Low GI, Low Carbohydrate Diets in Diabetes

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Outline

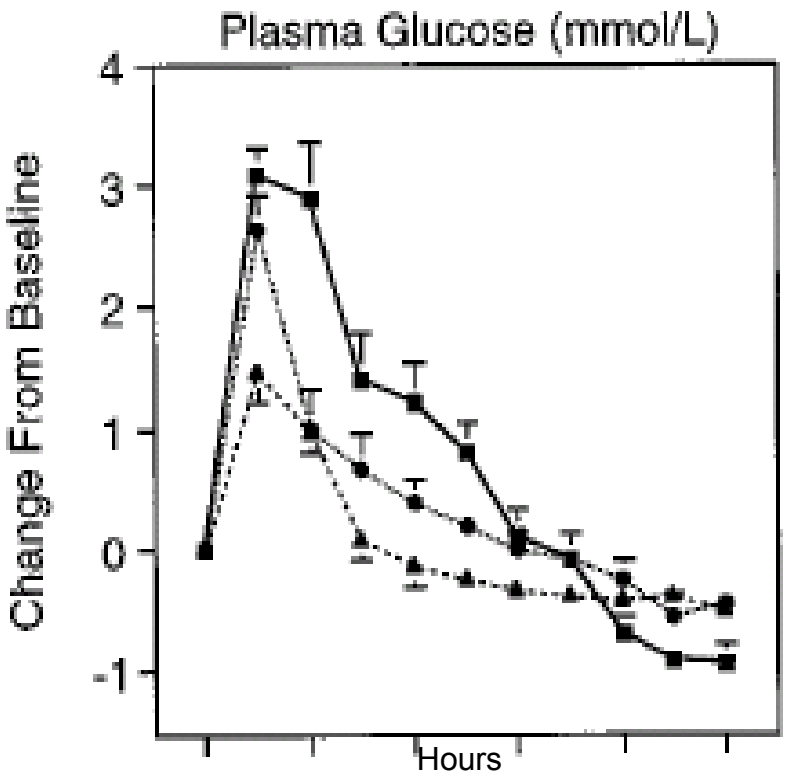
- Glycemic effect of carbohydrate-containing foods
- Physiologic basis for carbohydrate-restriction in diabetes
- Historical use of carbohydrate-restriction for diabetes
- Case series
- Clinical trials

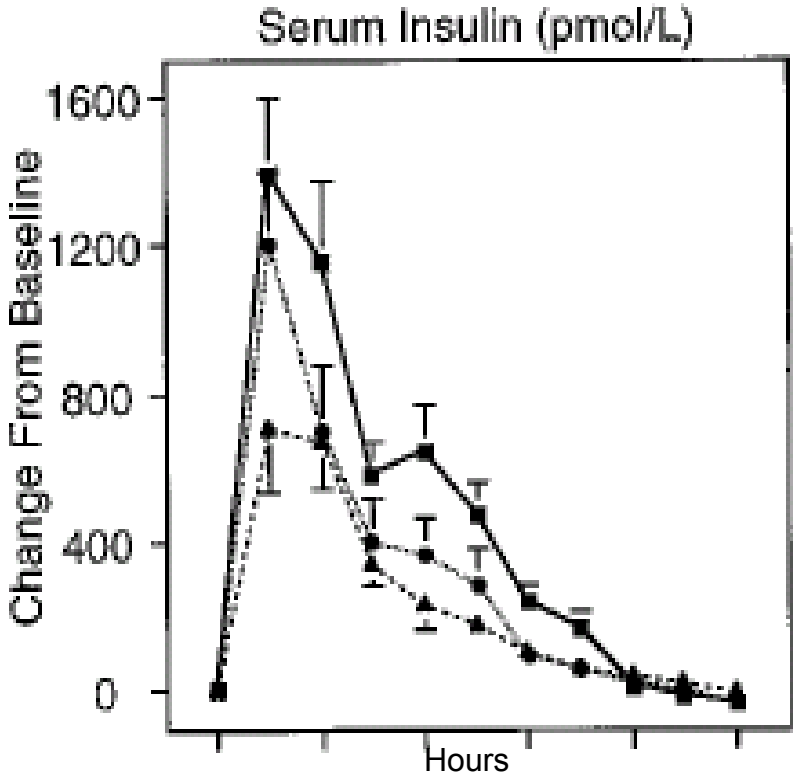
ADA Goals of Medical Nutritional Therapy for Diabetes

- Attain and maintain optimal metabolic outcomes including
  - Blood glucose levels in the normal range or as close to normal as is safely possible to prevent or reduce the risk for complications of diabetes
  - A lipid and lipoprotein profile that reduces the risk for macrovascular disease
  - Blood pressure levels that reduce the risk for vascular disease
- Prevent and treat the chronic complications of diabetes…
- Improve health through healthy food choices and physical activity…
- Address individual nutritional needs taking into consideration personal and culture preferences and lifestyle…

Position Statement of the American Diabetes Association. Nutritional principles and recommendations in diabetes. Diabetes Care. 2004;27:S36-S46.

Dietary Carbohydrate Leads to an Increase in Postprandial Glycemic/Insulin Response





Jenkins DJA et al. Diabetologia 1982;22:450-455. (Glycemic Index)
Foster-Powell K, Holt SH, Brand-Miller JC. Am J Clin Nutr 2002;76:5-56. (Glycemic Index)
Salmeron J et al. JAMA 1997;227:472-7. (Glycemic Load)

*Ludwig DS, Maizoub JA et. Al. High glycemic index foods, overeating, and obesity. Pediatrics 1999;103:E26.

Meals: GI is the Major Factor; More Fat Reduces Glycemic Effect

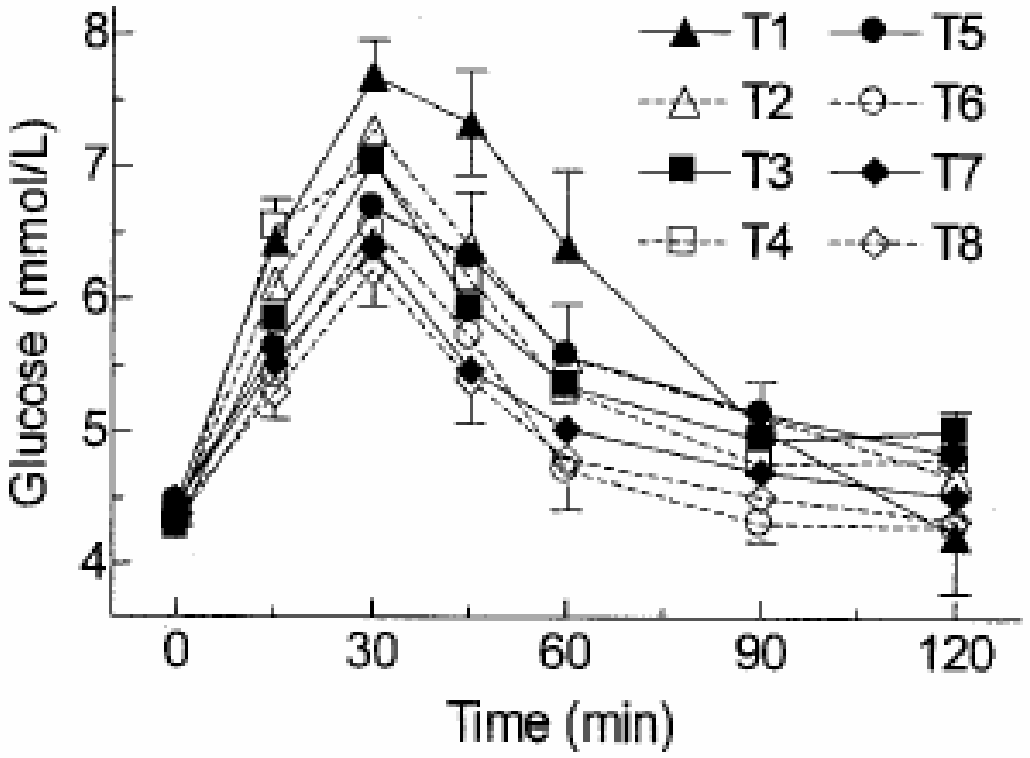
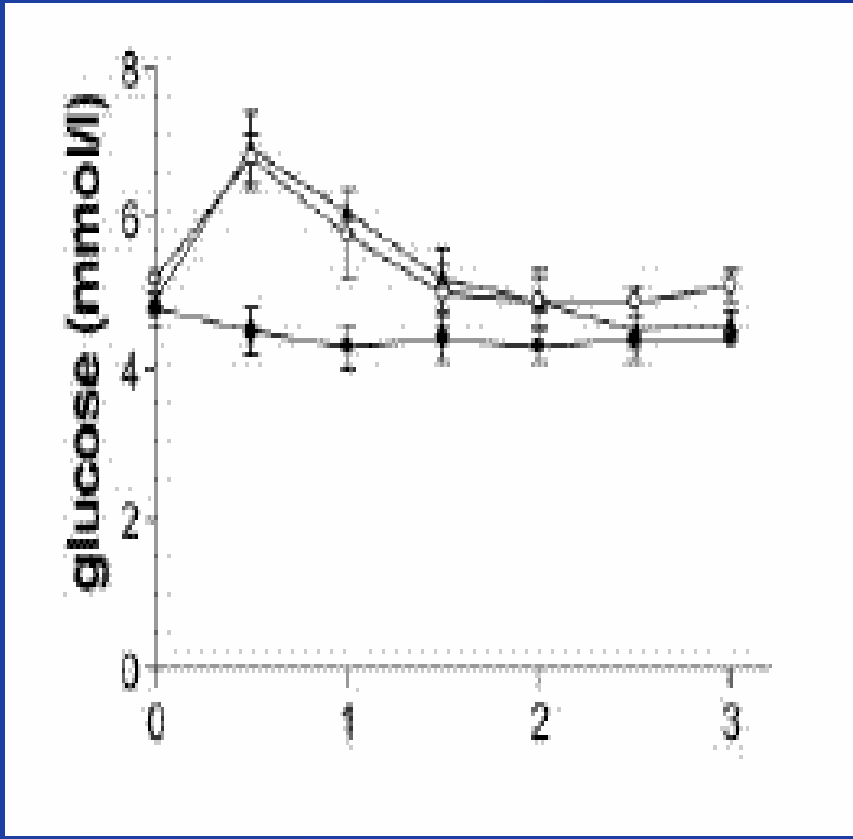


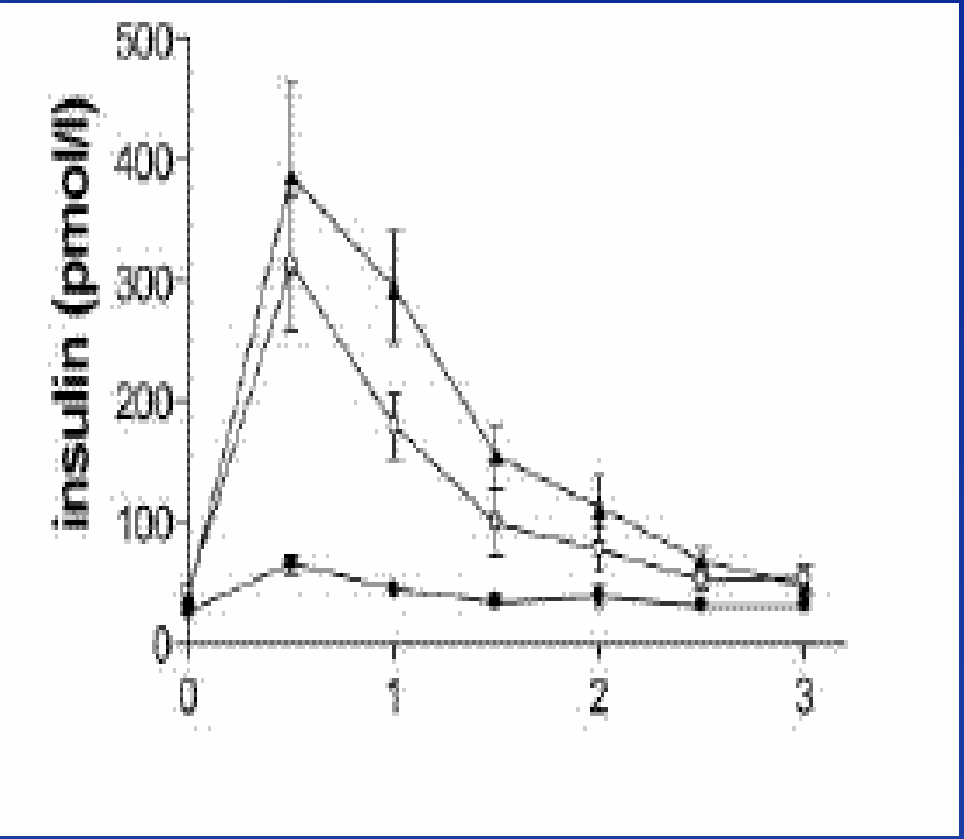
FIGURE 1. Mean (±SEM) glucose and insulin responses in normal subjects elicited by 14 different test meals. Test meals S1–S6 (top and middle) were tested by 16 subjects in Sydney; test meals T1–T8 (bottom) were tested by 10 subjects in Toronto.

Wolever TMS et al. Am J Clin Nutr 2006.;83:1306-12.

Glucose and Insulin Response to a 300 Kcal Meal

after 10 d of a high- (*triangles*), intermediate- (*open circles*), and low-carbohydrate (*closed circles*) diet (n=6).

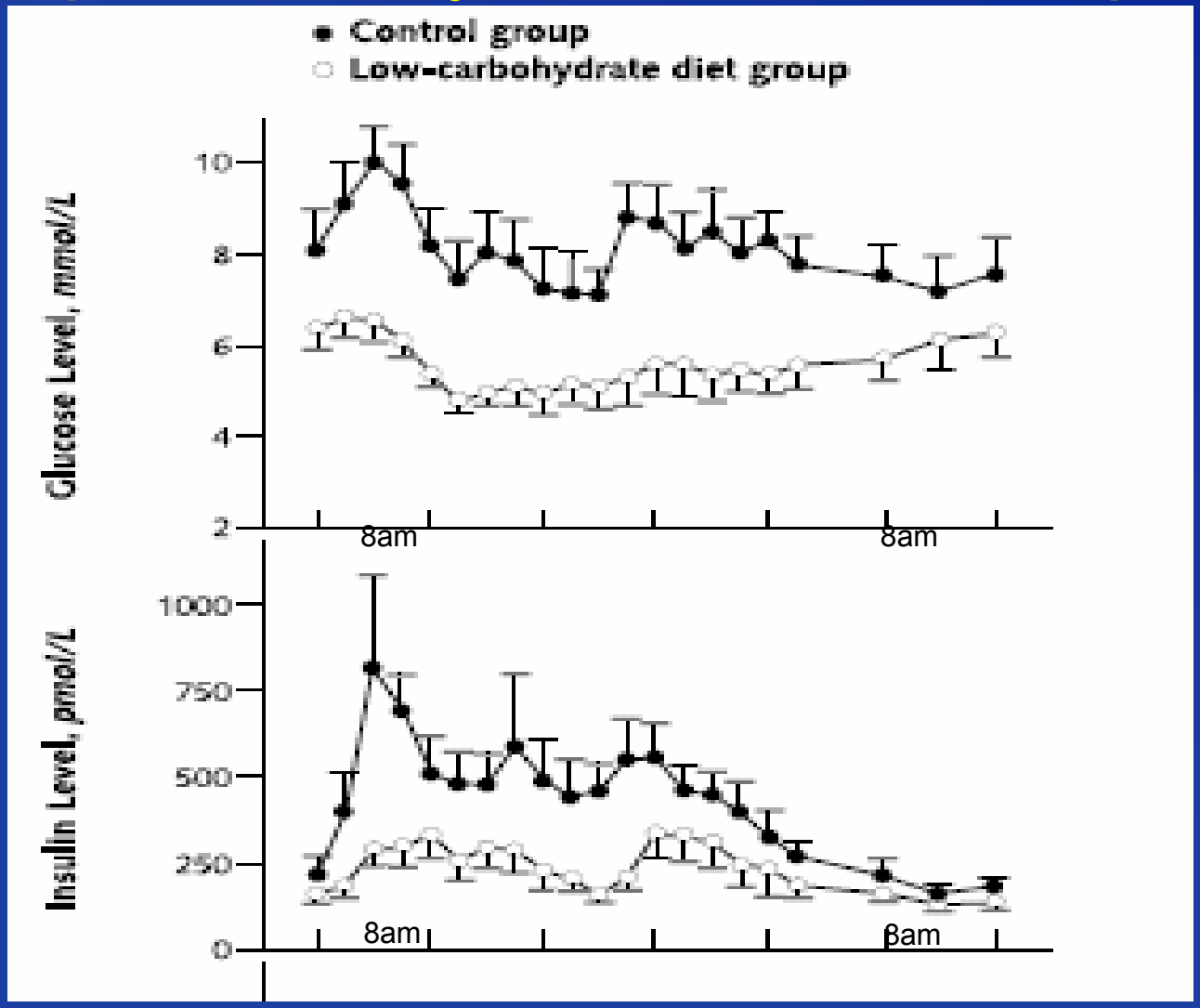




Glucose AUC was lowest for the low-carbohydrate diet (p=0.001).
Insulin AUC was different for each diet (p=0.001).

Bisschop et al. *J Clin Endocrinol Metab*;2003:88:3801–3805. Data are means (SE).

Very Low Carbohydrate Diet Decreases Postprandial Glycemic/Insulin Response



Boden G et al. Ann Intern Med 2005;142:403-11.

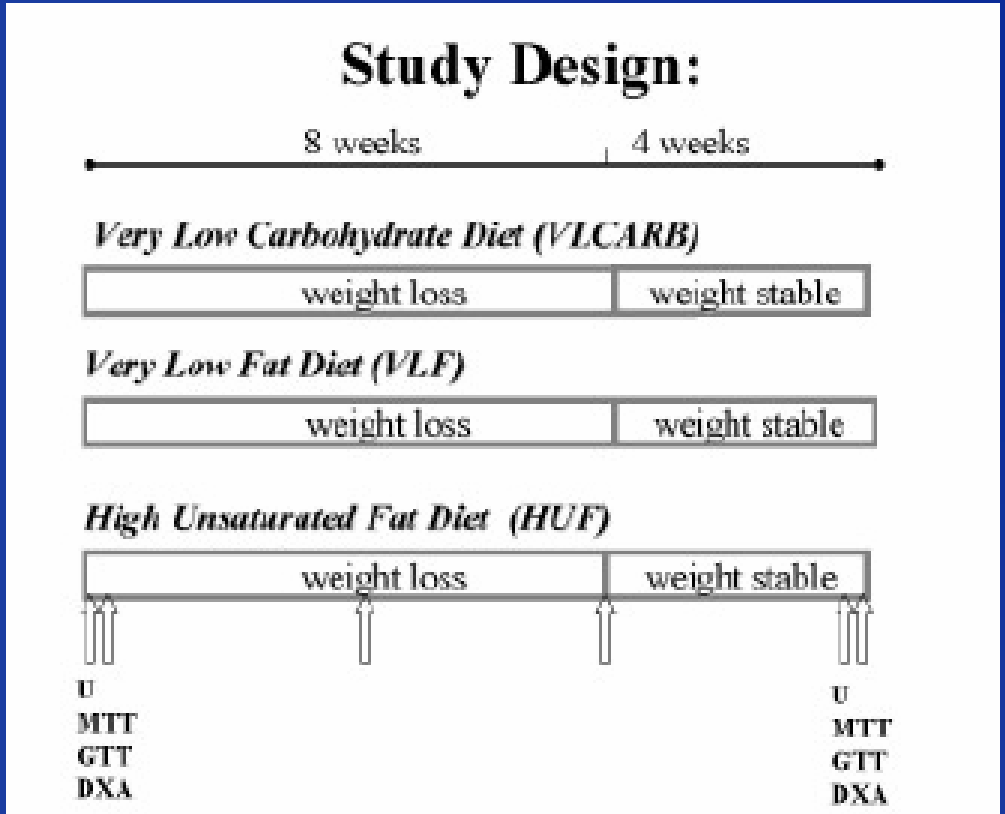


Figure 2
Schematic representation of study design. U = 24 hour urine. MTT = meal tolerance test. GTT = glucose tolerance test. DXA = Dual Xray Absorptiometry. ↑ = blood sample. VLCARB = very low carbohydrate diet (n = 24) VLF = very low fat diet (n = 22) HUF = high unsaturated fat (n = 21).

Noakes M, Foster PR, Keogh JB, James AP, Mamo JC, Clifton PM. Comparison of isocaloric very low carbohydrate/high saturated fat and high carbohydrate/low saturated fat diets on body composition and cardiovascular risk. Nutrition & Metabolism 2006;3:7.

Table 3: Nutrient intake by dietary treatment during weight loss and weight maintenance assessed using weighed food records[1,2]

	VLCARB		VLF		HUF	
Nutrient	**Weight loss**	**Maintenance**	**Weight loss**	**Maintenance**	**Weight loss**	**Maintenance**
Energy (kJ)	6193 (± 82)	7706 (± 167)	6061 (± 168)	7000 (± 333)	5996 (± 88)	7659 (± 201)
% energy protein[3]	33.1 (± 0.85)	30.5 (± 0.91)	19.9 (± 0.33)	20.3 (± 0.55)	22.6 (± 0.46)	21.4 (± 0.51)
% energy fat[3]	55.1 (± 1.96)	54.3 (± 2.53)	11.7 (± 0.32)	12.5 (± 0.59)	27.4 (± 0.84)	28.0 (± 0.88)
% energy carbohydrate[3]	8.8 (± 2.71)	12.4 (± 3.38)	67.7 (± 0.60)	66.0 (± 0.92)	47.9 (± 0.83)	48.7 (± 1.07)
% energy saturated fat[4]	17.6 (± 0.77)	17.7 (± 1.01)	4.5 (± 0.16)	5.1 (± 0.30)	5.4 (± 0.18)	6.0 (± 0.32)
% energy MUFA[3]	27.0 (± 1.16)	26.2 (± 1.41)	3.3 (± 0.11)	3.6 (± 0.21)	12.0 (± 0.48)	12.3 (± 0.51)
% energy PUFA[3]	6.3 (± 0.13)	6.5 (± 0.28)	1.7 (± 0.03)	1.8 (± 0.16)	7.6 (± 0.29)	7.2 (± 0.30)
Calcium (mg)[5]	959 ± 14	1297 ± 58	867 ± 32	1079 ± 55	969 ± 19	1169 ± 43

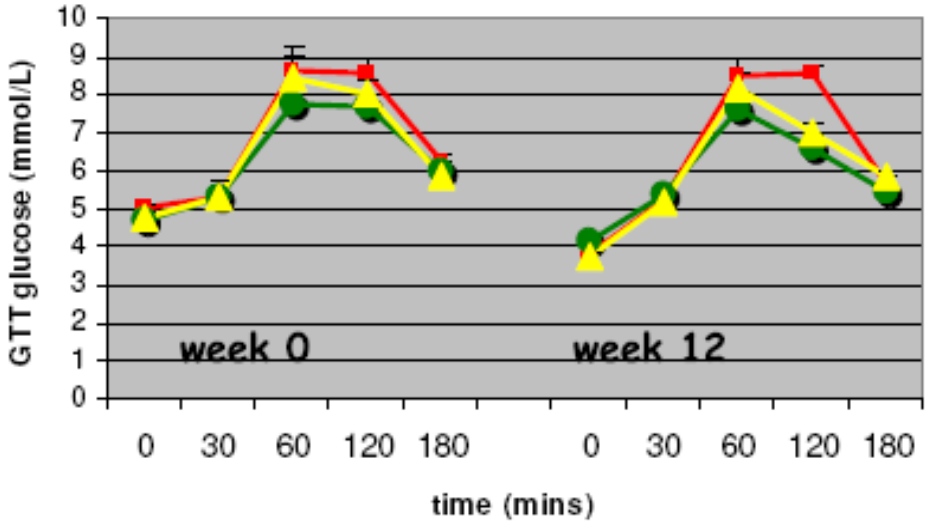
[1] mean ± SEM, VLCARB = very low carbohydrate (n = 24) VLF= very low fat (n = 22) HUF = high unsaturated fat (n = 21)
MUFA = monounsaturated fat, **PUFA** = polyunsaturated fat

Table 2A: Food profile of treatment diets

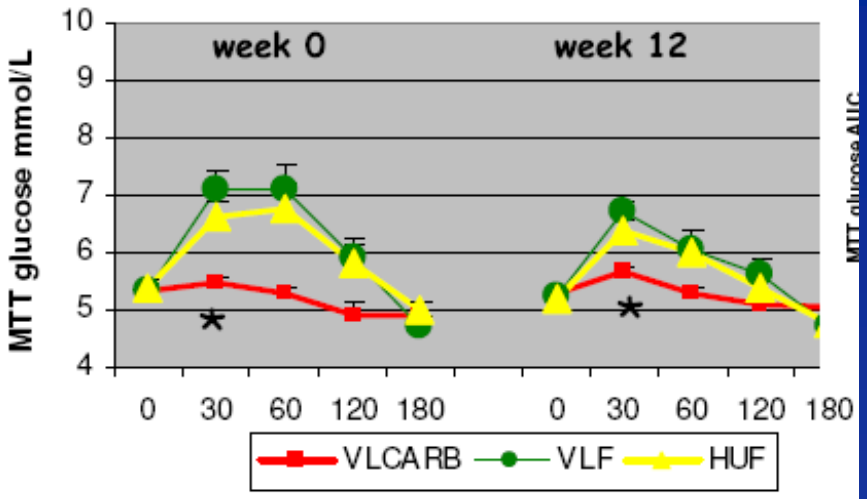
VLCARB		*VLF*		*HUF*	
Cheese, full fat	70 g	High fibre cereal	40 g	High fibre cereal	32 g
Milk, full fat	125 g	Bread, wholegrain	105 g	Bread, wholegrain	70 g
Lean meat, chicken	350 g	Low fat biscuits	60 g	Milk, skim	300 g
Eggs	2	Milk, skim	250 g	Cheese full fat	20 g 2/week
Very low carbohydrate vegetables	2 cups	Cheese low fat	20 g	Yoghurt, skim	200 g × 3/week
Almonds	50 g	Rice or pasta, dry	50 g	Pasta or rice, dry	100 g × 4/week
Butter	20 g	Fresh fruit	300 g	Nuts, mixed	20 g
		Dried fruit	50 g	Salad vegetables	100 g
		Lean meat, chicken	100 g	Fresh fruit	300 g
		Salad vegetables	100 g	Pulses, cooked	100 g × 2/week
		Low carbohydrate vegetables	2 cups	Lean meat, chicken,	150 g 5/week
				Fish	150 g/week
				Sardines	3 whole/week
				Tuna	50 g × 2/week
				Low carbohydrate vegetables	1.5 cups
				Potato	1 × 3/week
				Unsaturated oil or margarine	25 g

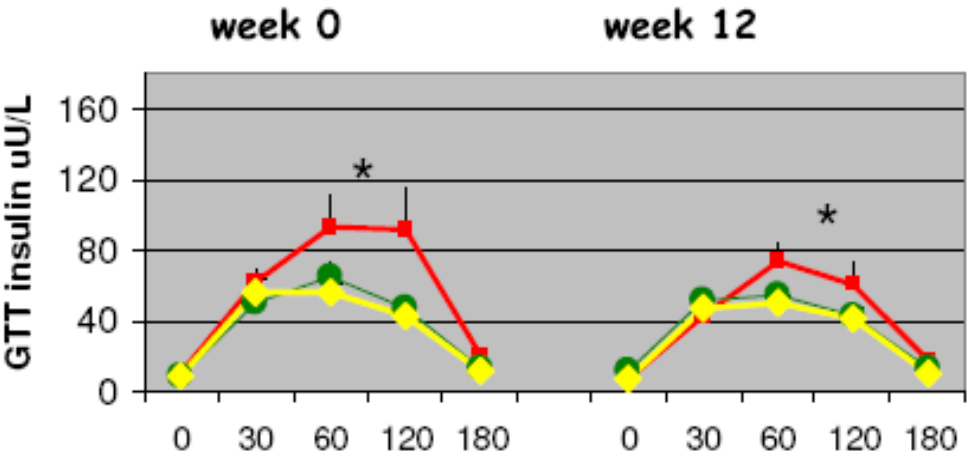
Noakes M, Foster PR, Keogh JB, James AP, Mamo JC, Clifton PM. Comparison of isocaloric very low carbohydrate/high saturated fat and high carbohydrate/low saturated fat diets on body composition and cardiovascular risk. Nutrition & Metabolism 2006;3:7.

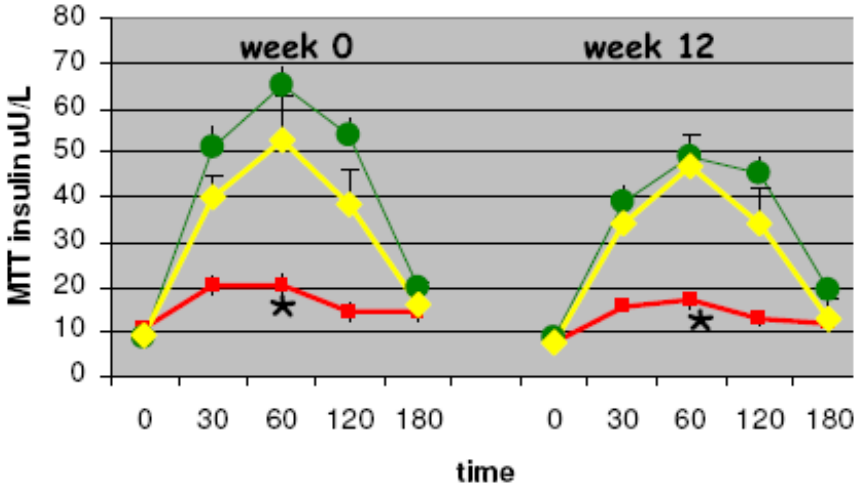
Oral Glucose (75 grams) Tolerance Test



Diet Specific GTT







Noakes M, Foster PR, Keogh JB, James AP, Mamo JC, Clifton PM. Comparison of isocaloric very low carbohydrate/high saturated fat and high carbohydrate/low saturated fat diets on body composition and cardiovascular risk. Nutrition & Metabolism 2006;3:7.

Diabetic Diet in the Pre-Insulin Era 1914-1921

"Quantity of food required by a severe diabetic patient weighing 60 kilograms"*

Food		Calories
Carbohydrate	10 grams	40
Protein	75 grams	300
Fat	150 grams	1,350
Alcohol	15 grams	105
		1,795

"Strict diet": Meats, poultry, game, fish, clear soups, gelatin, eggs, butter, olive oil, coffee, tea

* Osler W, McCrae T. The Principles and Practice of Medicine. NY: Appleton and Co., 1923.
Allen FM. Protein diets and undernutrition in treatment of diabetes. JAMA 1920;74:571-577.
Newburgh LH, Marsh PL. The use of a high fat diet in the treatment of diabetes mellitus. Arch Int Med 1921;27:699-705.

Recent Studies of Carbohydrate and Type 2 Diabetes

Reference	n	BMI	CHO %	Weeks	Post Glu mg/dl	Pre HA1c %	Post HAlc %	Wt Diff kg
Gutierrez	19	27.9	55	12	183	8.1	8.9	-0.8
1998			25	8	192	9.9	8.1	-1.4
Heilbronn	35	33	73	12	131	8.5	7.0	
1999			50 SF		119	7.8	6.8	-6.6
			50 MUF		122	7.5	6.6	
Heilbronn	45	22	60 HGI	12	110	6.7	6.1	-4.8
2002			60 LGI		116	6.7	6.0	-4.4
Gannon	12	31	55	5	114	8.0	7.7	0
2003			40		114	8.1	7.3	0
Rizkalla	12	31	38 HGI	4	176	7.5	7.6	-0.6
2004			36 LGI		165	7.6	7.2	-0.6
Gannon	8	31	55	5	198	9.8	9.8	-1.8
2004			20		126	9.8	7.6	-1.8

High Fat, Low Carbohydrate (~100gm/day) Diet in Type 2 Diabetes Mellitus Over 12 Months

	Control (n=132)			Low Carb (n=158)		
Variable *mg/dl*	*Before* *mean*	*After* *mean*	*Change*	*Before* *mean*	*After* *mean*	*Change*
Weight (kg)	92	94	+ 2%	92	87	- 5%
HgbA1c	8.4	7.6	- 10%	9.3	6.9	- 26%
Chol	226	215	- 5%	231	190	- 18%
Trig	204	207	+ 1%	229	183	- 20%
LDL-C	139	131	- 6%	134	105	- 22%
HDL-C	44	42	- 5%	43	47	+ 9%

Hays JH, Gorman RT, Shakir KM. Results of use of metformin and replacement of starch with saturated fat in diets of patients with type 2 diabetes. Endocr Pract. 2002 May-Jun;8(3):177-83.

Low Carbohydrate Diets for Type 2 Diabetes Pilot Studies

Reference	n	Weight kg	CHO	Follow-up	Pre HA1c %	Post HAlc %	Wt Diff %
Vernon 2003	14	123.2	~10%	8 months	10.0	5.9	-9.7
O'Neill 2003	20	82	~10%	10 months	8.4	5.8	-6.7
Nielsen 2005	16	100	~20%	12 months	8.0	6.6	-11.9
Yancy 2005	28	131.4	~7%	16 weeks	7.5	6.3	-6.6

Vernon MC et al. Metabolic Syndrome and Related Disorders 2003;1:233-238.
O'Neill DF et al. Metabolic Syndrome and Related Disorders 2003;1:291-298.
Nielsen JV et al. Upsala J Med Sci 2005;109:179-184.
Yancy WS Jr. et al. Nutrition & Metabolism 2005;2:34.

Case Series-Dr. Richard Bernstein

Variable	n	Baseline *Mean*	Follow-up *Mean*	Absolute change	P value
Weight, kg	23	82	77	- 5	0.01*
Total cholesterol	29	229	222	-7	0.41
Triglyceride	27	107	74	-33	0.005*
HDL	29	50	72	+22	0.0001*
LDL	24	155	130	-26	0.004*
Hemoglobin A1C	26	7.9	5.7	-2.2	0.0001*
Daily insulin dosage, units	27	32	25	-7	0.15

Mean duration 21.4 months. N=20 for type 2 DM; n=10 for type 1 DM.

O'Neill et al. *Metab Syndr Rel Dis* 2003:1:291-8.

Case Series-Dr. Mary Vernon

Variable	Baseline *Mean*	Follow-up *Mean*	Change	P value*
Weight, kg	123	111	- 10%	0.15
Total cholesterol	224	192	-14%	0.16
Triglyceride	317	157	-50%	0.01*
HDL	44.6	48.2	+8%	0.36
LDL	132	119	-10%	0.66
Hemoglobin A1C	10.0	5.9	-41%	<0.001*

*N=14. Median duration 18 months.

Vernon et al. ***Metab Syndr Rel Dis*** **2003:1:233-7.**

Low Carbohydrate Diet Program in Type 2 Diabetes Mellitus: Microalbuminuria

			Before Diet				After Low Carbohydrate Pgm			
Age	Sex	Duration	Weight (lb)	A1C	Trig	UAlb	Weight (lb)	A1C	Trig	UAlb
50	M	26 mos	273	7.0	6500	736	215	5.3	329	151
59	M	16 mos	182	12.0	336	300	192	7.4	245	114
49	F	12 mos	203	12.5	242	483	196	7.5	165	262
58	F	8 mos	252	6.4	121	50	197.6	5.5	68	13
49	M	12 mon	283	6.0	295	45.5	228.6	5.1	80	13

Vernon MC, unpublished data.

Low Carbohydrate Diet Program and Diabetes Mellitus

			Before Diet				After Low Carbohydrate Pgm			
Age	Sex	Duration	Weight (lb)	A1C	Trig	HDL	Weight (lb)	A1C	Trig	HDL
56	M	2 mos	182	12	336	43	186	6.8	169	37
39	F	3 mos	135	16.8	179	46	153	5.3	47	62
35	F	3 mos	188	11.3	503	27	175	6.3	145	41
44	M	4 mos	301	8.7	297	33	260	4.8	112	40
69	F	5 mos	247	8.1	186	61	233	5.4	146	63
33	M	15 mos	289	10.9	342	46	279	4.8	183	54
50	M	26 mos	275	9.0	6500	-	215	5.3	329	37
36	F	18 mos	264	9.2	150	48	202	5.5	122	53

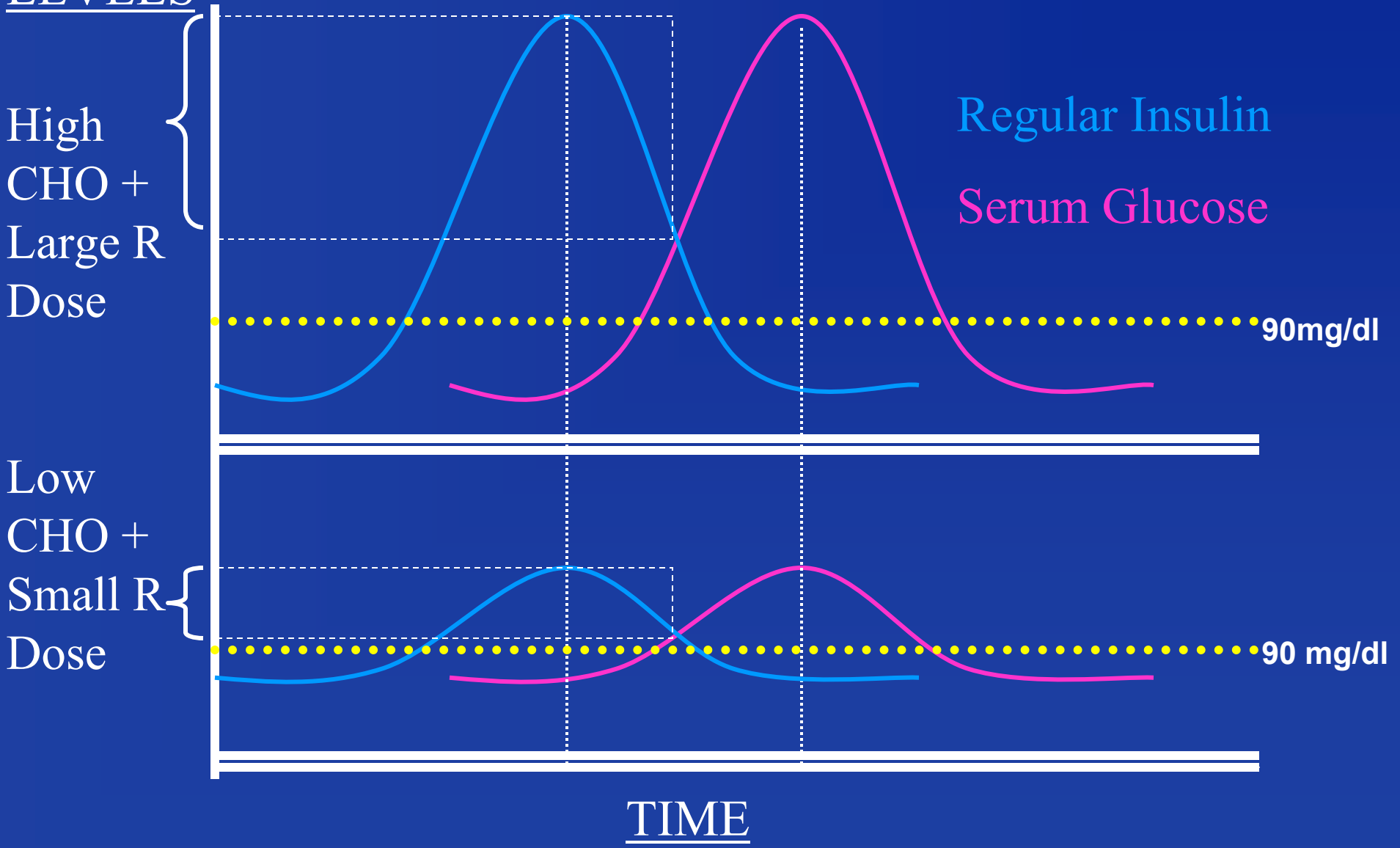
Vernon MC, unpublished data.

The Laws of Small Numbers

- "Big inputs make big mistakes; small inputs make small mistakes."
- With any system in the universe, these laws of small numbers apply.
- The larger the inputs, the more variation in the outputs.
- This fundamental principle is the basis of the Bernstein regimen, consisting of 3 basic laws:
  - -The Law of Carbohydrate Estimation
  - -The Law of Insulin Dose Absorption
  - -The Law of Insulin Timing

O'Neill DF et al. Metabolic Syndrome and Related Disorders 2003;1:291-298.

Insulin Reaction Time Compared with CHO Reaction Time:



Carbohydrate Intake and Glycemic Control

Study	Daily Carbs	Mean Hgb A1c
Effectiveness Study*		
• DCCT	230g (standard therapy)	8.9%
• DCCT	230g (intensive therapy)	7.1%
Efficacy Studies*		
• Hays	100g	6.9%
• Bernstein	30g	5.7%
• Vernon	20g	5.9%

***Effectiveness studies generally yield weaker results than efficacy studies.**

Effect of a Low-Carbohydrate Ketogenic Diet on Type 2 Diabetes

22 overweight, diabetic volunteers

→

Low-carbohydrate diet instruction
+ Counseling sessions
+ Exercise recommendation
+ Multivitamin
+ Medication adjustment

Yancy et al. *Nutr Metab* 2005;2(1):34.

Durham VAMC Study

Baseline Characteristics

Characteristic	Mean (SD) or % *(n=21)*
Age, years	56.0 (7.9)
Gender, male	20 (95%)
Race, Caucasian	13 (62%)
Body weight, kg	131.4 (18.3)
BMI, kg/m^2	42.2 (5.8)

Durham VAMC Study

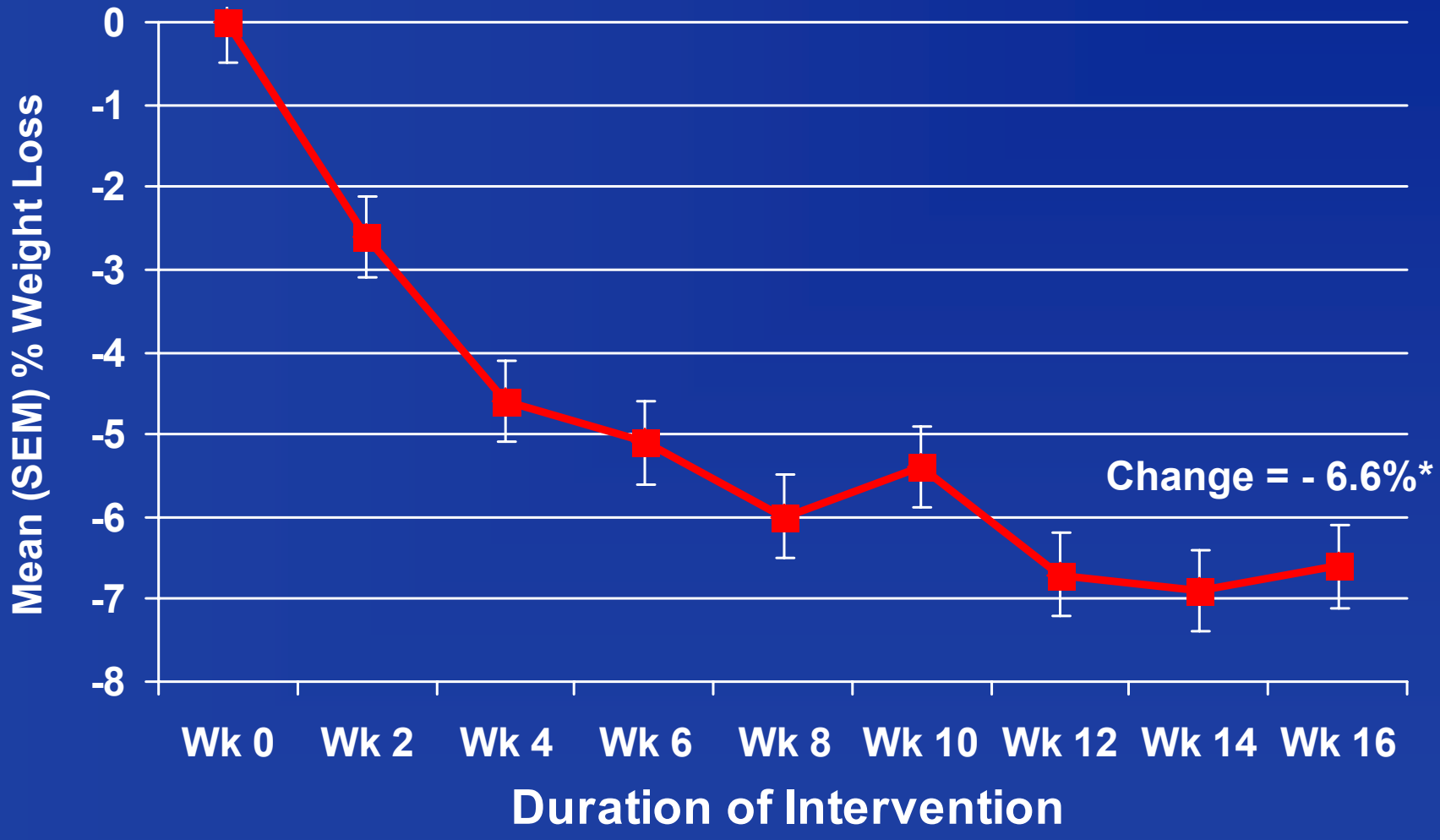
Dietary Intake by Food Records

Diet Component	Mean Daily Intake*
Protein	110 g (30%)
Fat	99 g (59%)
Carbohydrate	42 g (11%)
Energy	1,530 kcal

*Average is from food records obtained for four consecutive days, including a weekend, at weeks 2 (n=15), 8 (n=15), and 16 (n=8).

Durham VAMC Study

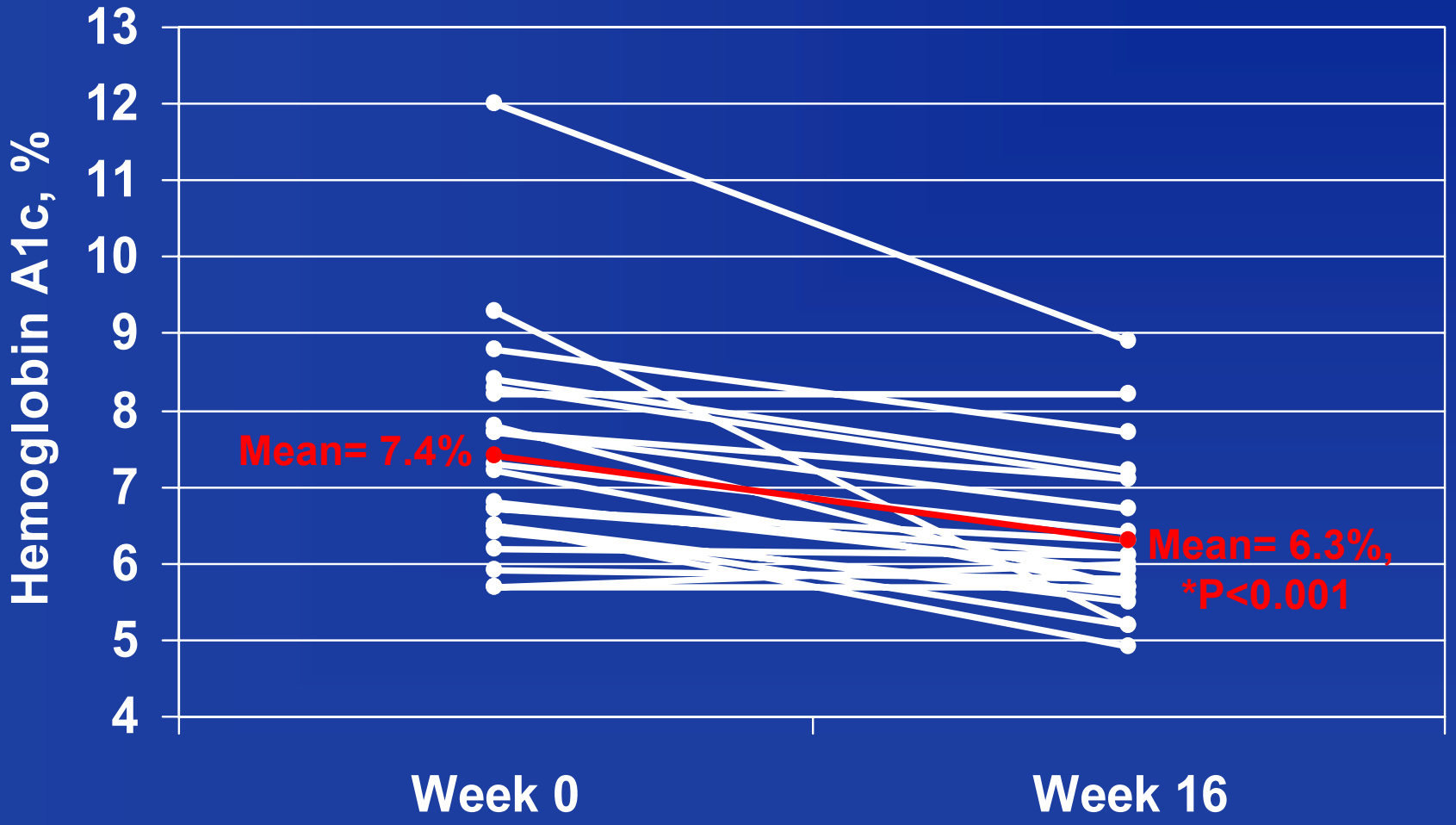
Percent Weight Loss



* p < 0.001 comparing Week 0 to Week 16.

Durham VAMC Study

Hemoglobin A1c



*Red line is the group mean. P value is for the mean change from baseline.

Patients with Diabetes Medications… Discontinued (7 of 21)

Subject	**Week 0** *total daily dose*	**Week 16** *total daily dose*
5	glipizide 10mg metformin 1000mg	none
6	glipizide 20mg metformin 1500mg	none
7	metformin 2000mg rosiglitazone 8mg	none
9	metformin 1000mg	none
15	metformin 1000mg	none
22	metformin 1000mg	none
24	metformin 1000mg	none

Patients with Diabetes Medications… Reduced (10 of 21)

Subject	Week 0 *total daily dose*	Week 16 *total daily dose*
3	metformin 1000mg 70/30 insulin 50units	metformin 1000mg
11	metformin 2000mg glyburide 20mg	metformin 2000mg
16	metformin 2000mg, glipizide 20mg, pioglitazone 45mg	metformin 2000mg
21	metformin 1500mg, pioglitazone 30mg	metformin 1000mg
8	metformin 1000mg NPH 145units	metformin 1000mg NPH 25units
13	metformin 2550mg 70/30 insulin 70units	metformin 2550mg 70/30 insulin 35units
23	pioglitazone 45mg 70/30 insulin 110units	pioglitazone 45mg, metformin 1000mg, 70/30 insulin 80units
25	metformin 2000mg, pioglitazone 45mg, NPH/Reg 100units	metformin 2000mg, pioglitazone 45mg, NPH 8units
27	metformin 2000mg 70/30 insulin 86units	metformin 2000mg 70/30 insulin 18units
28	glipizide 20mg NPH/lispro insulin 200units	glipizide 20mg NPH insulin 30units

Patients with Diabetes Medications… Unchanged (4 of 21)

Subject	**Week 0** *total daily dose*	**Week 16** *total daily dose*
1	none	none
2	metformin 1700mg	metformin 1700mg
10	none	none
26	metformin 2000mg	metformin 2000mg

Hemoglobin A1c depending on Diabetic Medication Change

Diabetic Medications	Week 0 Hgb A1c %	Week 16 Hgb A1c %	16-Week Change	p value
Discontinued	7.1	5.8	-18%*	0.04
Reduced	7.5	6.8	-9%*	0.03
No change	7.7	6.4	-17%*	0.03

Durham VAMC Study

Serum Lipids

Variable *(mg/dl)*	Week 0 (n=20)*	Week 16 (n=20)	16-Week Change	p value
Cholesterol	178	176	-1.5%*	0.7
Triglyceride	238	139	-42%*	0.001
LDL-C**	97	107	+10%*	0.1
HDL-C	36	38	+8%*	0.08

*** N=20 because one participant did not have tests at baseline.**

**** N=17 for LDL-C because 3 participants had triglyceride levels >400 mg/dL.**

“Turning it upside down”

- Let’s assume, for the sake of argument, that ANY increase in blood glucose shows a maladaptive insulin response, and is therefore bad.

- Let’s assume that NO post-prandial rise in glucose and insulin is the optimal situation.

Important Questions

Assuming that the absence of a post-prandial rise in glucose and insulin is desirable suggests these questions:

- How much carbohydrate can be consumed (with or without protein or fat), before the development of a post-prandial rise in glucose and insulin
- By definition, if 100g is consumed, the food by itself must have a GI index of 0 to have no effect on glucose
- The reduction of glycemic effect by fat of 25% suggests that consuming 100g of up to a GI index food of 25% with fat might avert a post-prandial rise of glucose
- But could a smaller portion of a GI index food of 100% be consumed with fat without a post-prandial rise in glucose?

Summary

- Very low carbohydrate diets are low glycemic diets
- Low glycemic diets are not necessarily very low carbohydrate diets (i.e., a low glycemic index diet may still have 50% of calories from carbohydrate)
- Effects in normals and diabetics will probably be different
- If “low GI” is better than “high GI,” what about “no GI”