36 M with type 1 diabetes and obesity who presents for Roux-En-Y Gastric Bypass

Rajesh Jain

Endorama January 7, 2016

HPI

36 M with type 1 DM and BMI 40 who presented for Roux-En-Y gastric bypass.

Type 1 DM History: diagnosed at age 7. He is on Lantus 45 units daily, novolog 2 u per 15 grams of carbs, SSI 2u:50>150.

Complications: mild neuropathy, CKD3, no retinopathy, no CV complications

Current A1c 7.3%, positive microalbumin

Extended History

PMH: T1DM, obesity, hypertension, CKD3, GERD

Home medications: amlodipine 10 mg qday, atenolol-chlorthalidone 50-25 mg daily, atorvastatin 40 mg qhs, Lantus 45 units daily, novolog 2 u:15 g carbs, lisinopril 20 mg qday, pantoprazole 40 mg qday

PSH: None

Allergies: NKDA

Social history: Graphic designer, sedentary lifestyle. Social use of alcohol, non-smoker, no recreational drugs. Engaged, fiance recently underwent gastric bypass surgery with good results

Family history: No DM2, stroke/heart disease in father, RA in sister

Is there a link between type 1 diabetes and obesity?

Type 1 Diabetes Prevalence

- T1DM has shown increasing prevalence over the past 15 years – 21.1% increase in one U.S. study between 2001 and 2009

Table 1. Prevalence of Type 1 Diabetes by Demographic Characteristics

	2001 Population			2009 Population				
	No. of Youth			No. of Youth				
	Cases With Diabetes	General Population	Prevalence per 1000 (95% CI)	Cases With Diabetes	General Population	Prevalence per 1000 (95% CI)	Difference in Prevalence (95% CI)	*P* Value
Total[a]	4958	3 345 783	1.48 (1.44 to 1.52)	6666	3 458 974	1.93 (1.88 to 1.97)	0.45 (0.41 to 0.48)	<.001
Sex								
Females	2420	1 635 589	1.48 (1.42 to 1.54)	3263	1 692 112	1.93 (1.86 to 2.00)	0.45 (0.40 to 0.49)	<.001
Males	2538	1 710 194	1.48 (1.43 to 1.54)	3403	1 766 862	1.93 (1.86 to 1.99)	0.44 (0.40 to 0.49)	<.001
Age, y[b]								
0-≤4	217	787 251	0.28 (0.24 to 0.31)	241	832 791	0.29 (0.26 to 0.33)	0.01 (−0.01 to 0.04)	.30
5-≤9	977	832 686	1.17 (1.10 to 1.25)	1143	844 923	1.35 (1.28 to 1.43)	0.18 (0.13 to 0.23)	<.001
10-≤14	1727	885 604	1.95 (1.86 to 2.04)	2335	867 403	2.69 (2.59 to 2.80)	0.74 (0.67 to 0.81)	<.001
15-≤19	2037	840 242	2.42 (2.32 to 2.53)	2947	913 857	3.22 (3.11 to 3.34)	0.80 (0.72 to 0.88)	<.001
Race/ethnicity								
White	3718	1 996 971	1.86 (1.80 to 1.92)	4804	1 885 451	2.55 (2.48 to 2.62)	0.69 (0.64 to 0.73)	<.001
Black	471	365 146	1.29 (1.18 to 1.41)	621	383 198	1.62 (1.50 to 1.75)	0.33 (0.25 to 0.42)	<.001
Hispanic	625	647 656	0.96 (0.89 to 1.04)	1042	809 267	1.29 (1.21 to 1.37)	0.32 (0.27 to 0.38)	<.001
Asian Pacific Islander	107	212 708	0.50 (0.42 to 0.61)	156	260 846	0.60 (0.51 to 0.70)	0.09 (0.03 to 0.16)	.006
American Indian	37	123 303	0.30 (0.22 to 0.42)	42	120 212	0.35 (0.26 to 0.47)	0.05 (−0.03 to 0.12)	.19

[a] Differences in the number of youth reported with type 1 diabetes in 2001[15] and in this report are due to exclusion of 1 prior study site in both years (Hawaii) and continued data cleaning.

[b] Age on December 23, 2001, and December 31, 2009.

Dabelea et al. Prevalence of Type 1 and Type 2 diabetes in children and adolescents from 2001 to 2009. JAMA 2014;311(17):1778-86.

Accelerator Hypothesis

- Argument: type 1 and 2 diabetes are the same disorder of insulin resistance, set against different genetic backgrounds
- Central to the hypothesis is that body mass is central to the development and rising incidence of all diabetes

Mechanisms

1) High rate of beta-cell apoptosis intrinsically – necessary but not sufficient for diabetes to develop

2) Insulin resistance resulting from weight gain/inactivity accelerates apoptosis of beta cells by making them work harder metabolically but also rendering them more immunogenic

3) Autoimmunity in response to stressed beta cells in genetically determined subset

Pozzilli et al. Obesity, autoimmunity, and double diabetes in youth. Diabetes Care 2011; 34(S2): S166-170.

Studies seem to support accelerator hypothesis

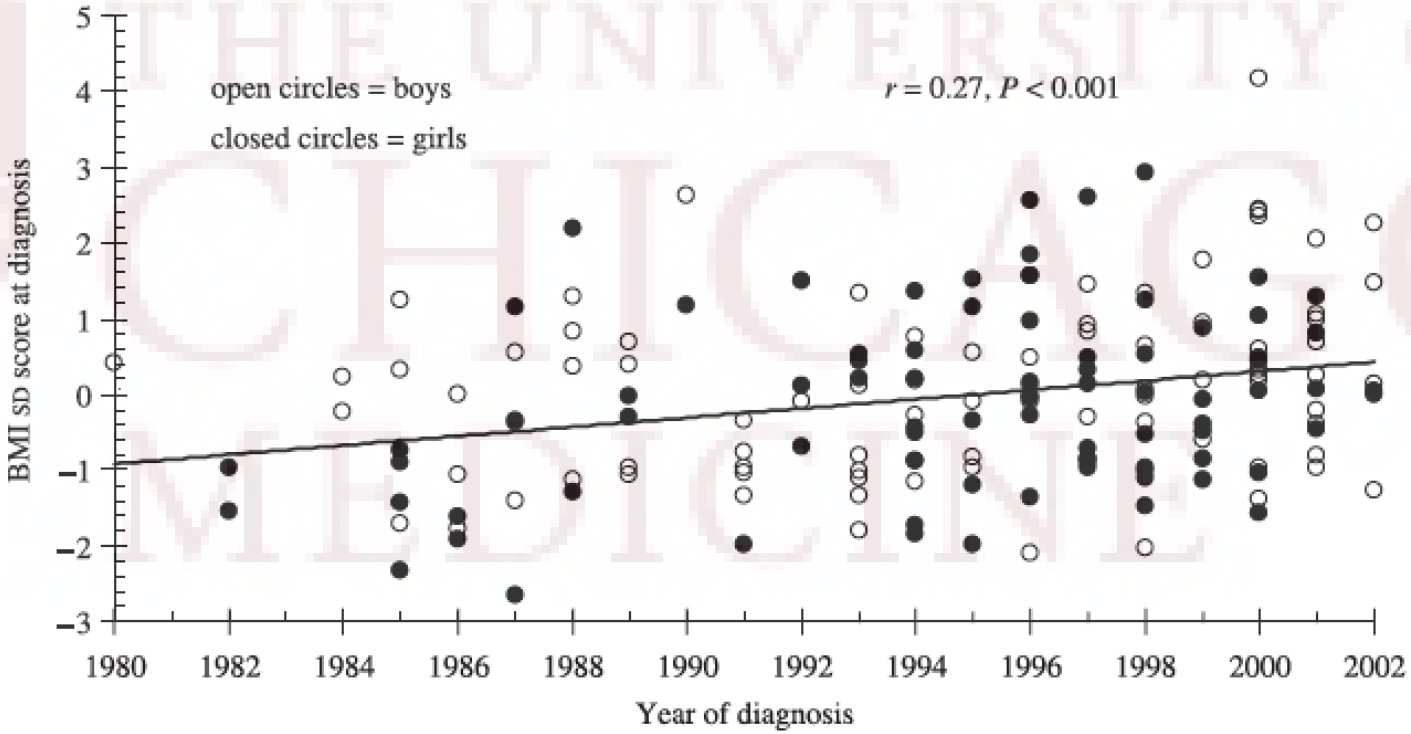
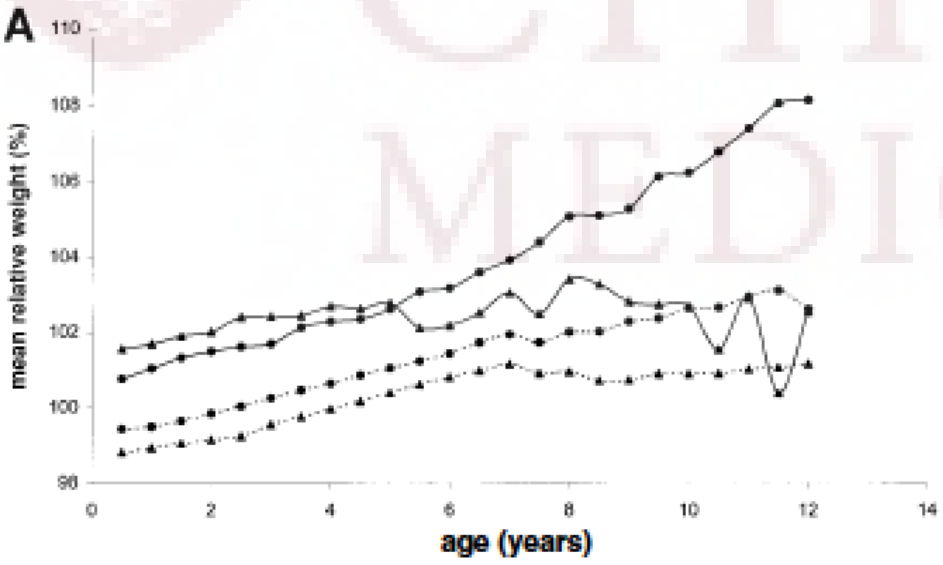


Figure 1 The relation between BMI standard deviation score and year of onset of Type 1 diabetes in 168 children age 1–16 years at diagnosis.

Betts et al. Increasing body weight predicts the earlier onset of insulin-dependent diabetes in childhood: testing the 'accelerator hypothesis'. Dia Med 2004;22:144-151.

Accelerator hypothesis

- In Finland, both boys and girls who developed T1DM were heavier and taller throughout childhood than control children
- A 10% unit increment in relative weight was associated with 50-60% increase in T1DM before age 3 and a 20-40% increase from 3-10 years of age.



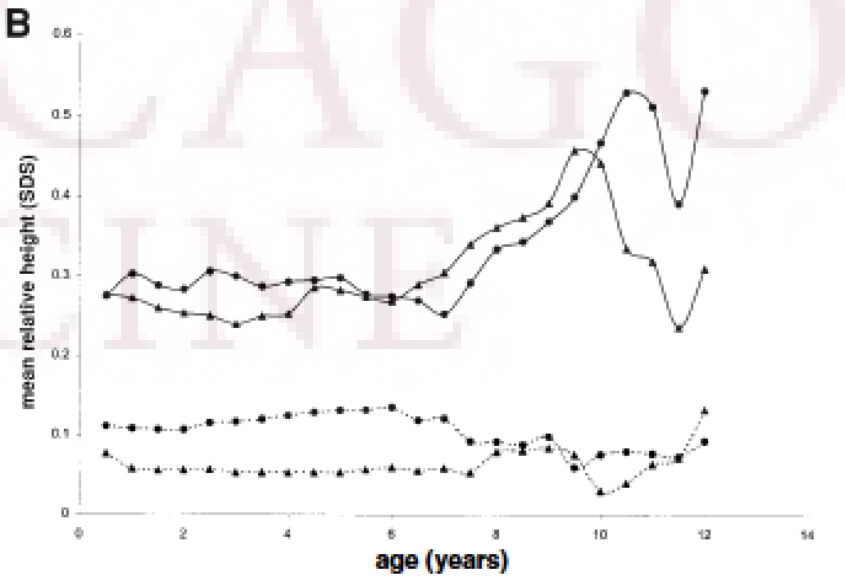


Figure 1—*Cross-sectional mean relative weights (A) and heights (B) for diabetic and control groups, calculated from the interpolated values.* —●—, *Diabetic boys;* - - ●- - , *control boys;* —▲—, *diabetic girls;* - - ▲- - , *control girls.*

Hypponen et al. Obesity, increased linear growth, and risk of type 1 diabetes in children. Diabetes Care 2000;23:1755-60.

Comparing T1DM, T2DM, and double diabetes

Table 1. Clinical and pathogenic features of DD, relative to T1D and T2D

	T1D	DD	T2D
Age at disease onset	Childhood +++ Adolescence +++ Adult +	Childhood ++ Adolescence ++ Adult (LADA) +	Childhood + Adolescence ++ Adult +++
Major genetic predisposition	MHC class I and II, *InsVNTR, CTLA-4* *PTPN22*	?	*APM1, PPARγ2* *PtdCho-1, TCF7L2*
Environmental factors	Diet, viruses Cow's milk in infancy	Life style (diet, sedentary life)	Life style (diet, sedentary life)
Circulating antibodies to β cells	+++	+	–
T cell-mediated immunity to β cells	+++	++	–
C-peptide secretion	–	+	+++
Insulin resistance	– or +	++	+++
Inflammatory markers (cytokines, adipokines)	+	++	+++
Macrovascular complications	+	++	+++

Key: +++, high frequency; ++, medium frequency; +, low frequency; –, absence; ?, unknown.

Pozzilli and Buzzetti. A new expression of diabetes: double diabetes. Trends Endocrinol Metab 2007;18.2:52-57.

What are the effects of weight loss drugs in type 1 diabetes?

10 patients
Residual beta cell function

9 patients
No residual beta cell function

10 Type 1 Controls

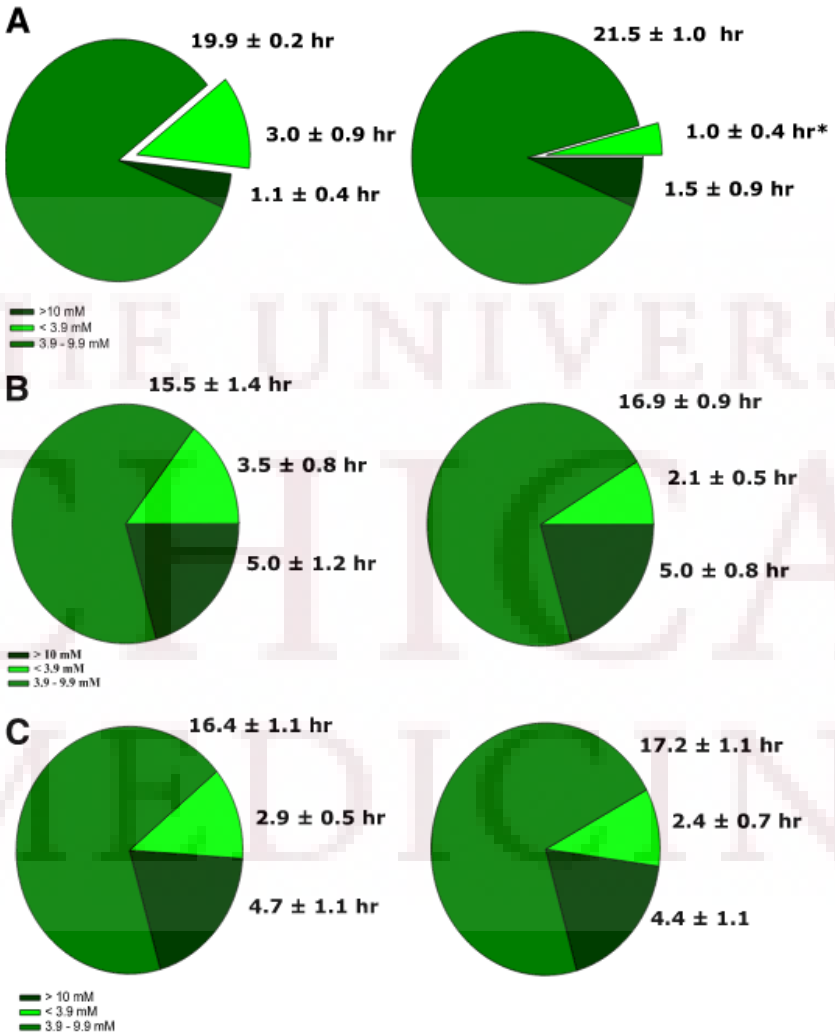
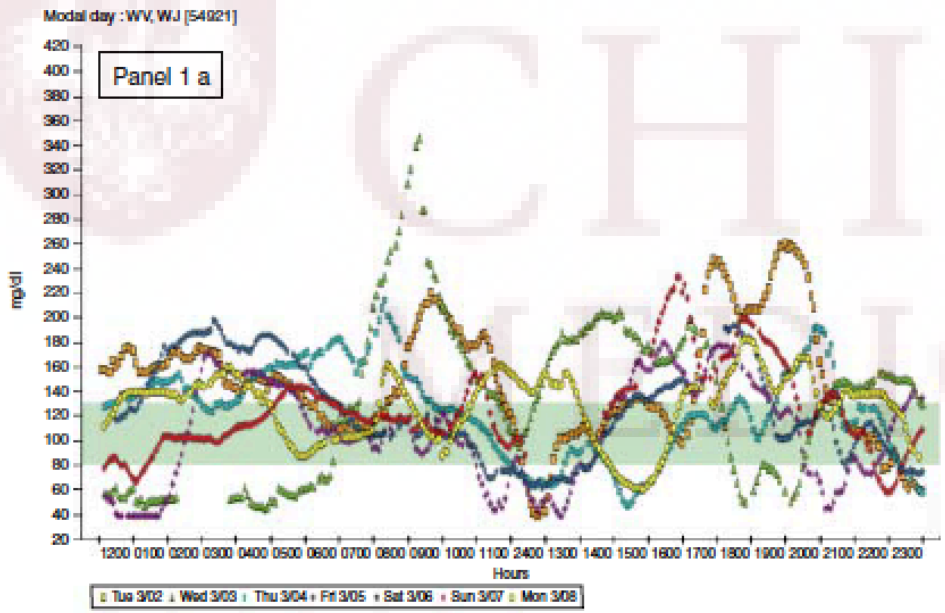


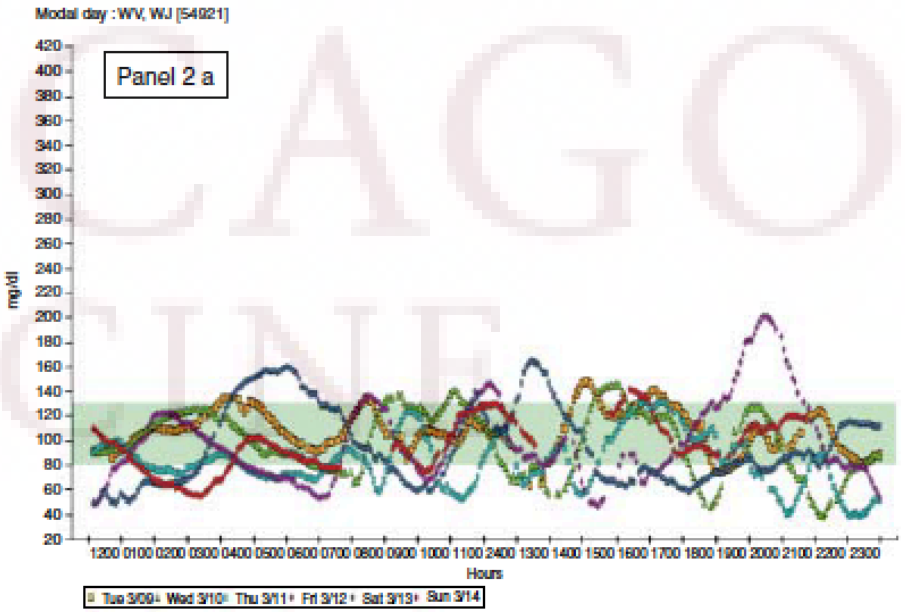
Figure 1—*Blood glucose evaluated from 24 h continuous glucose monitoring as mean blood glucose during 3 days with self-reported identical meals and physical activity before (week 0) and during (week 4) treatment with liraglutide. A: A total of 10 type 1 diabetic patients with residual β-cell function treated with liraglutide and insulin. B: A total of nine type 1 diabetic patients without residual β-cell function treated with liraglutide and insulin. C: A total of 10 type 1 diabetic patients without residual β-cell function treated with insulin alone. *P < 0.05 between week 0 and week 4 within the same group.*

Light green = <70
Middle green = 70-179
Dark green >180

Kielgast et al. Four weeks of treatment with liraglutide reduces insulin dose without loss of glycemic control in Type 1 diabetic patients with and without residual B-cell function. Dia Care 2011;34:1463-68.

One patient's CGM after Liraglutide





4 weeks of Liraglutide

Table 1—*Changes in insulin dose, mean BG, HbA_{1c}, and stimulated C-peptide in type 1 diabetic patients with (C-peptide positive) and without (C-peptide negative) residual β-cell function before (week 0) and during (week 4) 4 weeks of treatment with liraglutide or insulin alone*

	C-peptide positive		C-peptide negative		C-peptide negative	
	Liraglutide + insulin		Liraglutide + insulin		Insulin only	
Treatment	Week 0	Week 4	Week 0	Week 4	Week 0	Week 4
Insulin dose (units/kg per day)	0.50 ± 0.06	0.31 ± 0.08*	0.72 ± 0.08	0.59 ± 0.06†	0.62 ± 0.04	0.64 ± 0.05 (NS)
Mean blood glucose (mmol/L)	6.0 ± 0.2	6.3 ± 0.3 (NS)	7.5 ± 0.4	7.7 ± 0.4 (NS)	7.5 ± 0.4	7.5 ± 0.6 (NS)
HbA_{1c} (%)	6.6 ± 0.3	6.4 ± 0.2†	7.5 ± 0.2	7.0 ± 0.1†	7.1 ± 0.3	6.9 ± 0.2 (NS)
C-peptide (pmol/L)‡	520 ± 106	457 ± 79 (NS)	—	—	—	—

Data are means ± SE. Mean blood glucose levels are derived from continuous glucose monitoring as mean values during 3 days with identical food intake and physical activity in week 0 and week 4. NS, nonsignificant vs. week 0 in the same group. *$P < 0.001$ and †$P < 0.05$ vs. week 0 in the same group. ‡$n = 8$.

Long-term effects?

- Few studies looking at long-term effects

Table 4 Effects of liraglutide treatment for a mean duration of 24 weeks in eight patients.

Parameters	Before treatment (1 week)	On liraglutide (24 weeks)	*P* value
Weight (kg)	68±5	63.5±4	0.02
HBA1c (%)	6.5±0.5	6.1±0.4	0.02
Insulin dose (U/day)			
Basal	26.5±7	13.5±5	<0.01
Bolus	25.5±6	14±4	<0.01
Mean blood glucose (mg/dl)			
Fasting	128±10	108±8	<0.01
Weekly	134±20	111±12	<0.01
Time spent in hyperglycemia (% time)			
>150 mg/dl	27.5±6	21±5	0.02
>200 mg/dl	17.5±5	6.5±2	<0.01
>250 mg/dl	8.0±2	2.0±1	<0.01
Time spent in hypoglycemia (% time)			
<70 mg/dl	2.1.±2	2.3±2	0.08
<40 mg/dl	0.11±0.2	0.12±0.3	0.12
Mean S.D. weekly (mg/dl)	53±10	27±6	<0.01
Coefficient of variation weekly (%)	39.5±10	24.3±8	<0.01

Varanasi et al. Liraglutide as additional treatment for type 1 diabetes. Eur J Endo 2011; 165:77-84.

Long-term outcomes after bariatric surgery

Little data!

Table 1—Metabolic profile of patients with T1D after bariatric surgery (n = 10)

	Preoperative value	Postoperative value	P
BMI (kg/m^2)	41.6 ± 3.9	30.5 ± 5.9	<0.001
Insulin requirement (units/kg/day)	0.74 ± 0.32	0.40 ± 0.15	0.004
A1C (%)	10.0 ± 1.6	8.9 ± 1.1	0.039
A1C (mmol/mol)	86.2 ± 17.3	73.9 ± 11.9	0.042
LDL (mg/dL)	114.7 ± 17.8	91.7 ± 10.5	0.020
HDL (mg/dL)	57.5 ± 18.3	68.3 ± 19.8	0.001
Triglyceride (mg/dL)	96.0 ± 13.0	65.5 ± 13.3	0.007

Data are presented as mean ± SD.

Mean follow up 36.8 months ± 32.3 months

Brethauer et al. Bariatric surgery improves the metabolic profile of morbidly obese patients with Type 1 Diabetes. Diabetes Care 2014;37:e51-52.

Long-term outcomes after bariatric surgery

Table 1—Anthropometric and cardiometabolic risk factors and glycemic control at baseline (n = 10) and at 1 (n = 10) and 5 (n = 7) years following GB surgery

	Baseline	1 year	*P* value†	5 years	*P* value‡	*P* value§
Weight (kg)	121.9 ± 22.1	81.9 ± 15.8	<0.0001**	93.6 ± 21.0	<0.0001**	<0.01*
BMI (kg/m^2)	43.5 ± 7.5	29.3 ± 5.4	<0.0001**	33.8 ± 7.5	<0.0001**	<0.01*
HbA_{1c} (%)	8.1 ± 1.3	8.3 ± 1.4	0.47	9.8 ± 1.9	0.15	0.26
HbA_{1c} (mmol/mol)	65 ± 14.2	67 ± 15.3	0.47	84 ± 20.8	0.15	0.26
Basal insulin (units/day)	53.0 ± 29.7	23.0 ± 15.6	0.0005**	31.1 ± 22.8	0.02*	0.17
Basal insulin (units/kg/day)	0.42 ± 0.19	0.27 ± 0.13	0.0005**	0.37 ± 0.17	0.0021*	0.174
Insulin pump, *n* (%)	6 (60)	6 (60)		5 (71)		
Multiple daily injections, *n* (%)	4 (40)	4 (40)		2 (29)		
Systolic blood pressure (mmHg)	123.6 ± 8.3	112.6 ± 11.3	0.003*	118.7 ± 14.1	0.45	0.19
Diastolic blood pressure (mmHg)	72.8 ± 8.3	69.7 ± 4.2	0.32	72.4 ± 7.2	0.97	0.57
HDL (g/dL)	61.5 ± 18.4	63.0 ± 11.8	0.8	80.5 ± 16.7	0.04*	0.004*
LDL (g/dL)	102.3 ± 20.4	92.8 ± 20.5	0.41	91.5 ± 26.3	0.44	0.95
Total cholesterol (g/dL)	185.4 ± 30.9	172.7 ± 24.2	0.59	195.3 ± 27.5	0.72	0.07
Triglycerides (g/dL)	112.8 ± 55.1	80.6 ± 43.6	0.004*	111.2 ± 109.5	0.12	0.29
Microalbumin (mg/L)	62.2 ± 142	21.5 ± 26.7	0.34	14.2 ± 16.3	0.29	0.07

Data are presented as mean ± SD, unless otherwise noted. †1 year compared with baseline. ‡5 years compared with baseline. §5 years compared with 1 year. *Significant at $P < 0.05$. **Significant at $P < 0.001$.

Middlebeek et al. Gastric bypass surgery in severely obese women with Type 1 diabetes: anthropometric and cardiometabolic effects at 1 and 5 years postsurgery. Diabetes Care 2015;38;e104-05.

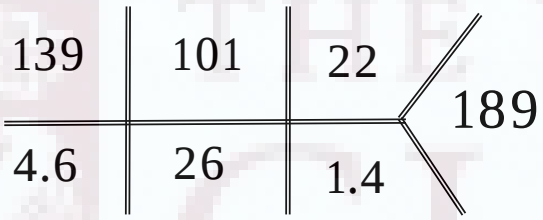
Back to case…

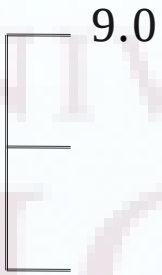
Endocrine now called after patient undergoes Roux-En-Y gastric bypass surgery …

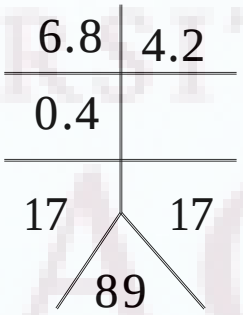
Peri-operative course

- Patient notes significant carbohydrate restricting prior to surgery with significant hypoglycemia
  - Subsequent blood sugar log review demonstrates blood sugar into the 50s nearly daily
- Patient underwent Roux-En-Y without complication

Pre-operative labs (2 weeks prior)







Peri-operative course

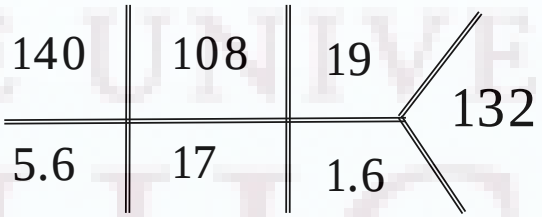
- Initial recommendations?

POD0

- Initial endocrine recommendations: ICU transfer, insulin drip, and dextrose-containing IV fluids

- Implemented: ICU transfer…….lantus 10 units

POD1



Ketones 3.36
U/A: pH 5.0, glucose 3+, ketones 3+

Ketones and gastric bypass surgery

- Ketones are very common after bariatric surgery or any other type of weight loss
- But how do we interpret them in a patient with Type 1 diabetes?

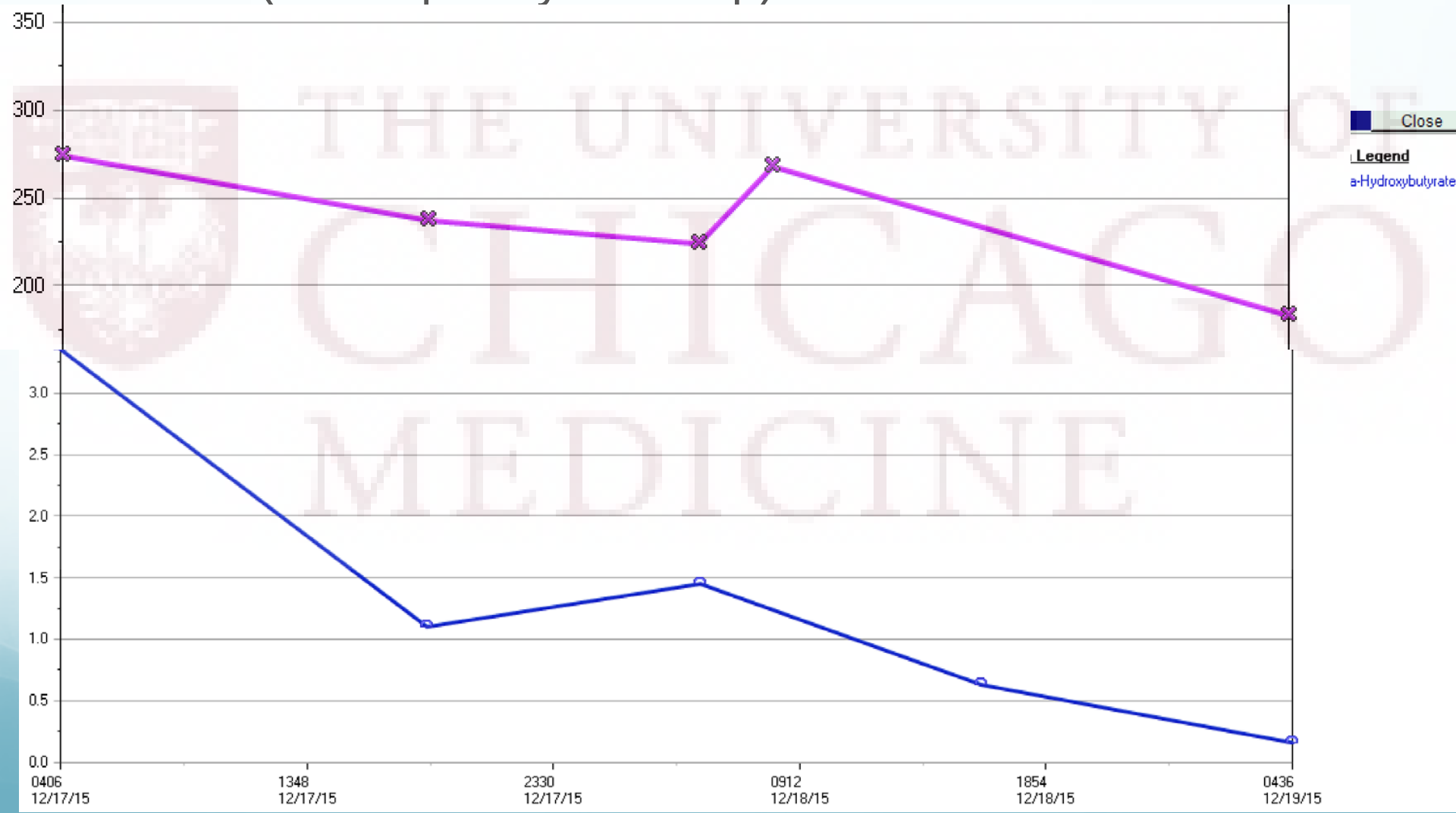
Can starvation ketones be dangerous?

- Moderate to severe metabolic acidosis as a result of starvation has been reported in pregnancy (pH 7.19, AG 18, bicarbonate 4)
- Case report of patient with T1DM with severe depression and anhedonia (BS 105, pH 7.3, AG 29, bicarbonate 10, no glycosuria)
- Case report of patient developing acidosis after gastric banding (pH 7.289, bicarbonate 9.7, AG 21) though also in the setting of PNA

Burbos et al. Severe metabolic acidosis as a consequence of acute starvation in pregnancy. Arch Gynecol Obstet 2009;279:399-400.
Joseph et al. Starvation-induced true diabetic euglycemic ketoacidosis in severe depression. J Gen Intern Med 2008;24.1:129-131.
Lulsegged et al. Starvation ketoacidosis in a patient with gastric banding. Clinical Medicine 2011;11.5:473-5.

Management

- Patient managed with Lantus, Novolog 2 units: 15 g, q4h SSI and D5 (subsequently D10 drip)



Management

- At this point, patient was still on a significant amount of D5 and eating minimal amounts…

Diet first 2 weeks after gastric bypass

- Size of stomach is ¼ cup (size of an egg)
- Daily caloric intake about 400 calories, often in 5-8 small meals daily
- Thicker liquids high in protein and low in fat and sugar
- Thicker liquids that are recommended: nonfat milk, sugar-free pudding, sugar-free nonfat yogurt, low fat cottage cheese, blended broth-based soup or other low-fat soups, refined hot cereal (e.g. cream of wheat), protein drinks

ICSF website: http://www.ucsfhealth.org/education/dietary_guidelines_after_gastric_bypass/

Guidelines?

- No guidelines exist for type 1 diabetes and bariatric surgery
- No reports exist of peri-operative management in these patients

What now?

What is the significance of ketones in these patients?

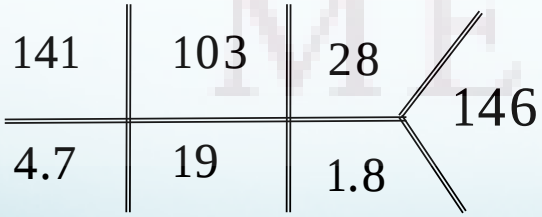
- Using the anion gap to determine significance? Other potential markers (pH, glycosuria?)?
- Managing these patients after discharge?

Discharge recommendations

- We recommended using cornstarch or carbohydrate powders to reach approximately 130 grams of carbs daily
- Dose insulin with each small meal but be careful not to let insulin stack
- Check urine ketones daily

Clinic follow-up

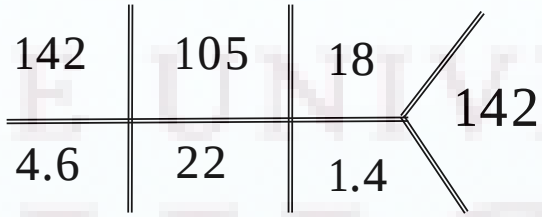
- Patient follows up and reports being only able to consume 30-60 grams of carbohydrates daily. Total daily insulin 35-40 units.
- Fluid intake: 32 oz daily (recommended 64 oz)
- Checking urine ketones daily – none or small only
- Labs drawn….



Ketones 3.13

What now?

Repeat labs



Ketones 0.86

Reports consuming about 65 grams of carbohydrates daily but planning to increase it soon

Food for thought – longer term management?

Recommended Meal Plan for Two to Six Months Post-Surgery

- Consume 900 to 1,000 calories and at least 65 to 75 grams of protein a day. For balanced nutrient intake, your daily servings should include:
- 3 servings milk and dairy products (nonfat and low-fat)
- 3 servings meat or meat alternative (lean and low-fat)
- 3 servings starch (limit bread and rice)
- 1 serving fruit (avoid dried fruits and fruits with skin)
- 2 servings vegetable (well-cooked only)
- Recommended portion sizes are 1/4 cup for solids and 1/2 cup for liquids.

ICSF website: http://www.ucsfhealth.org/education/dietary_guidelines_after_gastric_bypass/

Proposed guidelines

- Significant carbohydrate restricting should be discouraged in T1DM
- Patient should be seen in endocrine clinic the week prior to surgery
- Urine ketones should be checked the day before surgery
- On post-operative day 0 and 1, patient should be managed on an insulin drip with D5 until patient is allowed to eat [but what about patients with insulin pumps?]
- Serum ketones should be checked twice daily on day 1 and 2 and then as necessary
- At discharge, patients should be recommended ?130? Grams of carbohydrates and urine ketones should be checked daily
- Close clinic follow up

References

Dabelea et al. Prevalence of Type 1 and Type 2 diabetes in children and adolescents from 2001 to 2009. JAMA 2014;311(17):1778-86.

Pozzilli et al. Obesity, autoimmunity, and double diabetes in youth. Diabetes Care 2011; 34(S2): S166-170.

Betts et al. Increasing body weight predicts the earlier onset of insulin-dependent diabetes in childhood: testing the 'accelerator hypothesis'. Dia Med 2004;22:144-151.

Hypponen et al. Obesity, increased linear growth, and risk of type 1 diabetes in children. Diabetes Care 2000;23:1755-60.

Pozzilli and Buzzetti. A new expression of diabetes: double diabetes. Trends Endocrinol Metab 2007;18.2:52-57.

ICSF website: http://www.ucsfhealth.org/education/dietary_guidelines_after_gastric_bypass/

Varanasi et al. Liraglutide as additional treatment for type 1 diabetes. Eur J Endo 2011; 165:77-84.

Kielgast et al. Four weeks of treatment with liraglutide reduces insulin dose without loss of glycemic control in Type 1 Diabetic patients with and without residual B-cell function. Dia Care 2011;34:1463-68.

Brethauer et al. Bariatric surgery improves the metabolic profile of morbidly obese patients with Type 1 Diabetes. Diabetes Care 2014;37:e51-52.

Middlebeek et al. Gastric bypass surgery in severely obese women with Type 1 diabetes: anthropometric and cardiometabolic effects at 1 and 5 years postsurgery. Diabetes Care 2015;38;e104-05.

Burbos et al. Severe metabolic acidosis as a consequence of acute starvation in pregnancy. Arch Gynecol Obstet 2009;279:399-400.

Joseph et al. Starvation-induced true diabetic euglycemic ketoacidosis in severe depression. J Gen Intern Med 2008;24.1:129-131.

Lulsegged et al. Starvation ketoacidosis in a patient with gastric banding. Clinical Medicine 2011;11.5:473-5.

Waist circumference

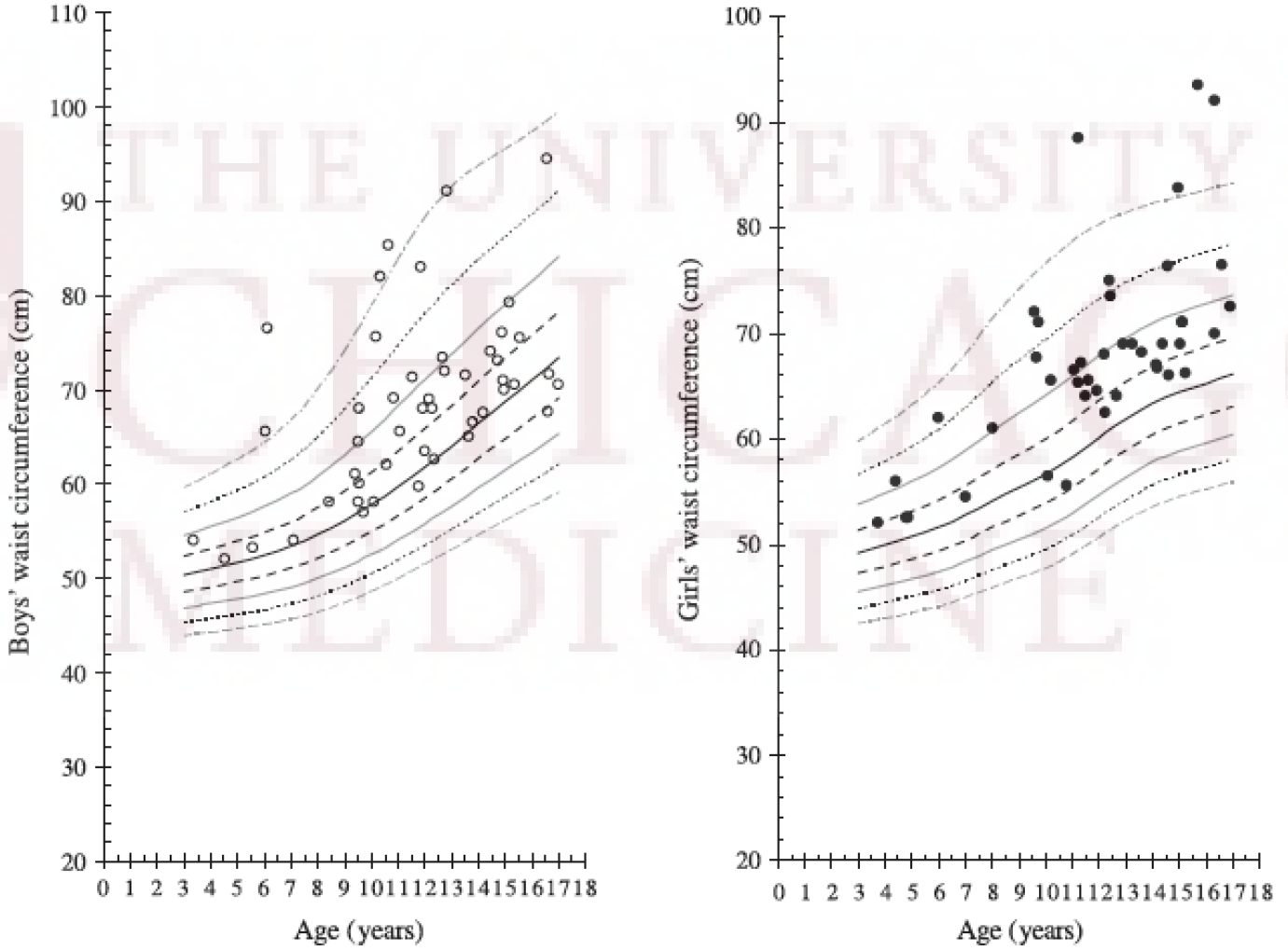


Figure 4 Waist circumference measurements for 47 boys and 43 girls with Type 1 diabetes plotted against the UK reference standards.