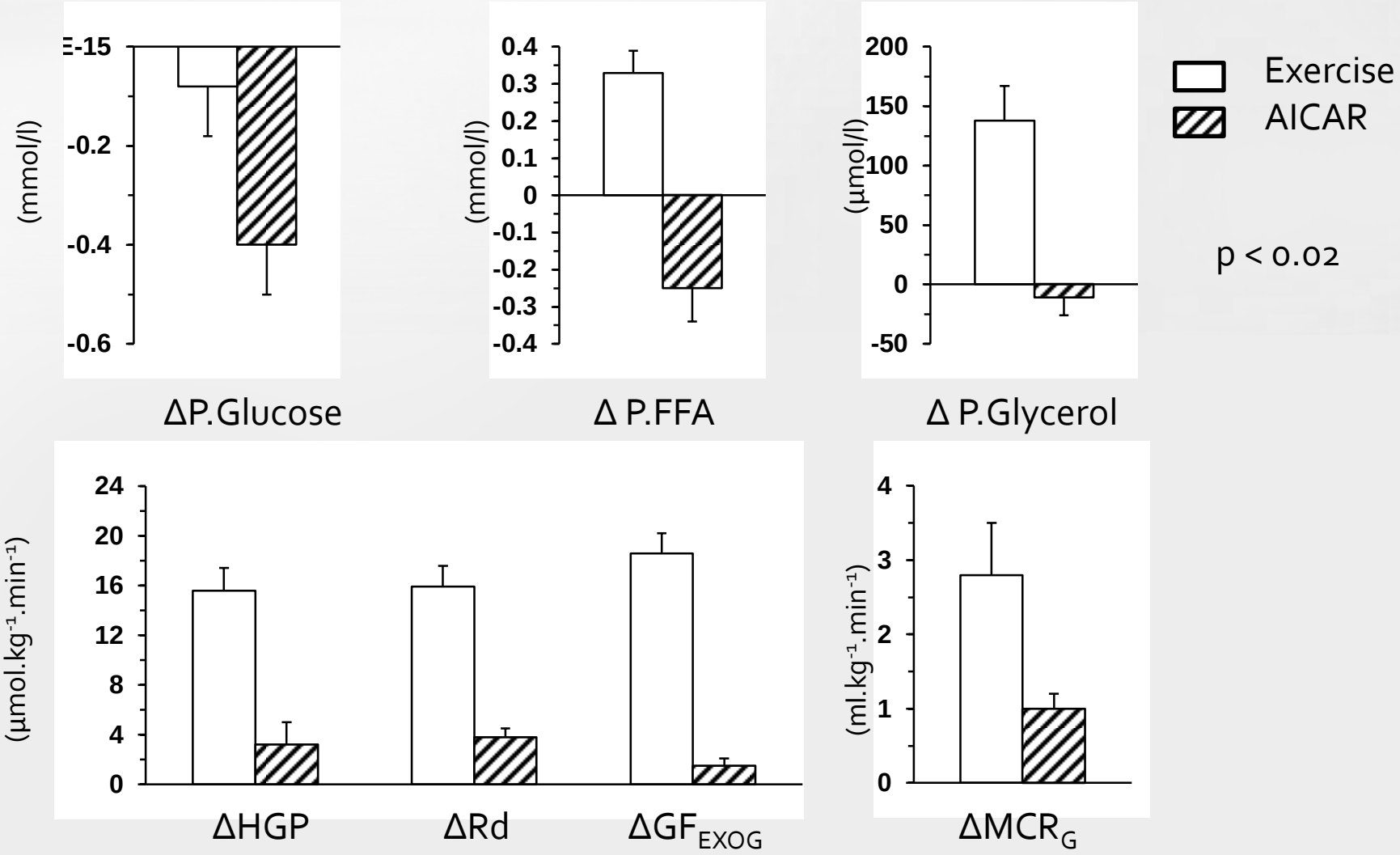
** $p<0.05$

*** $p<0.001$

Note: In diabetic dog: NO impact of AICAR on HGP, Rd_{TISSUE} and GF_{EXOG} in the presence of raised basal AMPK and ACCβ activities.

Christopher M et al, Am J Physiol 291:E1131, 2006

Comparison of the Effect of Exercise and AICAR on Metabolism and Plasma Metabolites



Rantzau et al, J Appl Physiol 104: 363, 2003

Conclusions

In normal dog:

- AMP pathway activated by Exercise and AICAR but with different responses

In sub-optimally controlled diabetic dog:

- **Chronically** elevated basal SkM AMPKα1+2 and ACCβ activities contribute to the ongoing normal supply of glucose (and fatty acid metabolism);
- Whether these raised basal AMPK and ACC activities of the diabetic state play a permissive metabolic role to **exercise** remains uncertain;
- The **acute** in vivo metabolic responses seen in normal dog to activation of AMPK and ACCβ by AICAR do not occur in diabetic dog.

Christopher M et al, J Appl Physiol 95: 2003

Interim Summary

- Glucose metabolism depends on:
  - Insulin sensitivity
  - Glucose sensitivity
  - β-cell function
  - Eu- vs. hyperglycaemia impact on partitioning of GS vs. GF
  - Both basal insulin and glucagon regulate fasting glucose, BUT
  - Glucagon's chronic metabolic action on liver in diabetes is uncertain
  - Hyperglucagonaemia of DM reflects intra-islet insulinopaenia
- HGP regulation appears to be secondary to the metabolic needs of peripheral glucose metabolism
- The potential therapeutic use of "rescue" metabolic "stress" pathways (eg. AMPK activation agonists) is complex.

Studies in Normo-glycaemic Relatives of Type 2 DM

- Young subjects <35y of age (i.e. ~10-20y before onset of DM2)
- Carefully age, BMI and sex matched controls
- Studied by Minimal Model IVGTT analysis and classical clamp studies with SkM biopsies
- Followed prospectively for 10y.

Hypothesis:

- If such subjects have detectable metabolic defects present initially, these abnormalities are most likely to be primary, and not secondary phenomena.

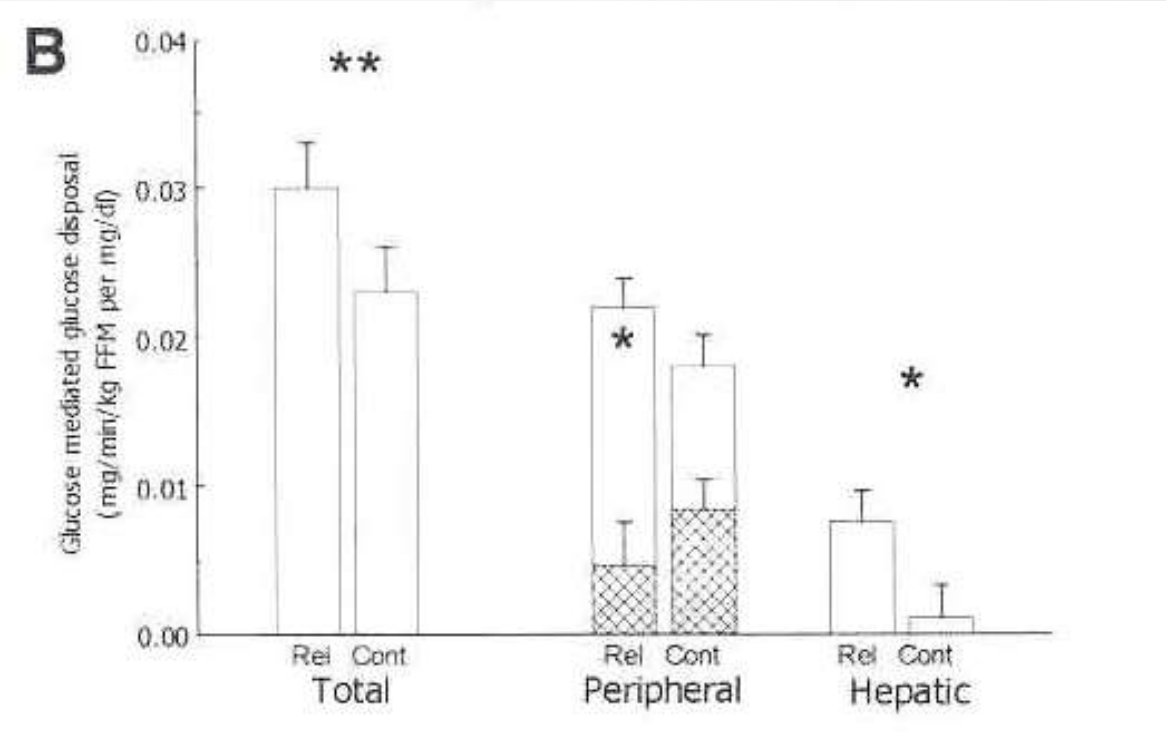
Glucose and insulin kinetic parameters derived from the FSIGT in Normoglycaemic Relatives of NIDDM patients.

	Relatives	**Controls**
Kg ($10^{-2}.min^{-1}$)	1.60 ± 0.14	1.59 ± 0.18
Sg ($10^{-2}.min^{-1}$)	1.93 ± 0.14 *	1.52 ± 0.16
Phi 1 ($mU.l^{-1}.min^{-1}$ per $mg.dl^{-1}$)	3.56 ± 0.53	4.13± 0.62
Phi 2 ($mU.l^{-1}.min^{-1}$ per $mg.dl^{-1}$)	10.27 ± 1.05	9.11 ± 1.71
Si ($10^{-4}.min^{-1}$ per $mU.l^{-1}$)	3.49 ± 0.43 *	4.80 ± 0.61
Si x Phi 1 ($10^{-4}.min^{-2}$ per $mg.dl^{-1}$)	11.5 ± 2.2 *	16.7 ± 2.0

* $p < 0.05$ vs Con

Henriksen et al, J Clin Invest 94: 1196, 1994

Clamp Sg



	REL	CON	p value
Sg_{HEP} ($min^{-1}.10^{-2}$)	0.8	0.1	<0.05
Sg_{PERIPH} ($min^{-1}.10^{-2}$)	2.1	1.8	NS

Henriksen J et al, Diabetes 49; 1209; 2000

The contributions of insulin sensitivity, glucose effectiveness, and insulin secretion to glucose restoration rate during an OGTT

	Relatives	Controls
OGTT		
Mean [G] ($mmol.l^{-1}$)	6.37 ± 0.20	6.07 ± 0.20
Mean incremental insulin ($mU.l^{-1}$)	25.5 ± 2.4	27.5 ± 2.6
Glucose restoration rate during OGTT*		
due to insulin [AIRg] ($10^{-2}.min^{-1}$)	0.78 ± 0.07	1.21± 0.14
percent of total (%)	30 ± 3	45 ± 4
due to glucose [Sg] ($10^{-2}min^{-1}$)	1.93 ± 0.07	1.52 ± 0.16
percent of total (%)	70 ± 3	55 ± 4
Total	2.72 ± 0.13	2.74 ± 0.15

* $\text{Glucose restoration}_{OGTT} = [Sg_{OGTT}] + [SI_{IVGTT} \times \Delta_{MEAN}\text{Insulin}_{OGTT}]$

Henriksen et al, J Clin Invest 94: 1196, 1994

Relative DEX Studies

Background

- ~40% of normoglycaemic REL of type 2 DM will develop future diabetes
- With aging, insulin sensitivity (SI) generally deteriorates

Questions

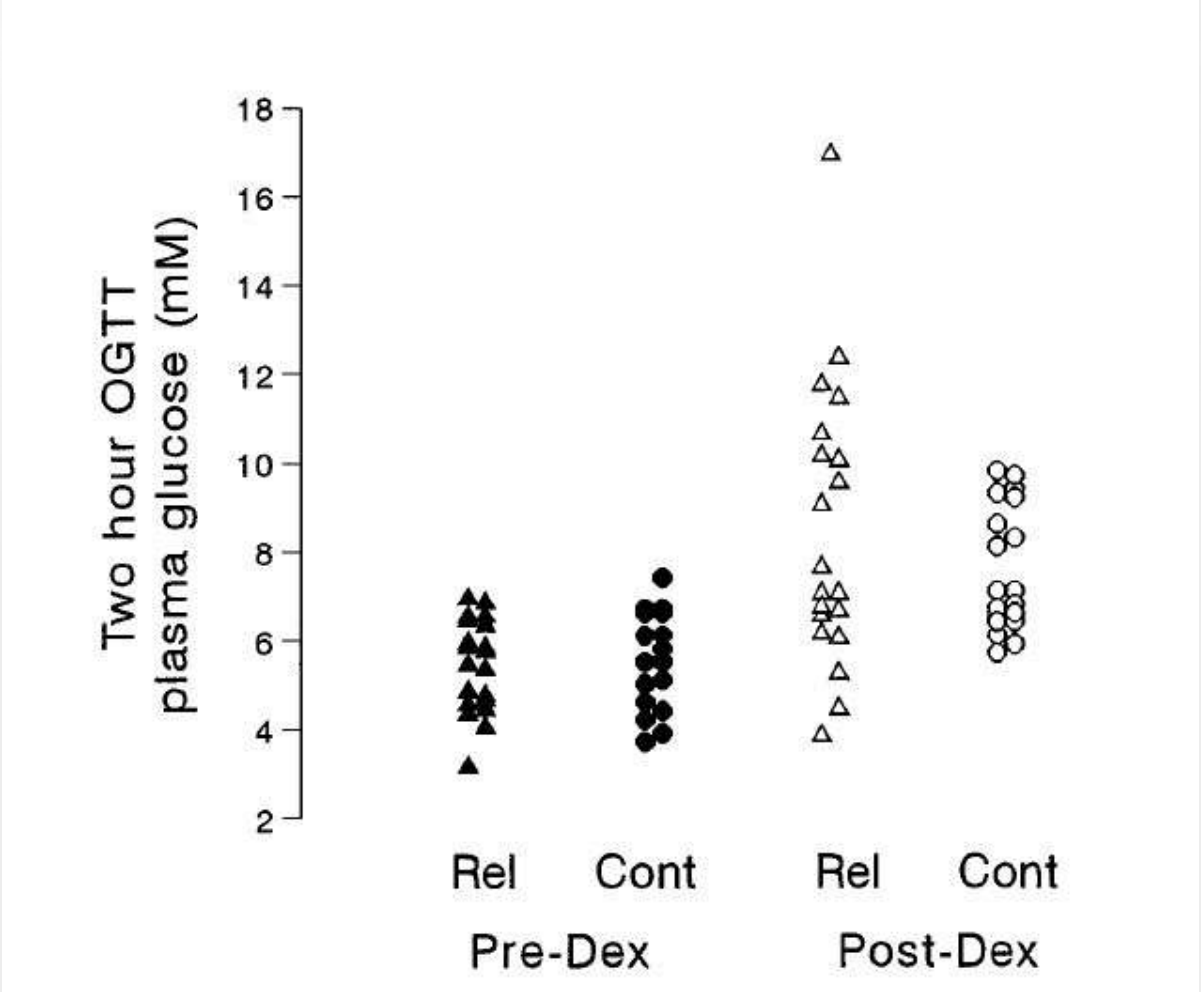
- What is the metabolic impact of DEX –induced insulin resistance on β-cell function in REL and CON subjects?
- Do the REL DEX- responses simulate those seen in later in life?

DEX and 10y Study Designs

- 20 normoglycaemic REL and 20 age, sex, and BMI matched Control subjects were studied at:
  - 0y: pre- and post-exposure to DEX (4mg/day for 5 days)
  - 10y followup.

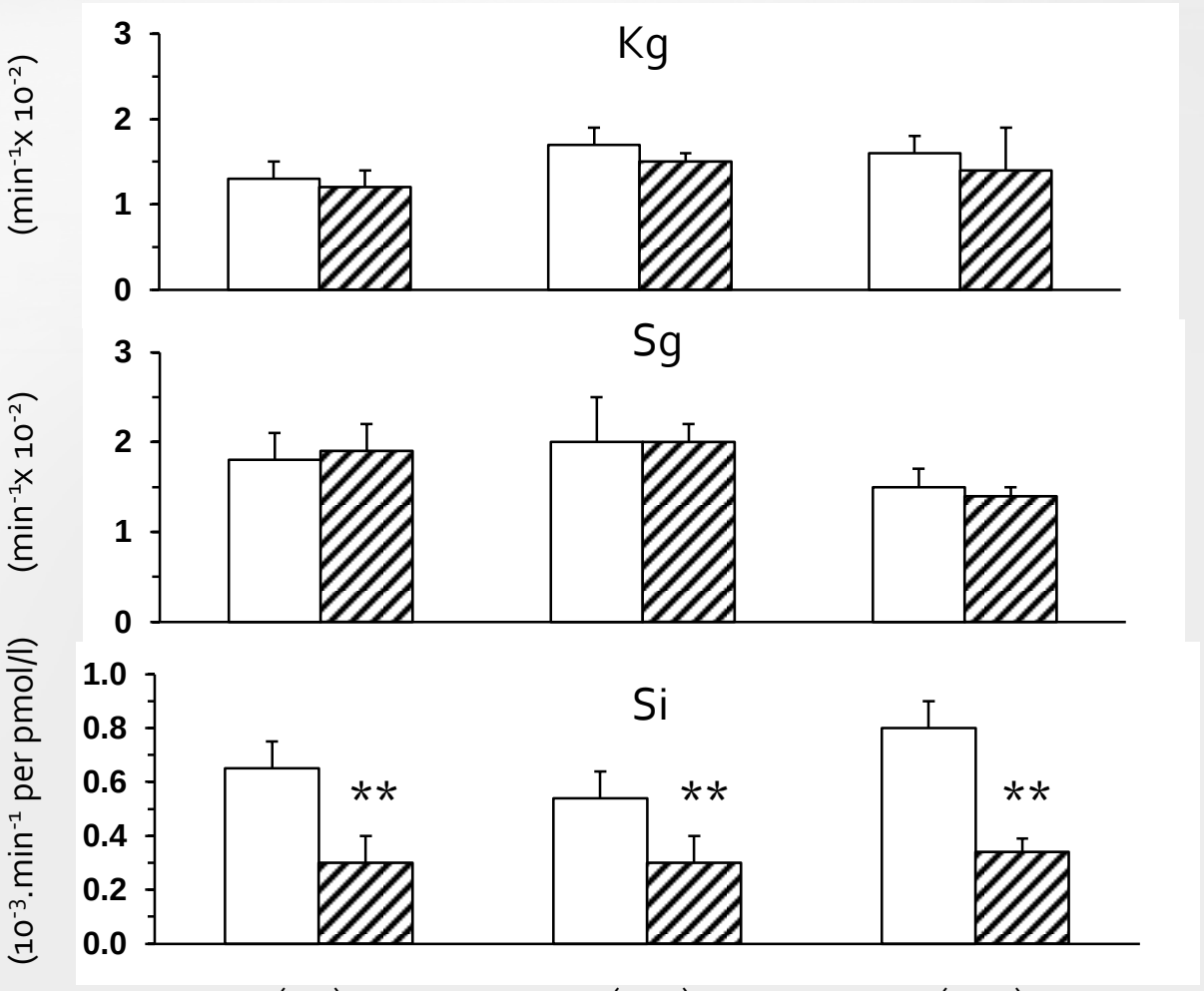
- Glucose tolerance, acute β-cell function and SI were measured.

Impact of DEX on OGTT in REL vs CON



Henriksen K et al Diabetologia, 40: 1349, 1997

DEX-induced changes in glucose metabolism in REL vs CON

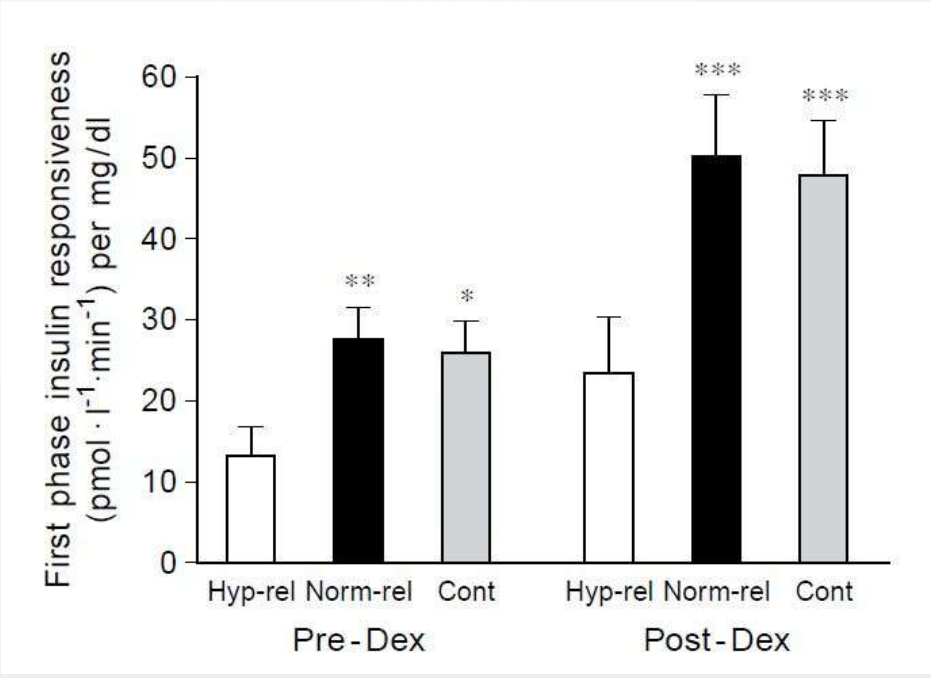


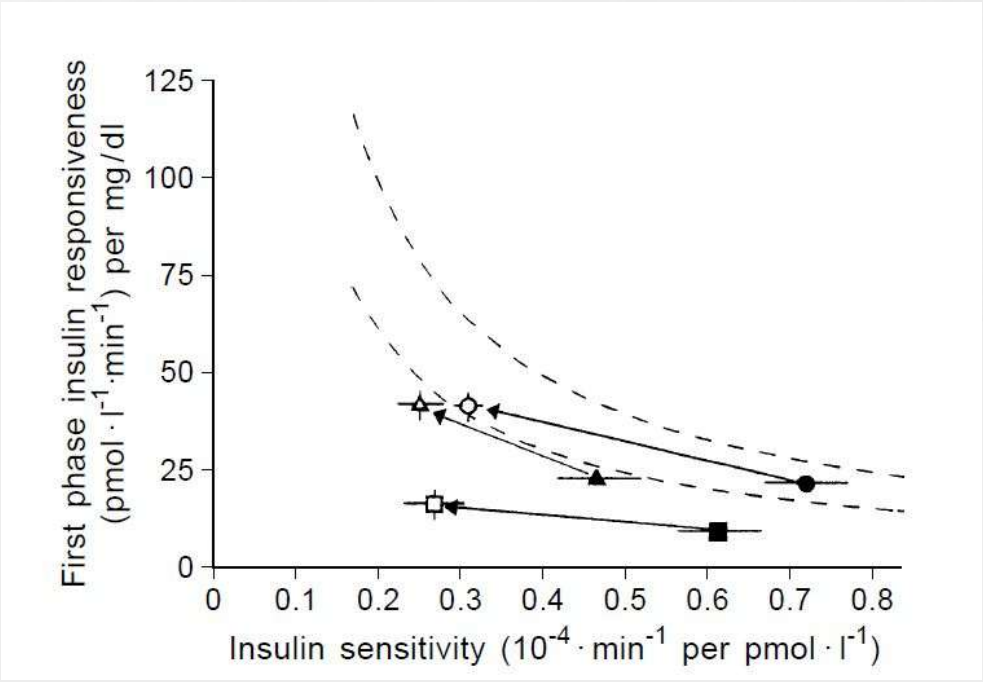
Pre DEX
Post DEX

** p < 0.01 Pre vs Post DEX

Henriksen J et al, Diabetologia 40: 1439 (1997)

DEX Study in REL and CON

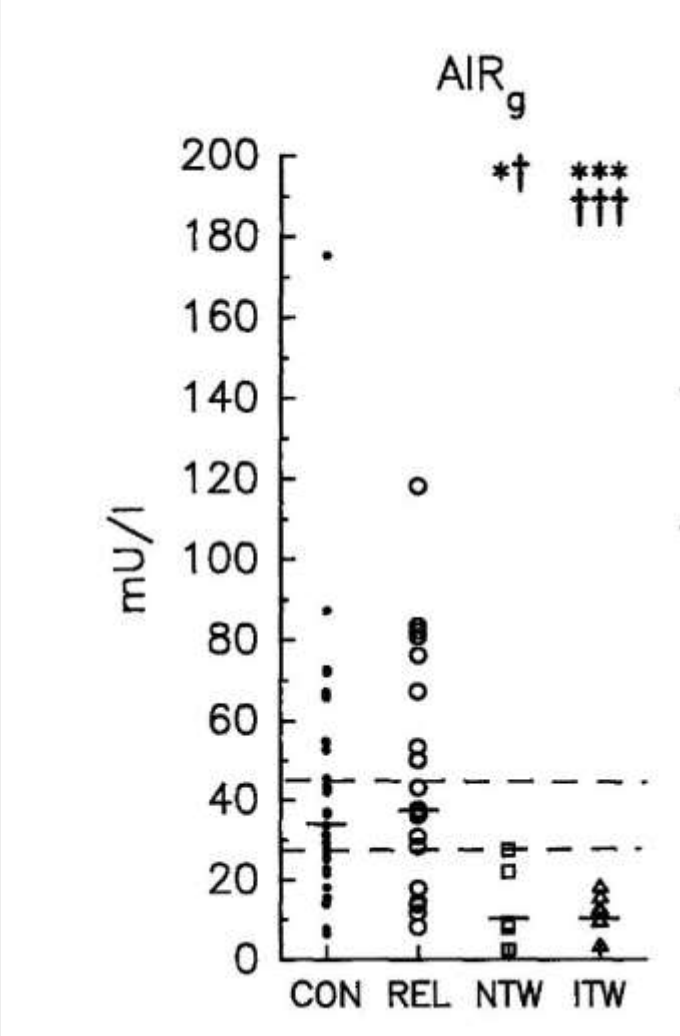


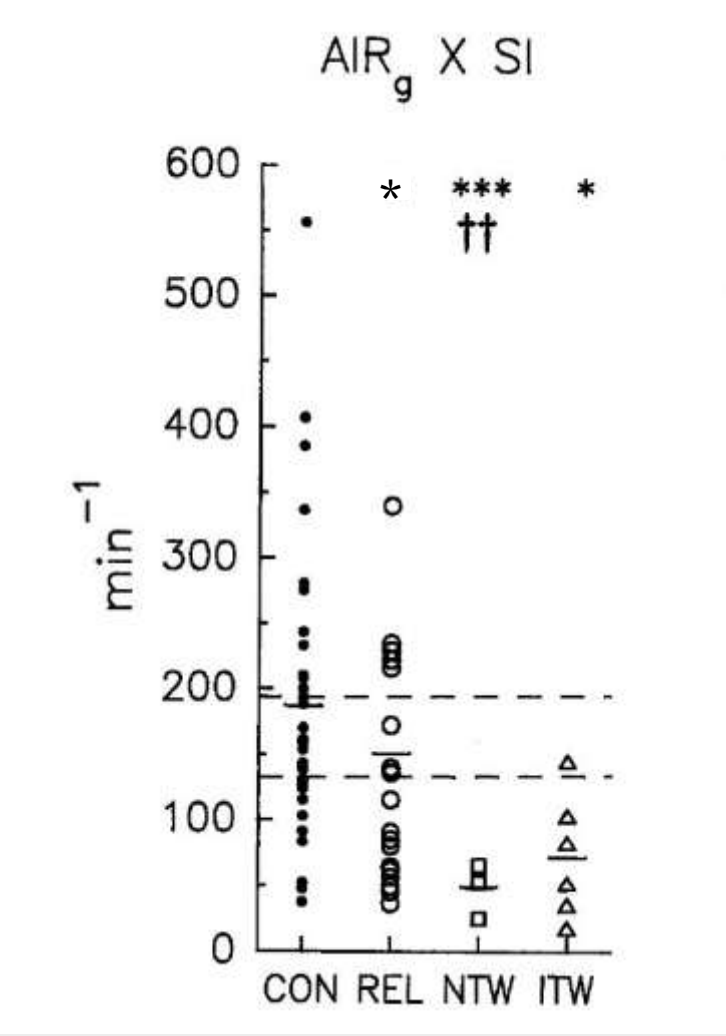


* $p < 0.05$; ** $p < 0.01$; *** $p < 0.005$ vs Hyp-rel

Henriksen J et al, Diabetologia 40: 1439 (1997)

Acute insulin secretion in CON, REL and Twins





Alford F et al, Metabolism 47:522, 1998

Summary of RELATIVES

In young insulin resistant normoglycaemic Relatives of type 2 DM:

- Sg is increased by 20%
- HGP is the main site of the hyperglycaemic effect
- Glucose storage and glycogen synthase activation in SkM is decreased (ie SI decreased)
- AIRg.SI is reduced

Conclusion:

- At oy, the metabolic characteristics (↓SI, ↑Sg, ↓↓ AIRg) are inherited.

Question:

- What about the future?

Sg_{oy} vs 10y Glycaemia Outcomes in REL

At 10y	DM_{REL}	$iIFG_{REL}$	NGT_{REL}	CON
Sg_{oy}	1.35 ± 0.10	2.00 ± 0.19*	2.15 ± 0.23*	1.53 ± 0.18^{t}

* $P < 0.05$ vs DM_{REL}; $^{t}p < 0.05$ vs NGT_{REL}

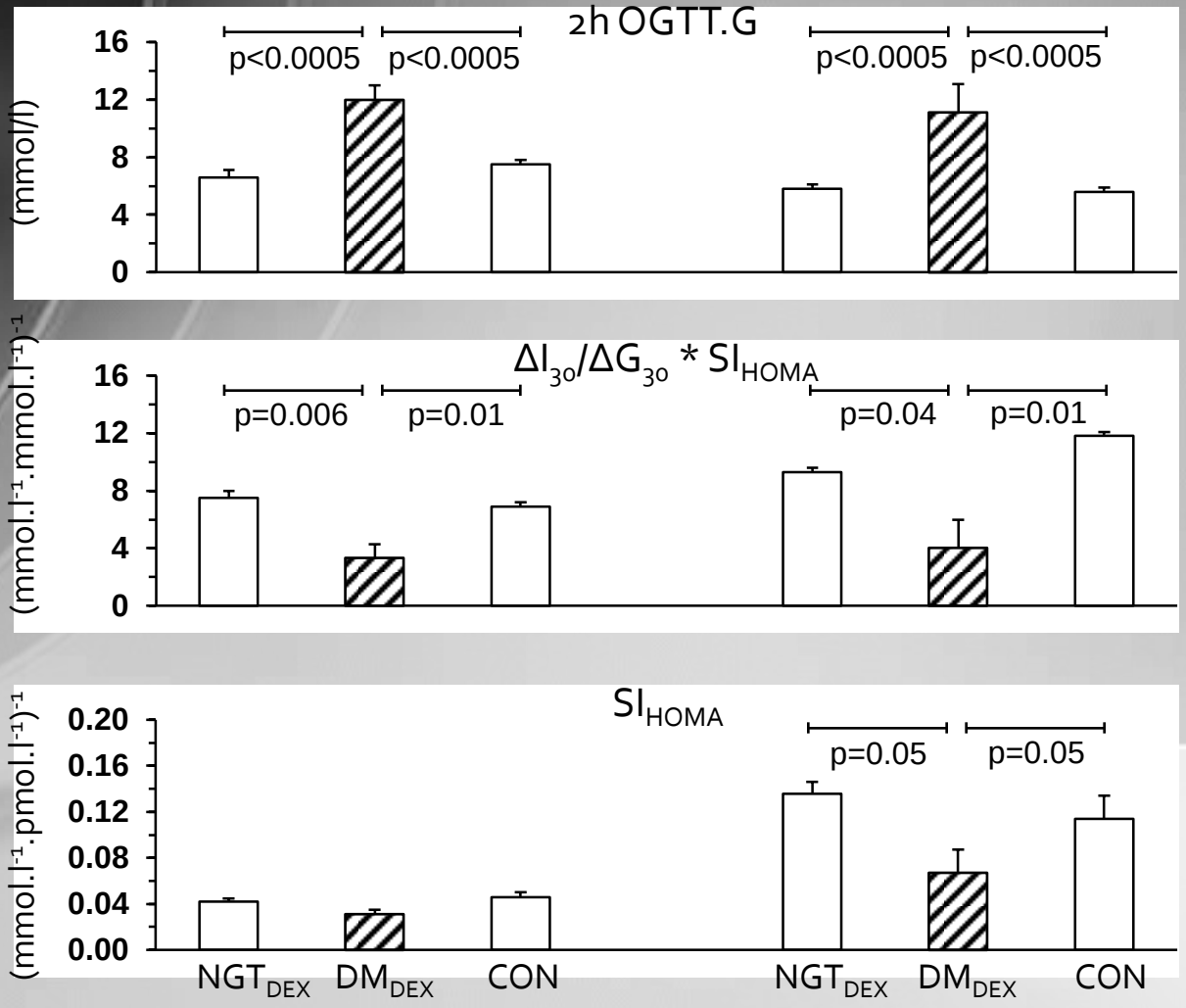
FG_{10y}	vs	FG_{oy}	r = 0.71	p < 0.005
	vs	$\sqrt{Sg_{oy}}$	r = -.044	p = 0.06
	vs	BMI_{oy}	r = 0.52	p < 0.05
$2h.G_{10y}$	vs	FG_{oy}	r = 0.48	p < 0.05
	vs	$\sqrt{Sg_{oy}}$	r = -.043	p = 0.06
$logAIR_{g10y}$	vs	FG_{oy}	r = 0.48	p < 0.05

Multiple Regression:

$FG_{10y} = FG_{oy} - \sqrt{Sg_{oy}}$; $r^2_{adj} = 53\%$, $p < 0.001$

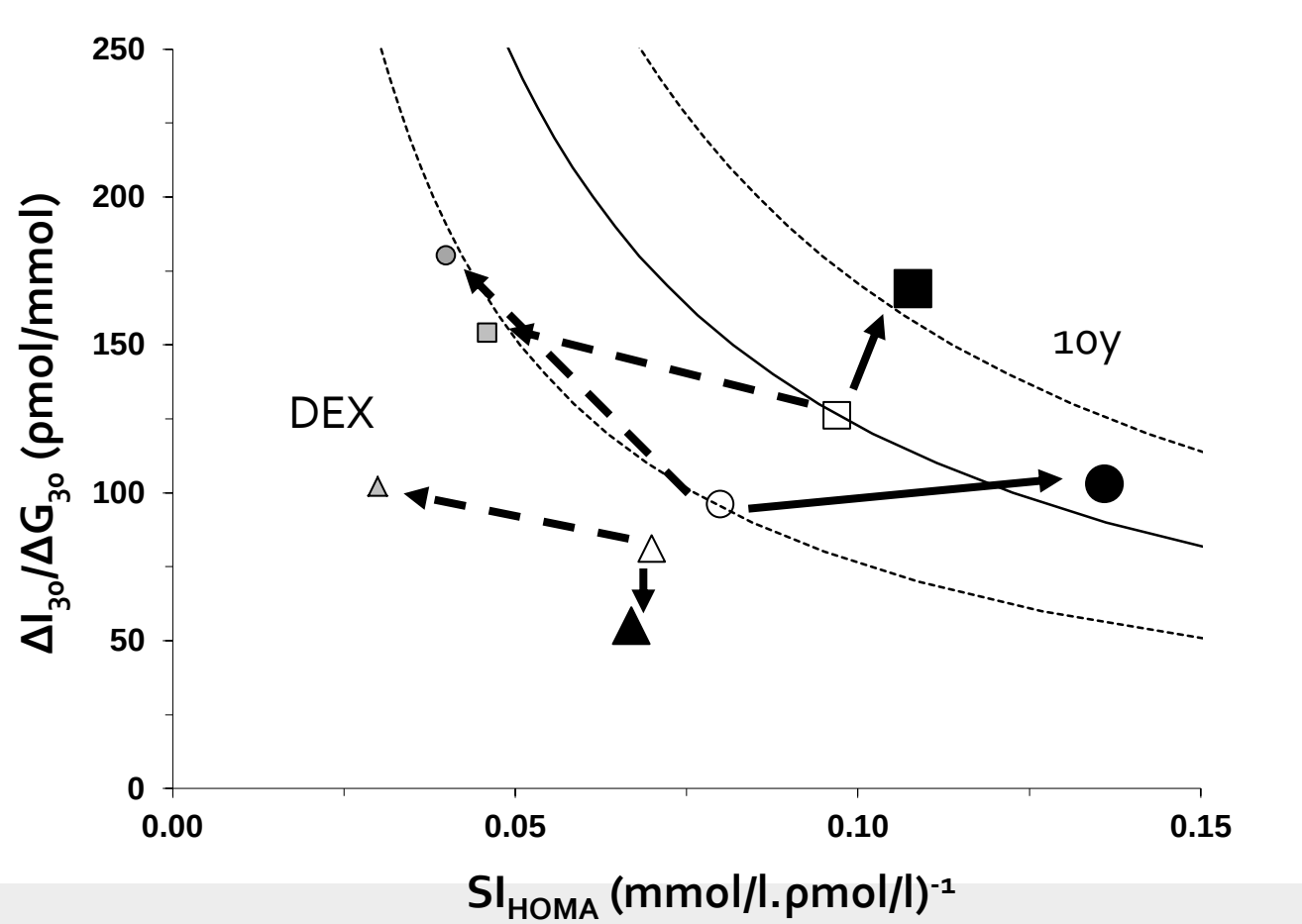
$2h.G_{10y} = FG_{oy}$ alone; $r^2_{adj} = 29\%$, $p < 0.03$

Acute DEX vs 10y Responses



Alford, F et al submitted (2011)

DEX- and 10y-induced relative changes in REL and CON of insulin secretion and insulin sensitivity



Alford, F et al submitted (2011)

Conclusion of the Dex vs. 10 y Study

- The metabolic responses to DEX mirror those seen in REL after 10y, particularly the DM_{DEX} subgroup, who had the most profound abnormalities at 10y.
- Diabetes emerged at 10y in 4/7 subjects only from the DM_{DEX} subgroup of the REL.
- iIFG emerged in 5 REL at 10y, unrelated to their DEX responses, (but related to their Sg_{0y}).

β cell function deteriorates over time with progression to glucose intolerance –

What happens to the Incretin Effect in Relatives and Controls over 10y?

Background to the Incretin Effect Study

1. The Incretin Effect is due to the release of the gut incretin hormones GLP-1 and GIP, which together augment nutrient stimulated insulin release from the β cell;

2. The magnitude of the GLP-1 and GIP release depends on
   a. the size of the oral/intraduodenal glucose load;
   b. the magnitude and biological efficacy of GLP-1 and GIP determine the β-cell response;
   c. GLP-1 and GIP secretions during an OGTT are biphasic;

3. Oral glucose tolerance is critically dependent on the magnitude of the acute phase insulin release (AIR_{OGTT}/AIR_{IVGTT});

4. It is estimated that 60% of AIRg is due to the GLP-1 and GIP augmentation of the β cell function;

Background to the Incretin Effect Study

5. Traditionally, the measurement of the Incretin Effect is based on an OGTT induced insulin release matched to an identical IV glucose infusion glycaemic profile over 0-120 minutes;

6. The insulinogenic index ($\Delta I_{AREA}/\Delta G_{AREA}$)is the most "physiological measure of AIRg;

7. Incretin hormones increase Sg (as well as β-cell secretion);

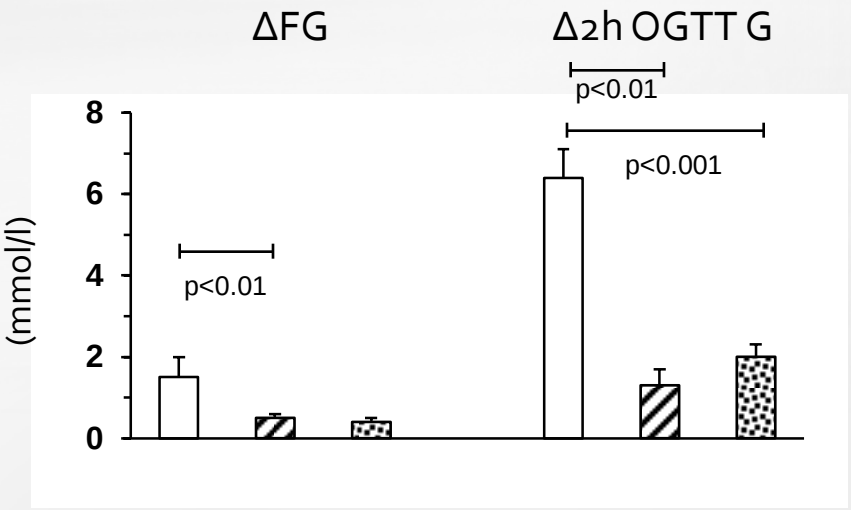
8. Genetic factors are linked to decreased incretin hormone action on the β cell e.g. TCF7L2 allele in Type 2 DM].

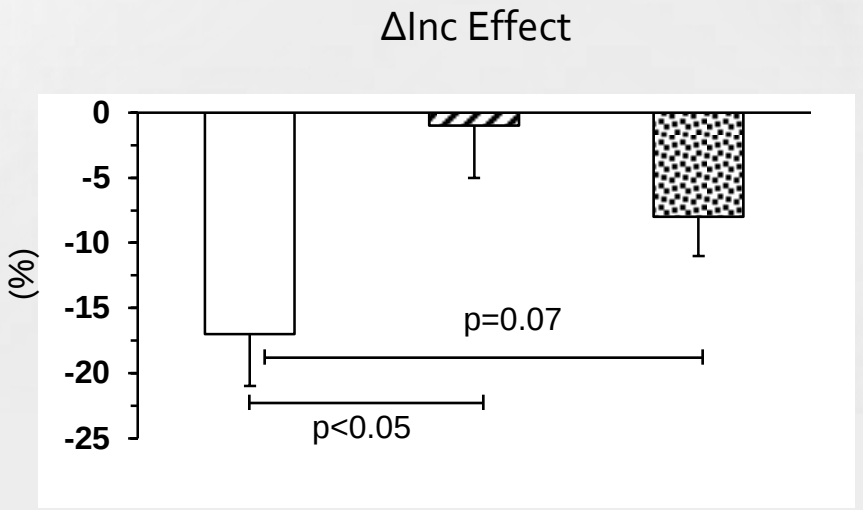
9. Previous REL studies: blunted beta cell response to GIP infusion; in vivo Incretin effect REL = CON (Nauk/Meier 2001/2004)

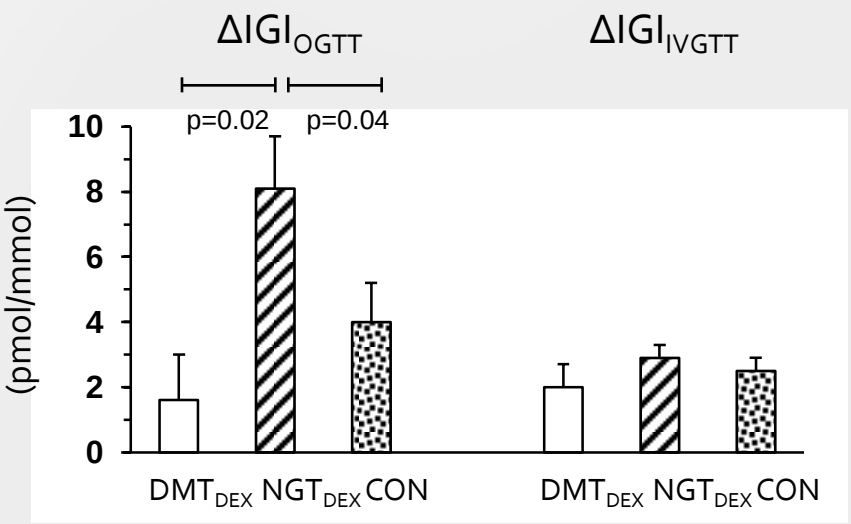
Study Design

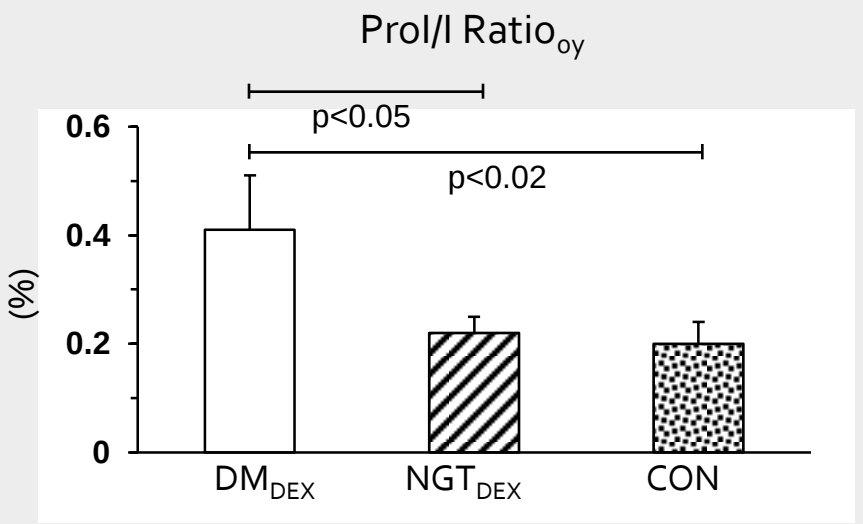
- 20 REL and 20 CON subjects were followed for 10y, with measurements for:
  - Glucose tolerance: OGTT and IVGTT
  - Acute insulin secretion:
    - OGTT : $\Delta I_{AREA\ 0\text{-}30'} / \Delta G_{AREA\ 0\text{-}30'} = IGI_{OGTT\ 0\text{-}30'}$
    - IVGTT : $\Delta I_{AREA\ 0\text{-}5'} / \Delta G_{AREA\ 0\text{-}5'} = IGI_{IVGTT\ 0\text{-}5'}$
  - Insulin Sensitivity (SI_{HOMA})
  - Incretin Effect:
    - % = $(IGI_{OGTT} - IGI_{IVGTT} / IGI_{OGTT}) \times 100$

Cremental (Δ) Changes Induced by DEX





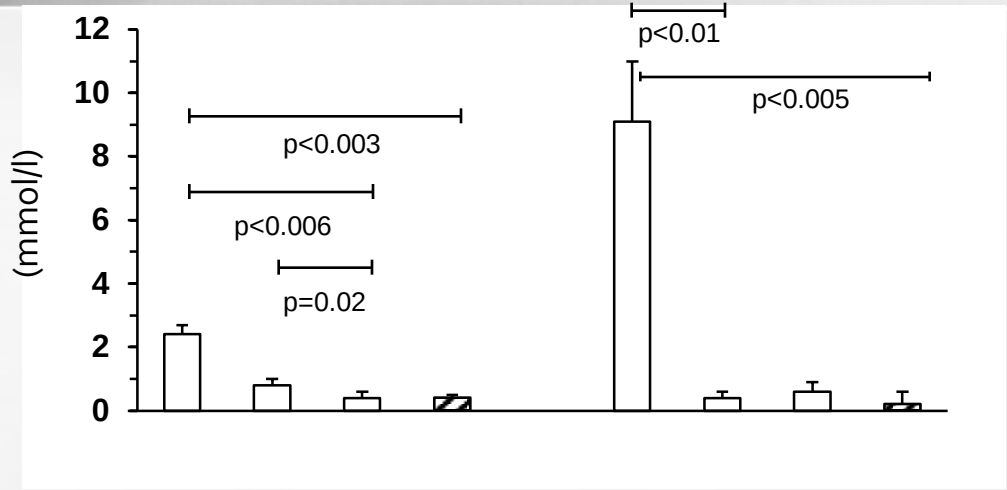




Alford et al, submitted (2011)

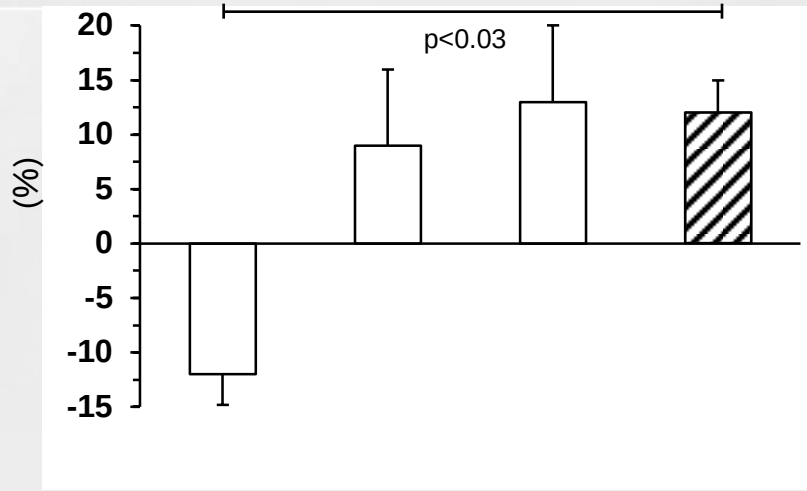
Cremental (Δ) Changes Over 10y

ΔFG

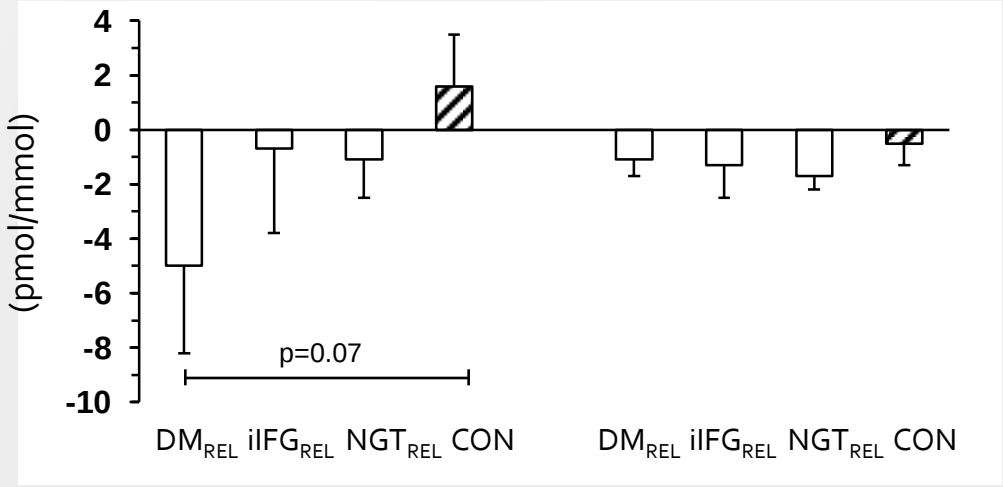


Δ2h OGTT G

ΔInc Effect

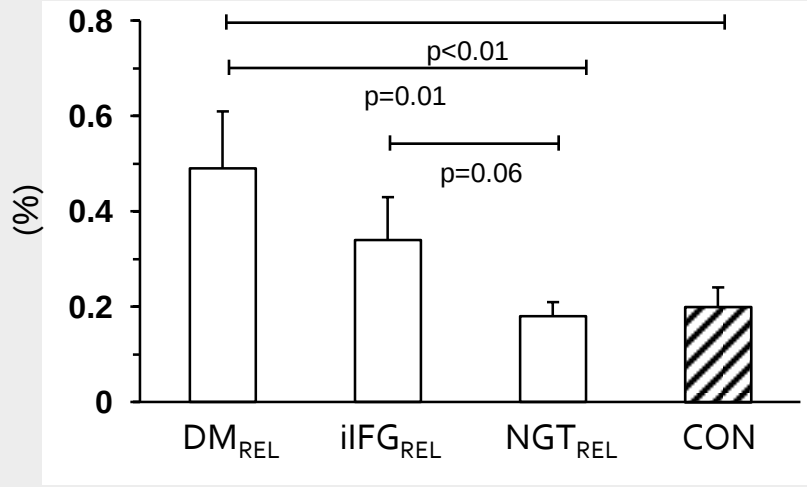


ΔIGI_{OGTT}



ΔIGI_{IVGTT}

$ProI/I\ Ratio_{oy}$



Alford et al submitted (2011)

Summary

- The DEX-induced changes of AIR_{OGTT} and Glucose tolerance in mildly insulin resistant normoglycaemic REL are secondary to a marked inhibition of the acute incretin effect on the β-cell.
- A preserved or even raised acute incretin effect (i.e. compensatory) is present at oy in normoglycaemic REL who have the most severe initial defect of $AIRg_{OGTT}$ (data not shown).
- The acute incretin effect does not deteriorate over time in CON subjects nor in normoglycaemic REL who develop iIFG or those REL who do not develop diabetes.
- The time (10y) induced deterioration of AIR_{OGTT} in diabetic subjects is primarily due to β-cell dysfunction and not a failing incretin effect.

General Conclusions

- Insulin resistance has a relatively mild "genetic" metabolic impact (i.e. ↓glycogen synthase activity) and becomes important in those subjects who have a low-normal or normal Sg, and/or in those who have declining β cell function; and/or develop progressive ↑ intracellular SkM lipid.

- "Abnormal" HGP seems to be a secondary phenomenon in the pathogenesis of dysglycaemia of diabetes.

- The metabolic role of the chronic hyperglucagonaemia on increasing hepatic insulin resistance and the development of the dysglycaemia of diabetes remains to be determined.

General Conclusions

- Over time, β-cell dysfunction remains the primary "genetic" factor (together with declining Sg) in the development of type 2 diabetes.
- Incretin agonist therapy needs to be commenced early whilst sufficient β-cell reserve is present.
- Given the complexities of the metabolic responses to activation of the rescue stress AMPK pathways in different tissues, its future as an effective therapeutic agent is guarded.
- Future therapies should be aimed at (i) preserving β-cell function and (ii) minimising the impact of reduced SI and Sg.

Acknowledgements

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- Steven Bloom for exposing me to glucagon pathophysiology
- Henry Burger for introducing me to GH hormone physiology and kinetics

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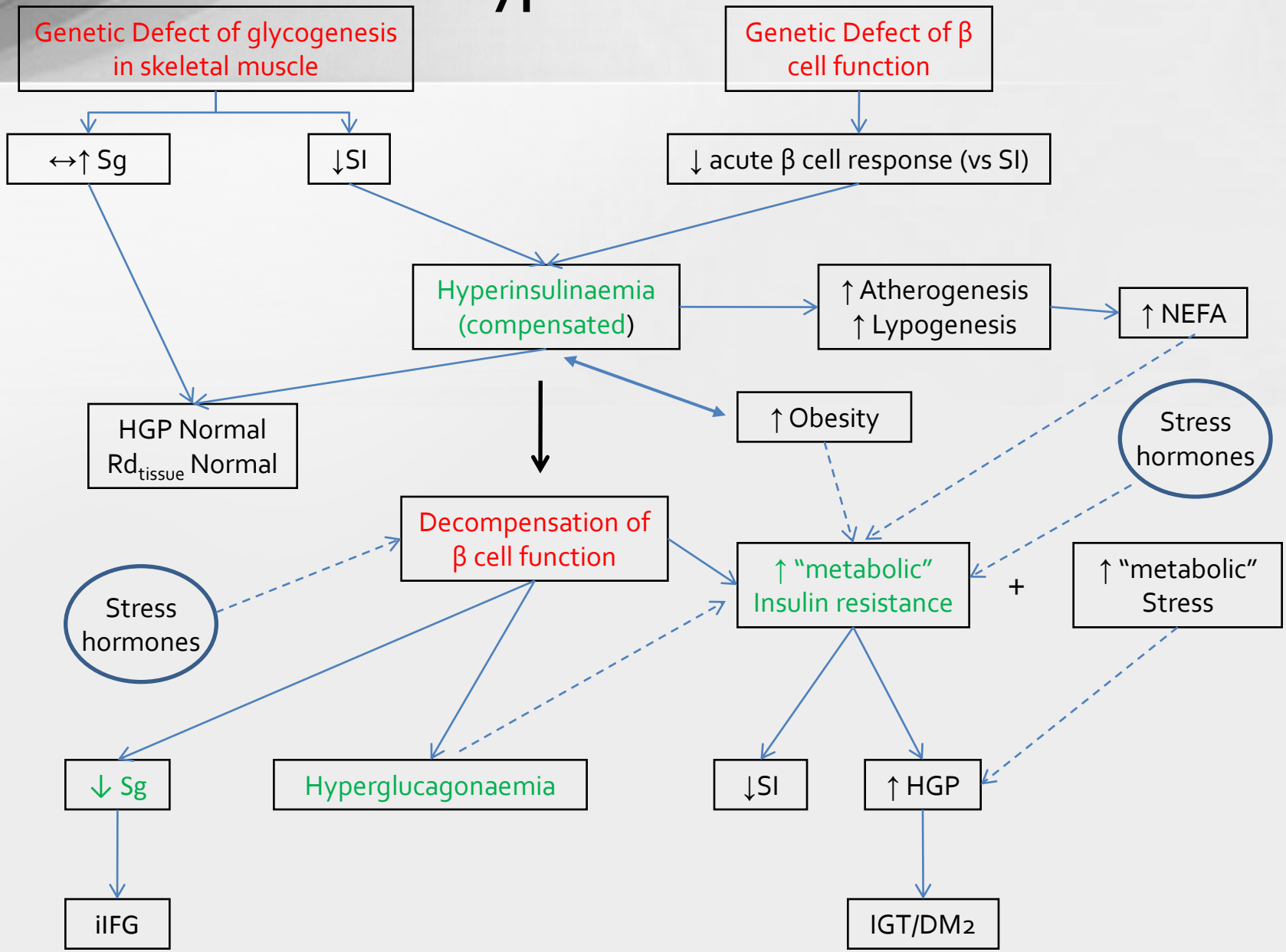
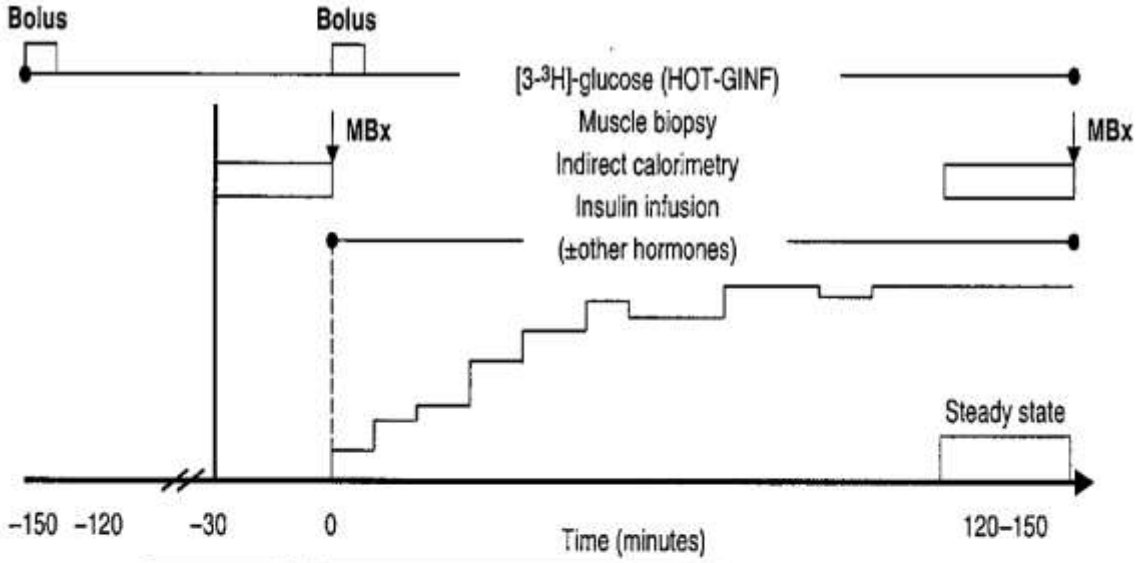
Hypothesis: Pathophysiology of Dysglycaemia and Type 2 DM



Extras

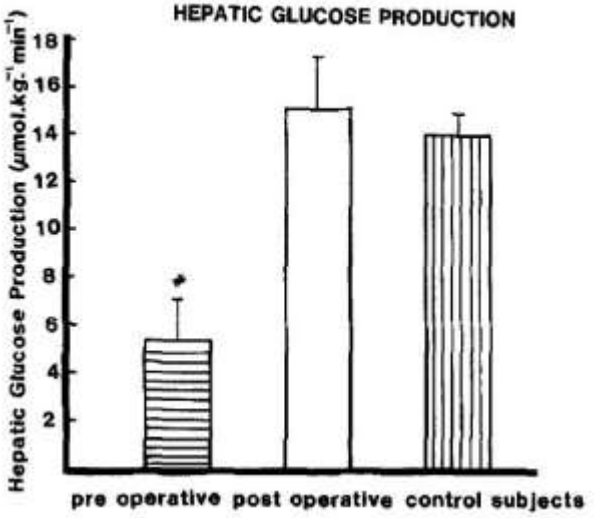
What is measured in a Clamp Study

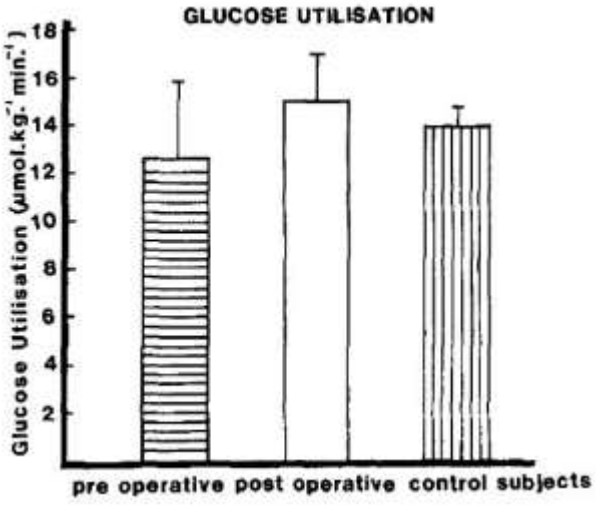


Method	Basal state	Insulin clamp
No tracer	–	M or M/I
Tracer	$HGP_b = R_{a_b}$ R_{d_b} GF_b (from ^3H_2O)	R_{d_i} $HGP_i = R_{d_i} - GINF_{HOT}$ GF_i (from ^3H_2O) $GS_i = R_{d_i} - GF_i$
Indirect calorimetry	GOx_b LO_b RQ_b	GOx_i LO_i RQ_i Non-Ox GS = $Rd_i - GO_i$
Muscle biopsy	$Glycogen_b$ $Glucose_b$, G-6-P_b, $lactate_b$ etc $Enzyme\ activities_b$ $Lipid\ metabolites_b$	$Glycogen_i$ $Glucose_i$, G-6-P_i, $lactate_i$ etc $Enzyme\ activities_i$ $Lipid\ metabolites_i$

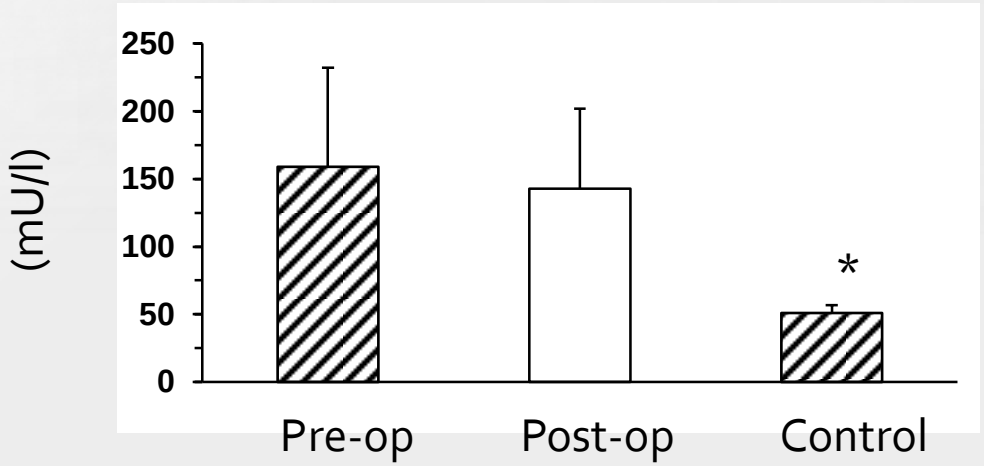
Beck-Nielsen et al, Insulin Resistance: p155 (2004)

Insulinoma Study





ED50 Dose Response Curves



* $p < 0.01$

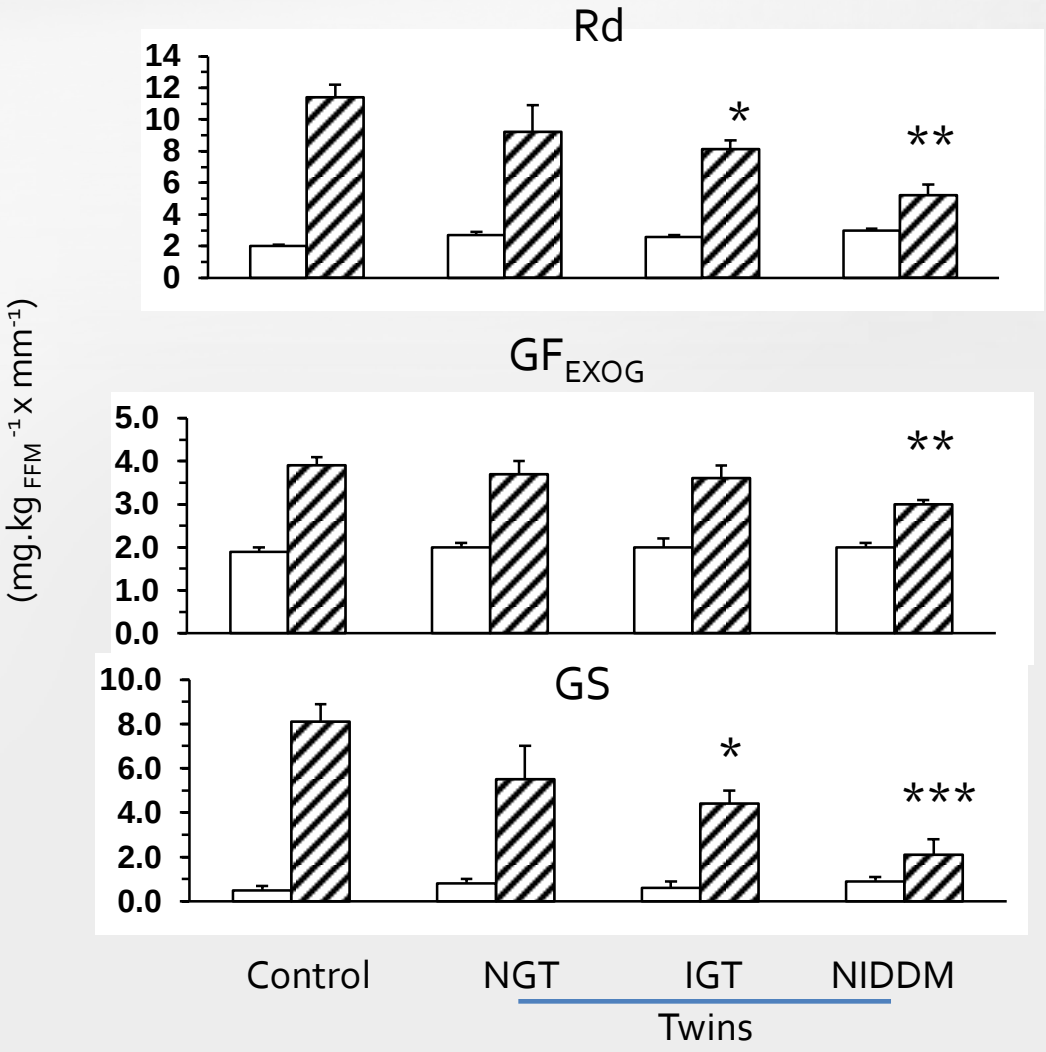
Nankervis A et al Diabetologia 28:427, 1985

Glucagon kinetics in cirrhosis

Group	Basal $\overline{IRG}$ (pg/ml)	MCR (ml/kg/min)	$t_{\frac{1}{2}}$ (min)	BSDR (pg/kg/min)
Controls	53 ± 13	13·0 ± 1·3	3·8 ± 0·4	750 ± 244
Cirrhotics Pre-op	213 ± 27***	13·3 ± 1·7	4·0 ± 0·3	3042 ± 454***
Cirrhotics Post-op	382 ± 73***†	7·6 ± 1·3*‡	3·5 ± 0·5	2518 ± 535**

Alford F et al Clinical Endocrinology 11: 413, 1979

Twin Study



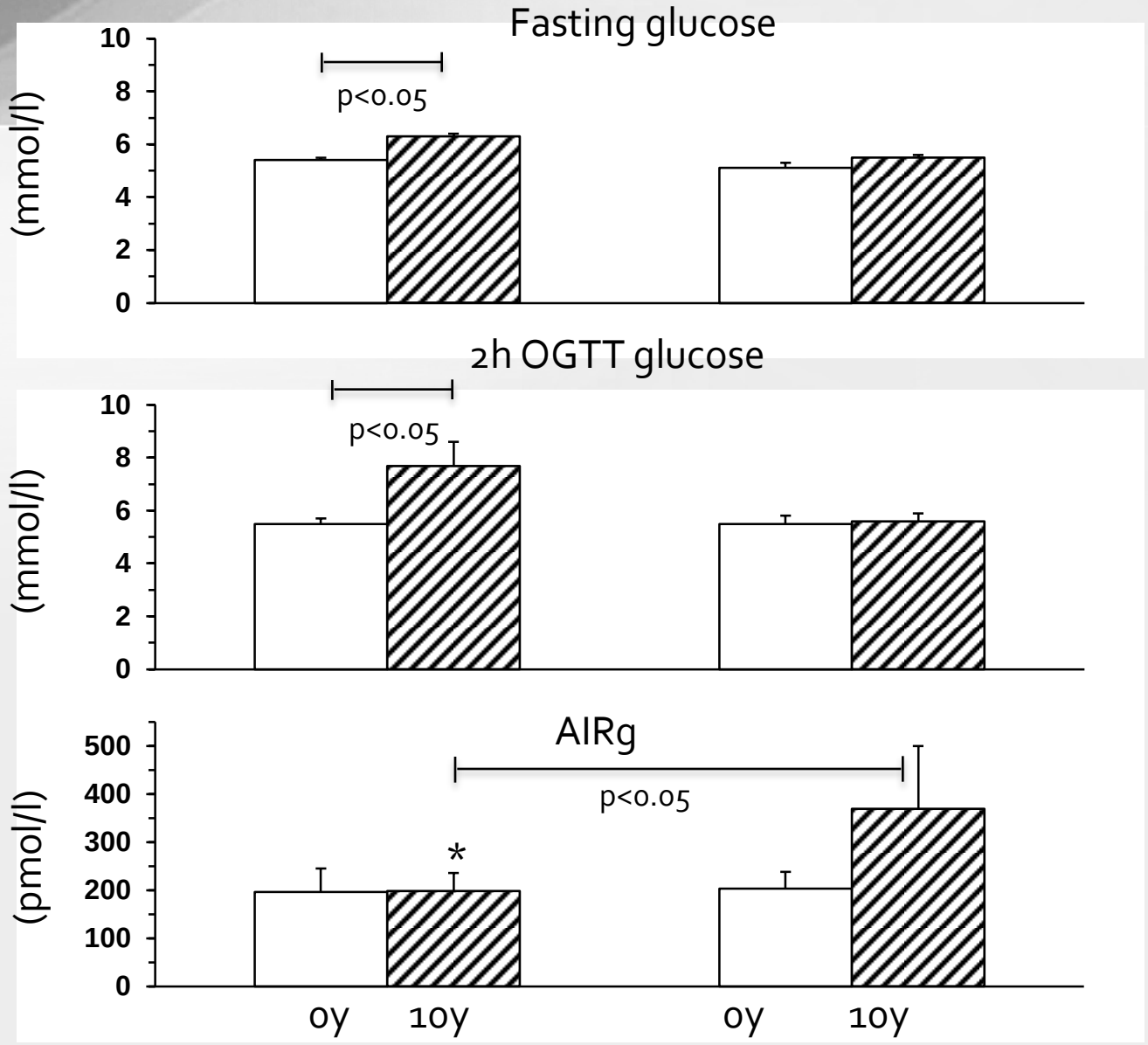
Baseline
Clamp

* p < 0.05
** p < 0.01
*** p < 0.005

Vs CON

Vaag, A et al Diab Med 13: 806 (1996)

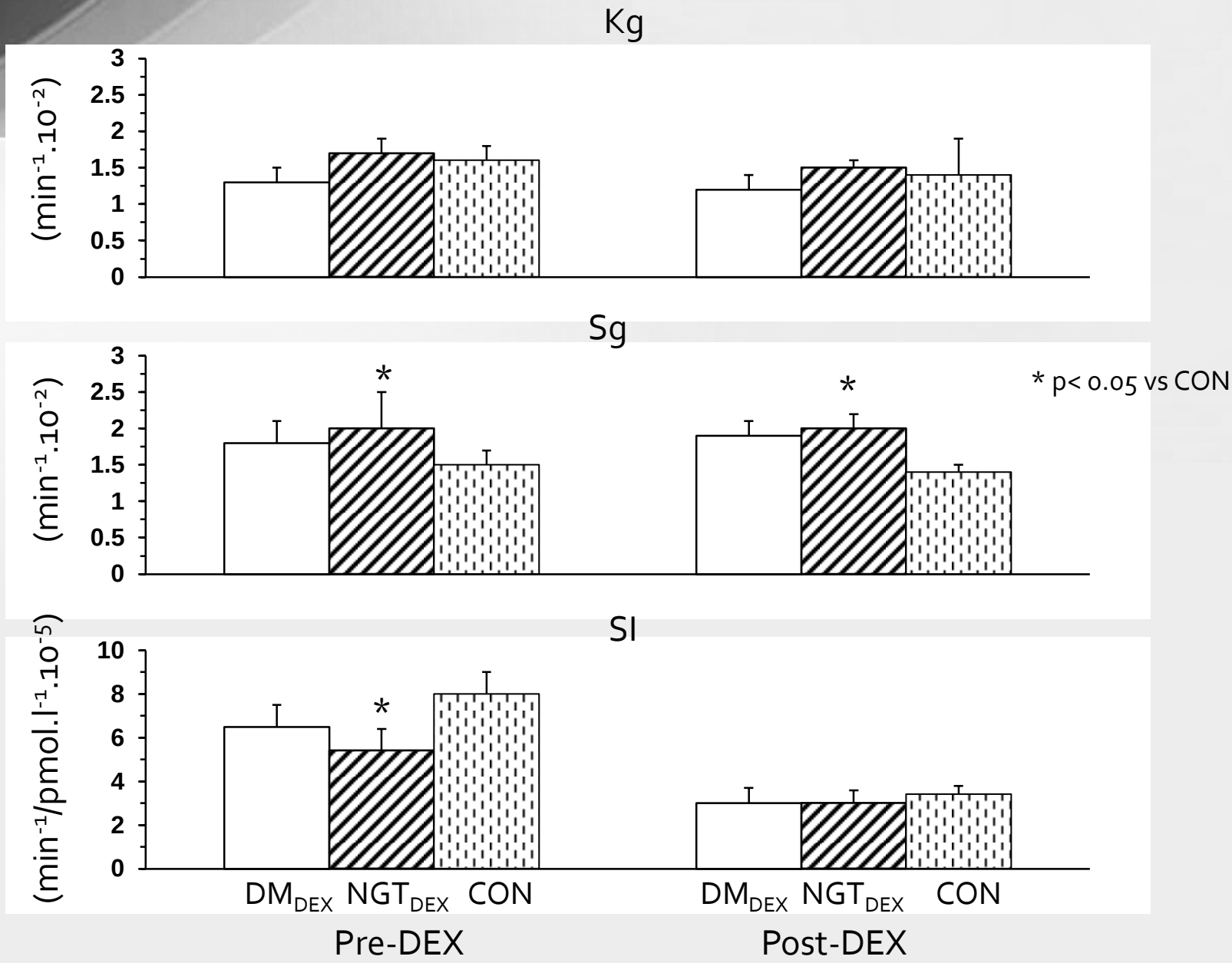
Metabolic Parameters in REL and CON at 0y and 10y



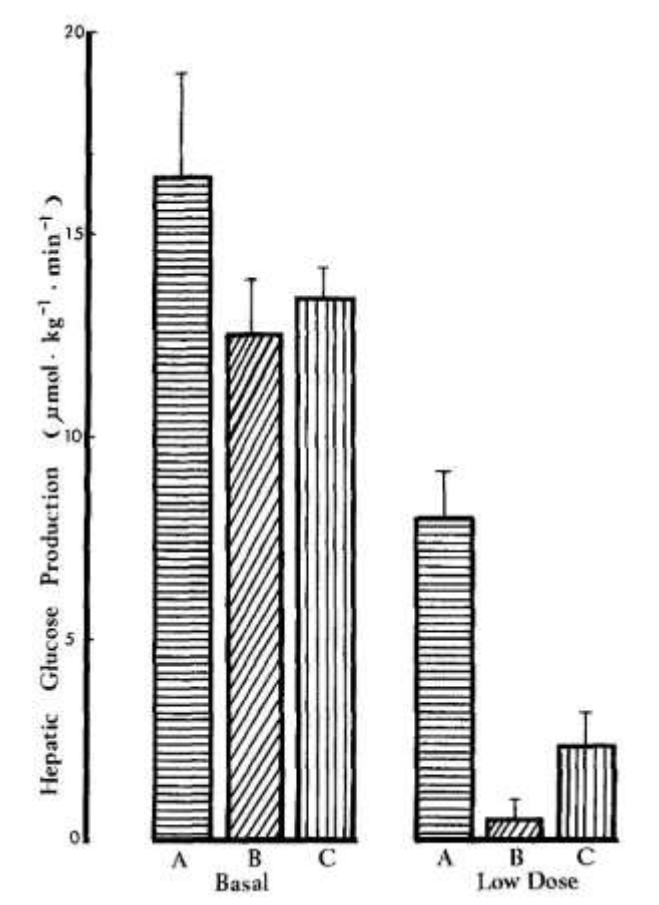
Note: 4 REL: DM2 at 10y; 5 REL: iIFG at 10y

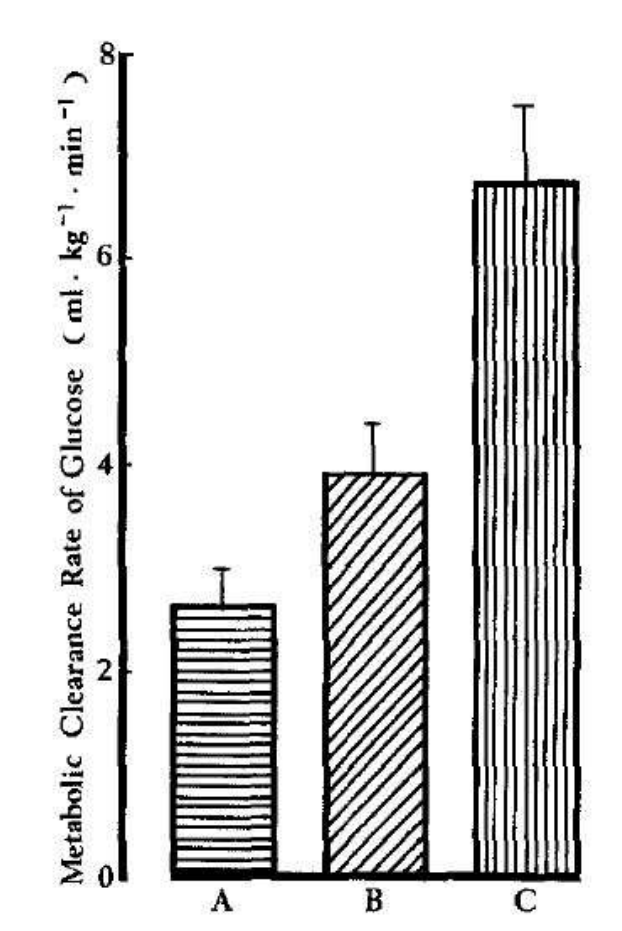
Alford, F et al submitted (2011)

Glucose Kinetic Parameters Before and After DEX Exposure

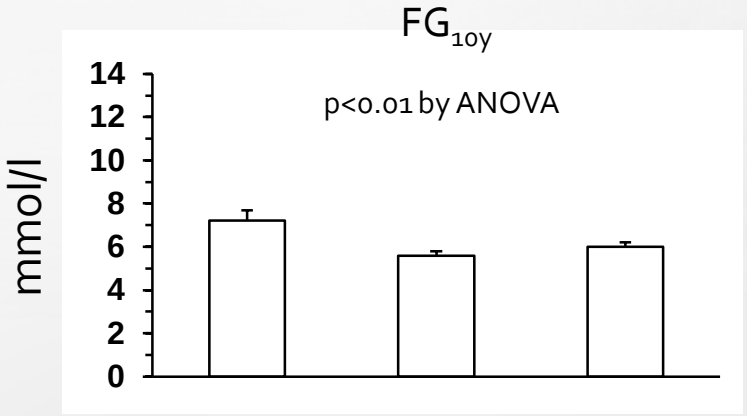


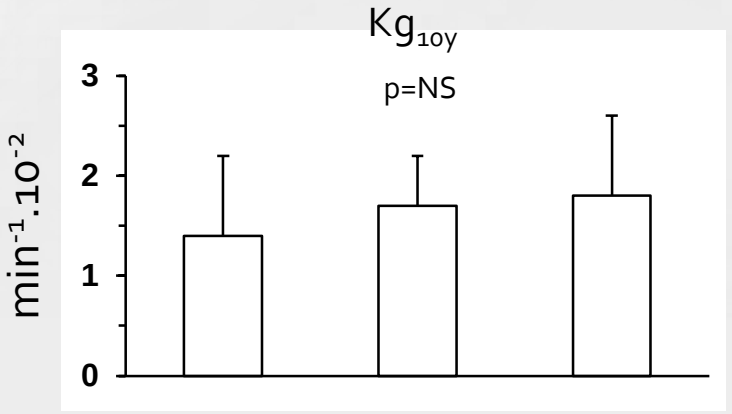
Henriksen, J et al Diabetologia 40: 1439 (1997)

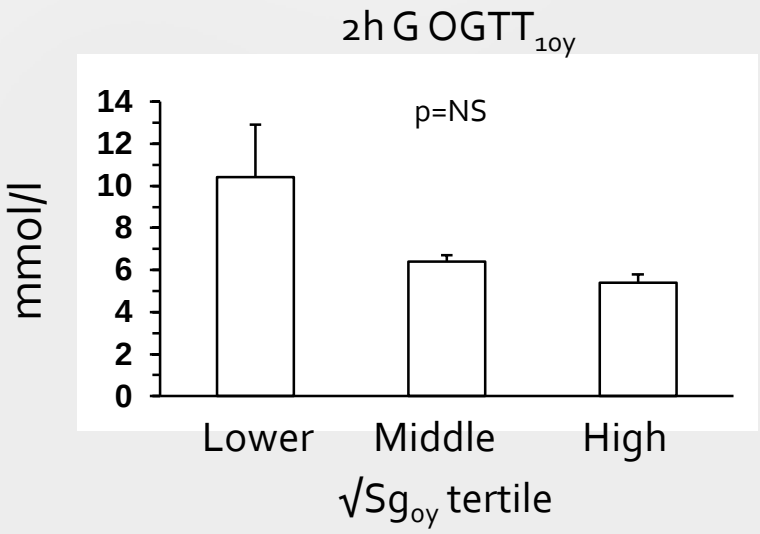

Hepatic Glucose Production (μmol · kg⁻¹ · min⁻¹)
20
15
10
5
0
A
B
C
Basal
A
B
C
Low Dose

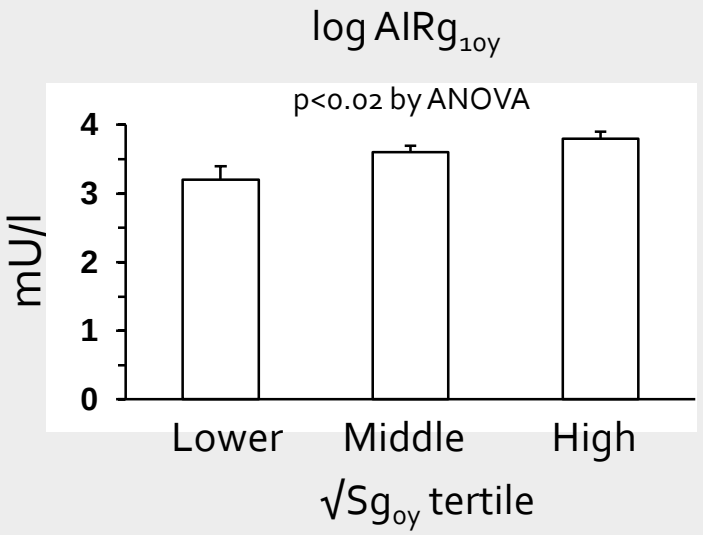

Metabolic Clearance Rate of Glucose (ml · kg⁻¹ · min⁻¹)
8
6
4
2
0
A
B
C

P. Glucose, Kg and AIRg at 10y, grouped by Sg tertiles









Alford, F et al submitted (2011)

Determinants of FG and 2hOGTT glucose at 10y

$FG_{10y} \ \alpha \ FG_{0y} + 2hOGTT.G_{0y} + \log SI_{HOMA}$

(r^2_{adj} 66%; $p<0.0005$)

$2hOGTT.G_{10y}$

$\alpha \ FG_{postDEX} + 2hOGTT.G_{postDEX} + \log SI_{HOMA\ post\text{-}DEX}$

(r^2_{adj} 56%; $p<0.001$)

Note: No oy pre-or post-DEX insulin secretion parameters entered into the models.

Alford, F et al submitted (2011)

Conclusions

- "The postulate is that active treatment of a 'potential' diabetic might delay the onset of islet cell failure;
- The testing of such a hypothesis must depend on the ability to diagnose with absolute certainty an 'early' diabetic abnormality of glucose tolerance;
- A confident diagnosis of diabetes mellitus in patients with mild abnormalities of oral glucose tolerance alone cannot be made readily."

Alford F et al Diabetologia 7:173, 1971