

After Lifestyle Changes: What's Next and What's New in Diabetes?

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Disclaimer

- Diablo Clinical Research performs studies for:
 - Almost all major pharmaceutical companies.
 - Many minor pharmaceutical companies.
 - Device companies.

Outline

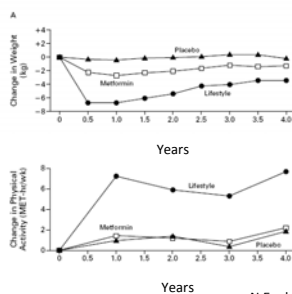
- Role of Food Choices and Activity Level
- DM1
 - Altering Beta Cell Destruction
- DM2
 - Newer variations on older themes
 - Newer tricks

Role of Food Choices and Activity Level

- Diabetes Prevention Program
 - 3234 individuals at 27 centers with either impaired fasting glucose or impaired glucose tolerance (1997 ADA definitions).
 - Randomly assigned to either:
 - Lifestyle intervention
 - Metformin
 - Placebo
 - Followed for 2.8 years on average.
 - Study ended 1 year early due to the results.

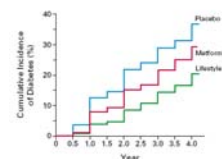
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Responses by Treatment Group



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DPP: Progression to Diabetes



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Role of Food Choices and Activity Level

- Results:
 - Lifestyle group
 - 50% lost 7% of their weight at 24 weeks
 - 74% exercised 150 minutes/week
 - 58% lower risk of progressing to DM2 compared to placebo group.
 - Lifestyle effect seen in all age groups, races, and equally well in both genders.
 - More effective than metformin in older, thinner individuals.

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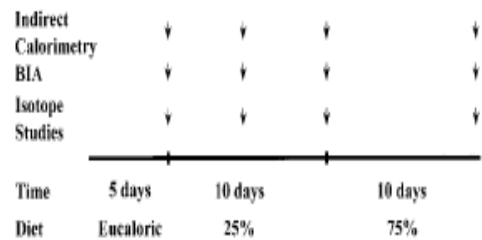
Energy Restriction and DM2

- Is it weight loss, caloric restriction, or both?
- How much weight must one lose in order to see benefit in DM2?
- How long does any effect persist after caloric restriction?

Energy Restriction and Effects Upon Diabetes Mellitus Type 2

- 4 men, 4 women
 - Average age 51 years
 - Average duration of DM2 5 years
 - Average HbA1c 8.1%
 - BMI 36 (average weight 107 kg)
 - Off oral agents for 2 weeks prior to admission to the GCRC
 - RD consultation at GCRC
 - Basal diet (weight maintenance) 18% pro, 35% fat, 47% carb
 - 25% eucaloric diet: 30% pro, 9% fat, 61% carb
 - 75% eucaloric diet: 20% pro, 30% fat, 50% carb

Overall Study Design



Diabetes 49:1691–1699, 2000

Results

Body weight and composition by phase

	Day			
	0	5	10	20
Weight	107 ^a ± 14	105 ^b ± 13	104 ^c ± 13	104 ^c ± 13
Fat free mass	58 ± 6	58 ± 6	58 ± 6	58 ± 6
Fat	49 ^a ± 9	48 ^b ± 8	46 ^c ± 8	46 ^c ± 8

Data are means ± SD. Values are expressed in kilograms. Values with different superscripts in the same row are significantly different at $P < 0.05$.

Diabetes 49:1691–1699, 2000

Results

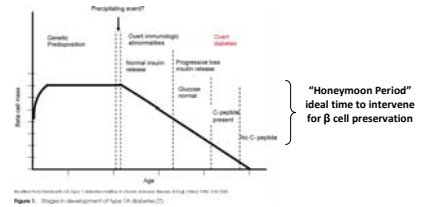
	Baseline	Day 5	Day 10	Day 20
FBG (mg/dl)	214	160	133	158
NPRQ	0.74	0.71	0.71	0.74

Diabetes 49:1691–1699, 2000

Conclusions

- Caloric restriction *per se* leads to improved glucose levels.
- Results are short lived.
- Reduction in endogenous glucose production correlates with improved fasting glucose.
- Lipid metabolism is elevated in DM2 and does not (cannot?) increase in response to caloric restriction.

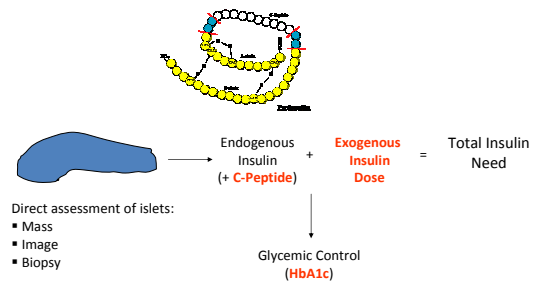
Progressive Beta Cell Loss in DM1



Can We Alter the Course of DM1?

- Immune mediated disease.
 - Cyclosporine
 - Rituxan
 - Abatacept
 - Otelixizumab
 - GAD 65 vaccine

How Best to Assess Beta Cell Function?



C-peptide

- Considered optimal endpoint for T1DM β cell preservation trials by scientific community, FDA
 - ADA Workshop, 2004 (Chair: Jerry Palmer MD, Univ Washington, Seattle)
 - FDA Guidance, 2008
 - Ph 3 studies can designate C-peptide compared to control at 1 year as the primary efficacy endpoint
 - Studies should also show “clinically meaningful” reductions in insulin use and equal glycemic control between Rx and control arms

GAD 65

- Age 10 to 20 years, newly diagnosed within 90 days of screening.
- C-peptide above 0.1 nmol/L, positive GAD 65 Ab
- Vaccine/placebo at 0,30, 90, and 270 days
- Main outcome: AUC stimulated C-peptide

Abatacept

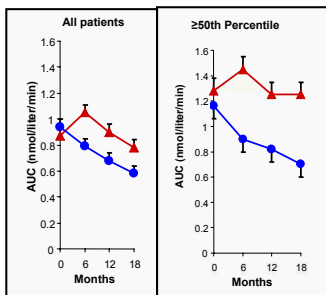
- IgG that interferes with the activation of T-cells.
- Does not lead to a depletion of T-cells and therefore may be “safer” than other immunosuppressive agents
- Ages 6-45, diagnosed within 100 days, C-peptide >0.2 nmol/L (MMTT), positive antibodies.

BDR Phase II Study of Otelixizumab in New-Onset T1DM

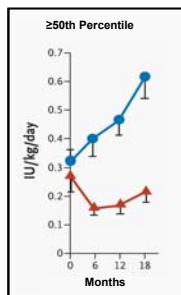
- Study design:
 - 80 subjects randomized 1:1; double-blind, placebo controlled
 - ≤ 4 weeks insulin Rx, fasting C-peptide > 0.2 nmol/L
 - 6 consecutive daily doses otelixizumab, 8 mg/dose
- Endpoints:
 - Change in stimulated C-peptide (hyperglycemic clamp then glucagon) at 6, 12, 18, 24, 36, 48 Mo
 - Insulin Dose

BDR Phase II Study of Otelixizumab in New-Onset T1DM

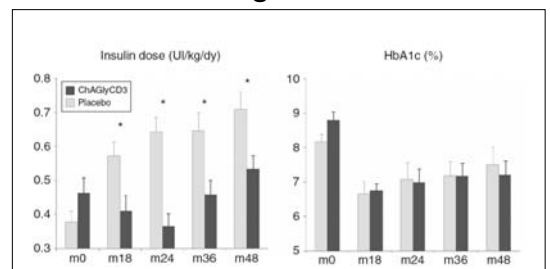
Stimulated C-peptide



Insulin Use



BDR Study: Single 8-Day Course of Otelixizumab Reduced Insulin Use Through 48 Mo



Otelixizumab DEFEND-1

- Mab against CD-3 T-cells
- Ages 12 to 45, within 90 days of diagnosis.
- At least one positive antibody, C-peptide > 0.2 and under 3.5 nmol/L during MMTT.
- Primary outcome: AUC C-peptide at 12 months.
- 2 year study.

DM-2 Pathophysiology 1999

- Insulin Resistance
 - Muscle
 - ?
 - Liver
 - Metformin
- Insulin Secretion
 - Pancreas beta cells
 - Sulfonylurea

DM-2 Pathophysiology 2010

- Insulin Resistance
 - Muscle
 - TZD
 - Liver
 - Metformin
 - 11 β HSD
 - SCD
 - Adipose Tissue
 - Brain
 - Cannabinoid Receptor Blockers
- Insulin Secretion
 - Pancreatic beta cells
 - Pancreatic alpha cells
- Exendin
 - Exenatide
 - Liraglutide
 - Taspoglutide

Conclusions

- Diet and activity are still the cornerstones of care.
- New therapies exist based upon newer understandings of pathophysiology.
- Safety in addition to efficacy need to be assessed.