The latest on VLEDs and type 2 diabetes remission

Presented by

Associate Professor Samantha Hocking

Charles Perkins Centre

University of Sydney

Department of Endocrinology

Royal Prince Alfred Hospital

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Disclosure

A/Prof Samantha L Hocking has received research grants from The Diabetes Australia Research Trust/Program and The National Health and Medical Research Council of Australia; received honoraria for lectures from Eli Lilly, Novo Nordisk, Inova, Sanofi Aventis, Astra Zeneca, Servier and Amgen and has been or is on advisory boards for Novo Nordisk, Eli Lilly, Inova, Seqirus and Pfizer; and has been an investigator for industry-sponsored clinical trials run by Novo Nordisk, Eli Lilly, Rhythm pharmaceuticals, Millendo, Spruce Biosciences and Amgen.

Clinical Case – Pauline

Age: 53 years
Weight: 112.2 kg **Height:** 171 cm **BMI:** 38.4 kg/m^2 **Waist:** 106 cm
Occupation: Book-keeper
Diagnosed with type 2 diabetes with HbA1c 6.8%

Hypertension
Dyslipidaemia
Depression
Painful knee osteoarthritis

Paracetamol 1000 mg bd
Perindopril 5 mg daily
Atorvastatin 20 mg daiily
Citalopram 20 mg daily

What treatment should you recommend for Pauline?

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What are the current diabetes management guidelines?

What are the current obesity management guidelines?

The Australian Obesity Management Algorithm: A simple tool to guide the management of obesity in primary care☆

Tania P. Markovic [a,b,*], Joseph Proietto [c], John B. Dixon [d], Georgia Rigas [e], Gary Deed [f,g], Jeffrey M. Hamdorf [h], Erica Bessell [b], Nathalie Kizirian [b], Sofianos Andrikopoulos [i], Stephen Colagiuri [b]

[a] Metabolism & Obesity Service, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia
[b] Boden Initiative, Charles Perkins Centre, Faculty of Medicine and Health, University of Sydney, NSW 2006, Australia
[c] University of Melbourne, Parkville, VIC 3010, Australia
[d] Iverson Health Innovation Research Institute, Swinburne University of Technology, Hawthorn, VIC 3122, Australia
[e] St George Private Hospital, Kogarah, NSW 2217, Australia
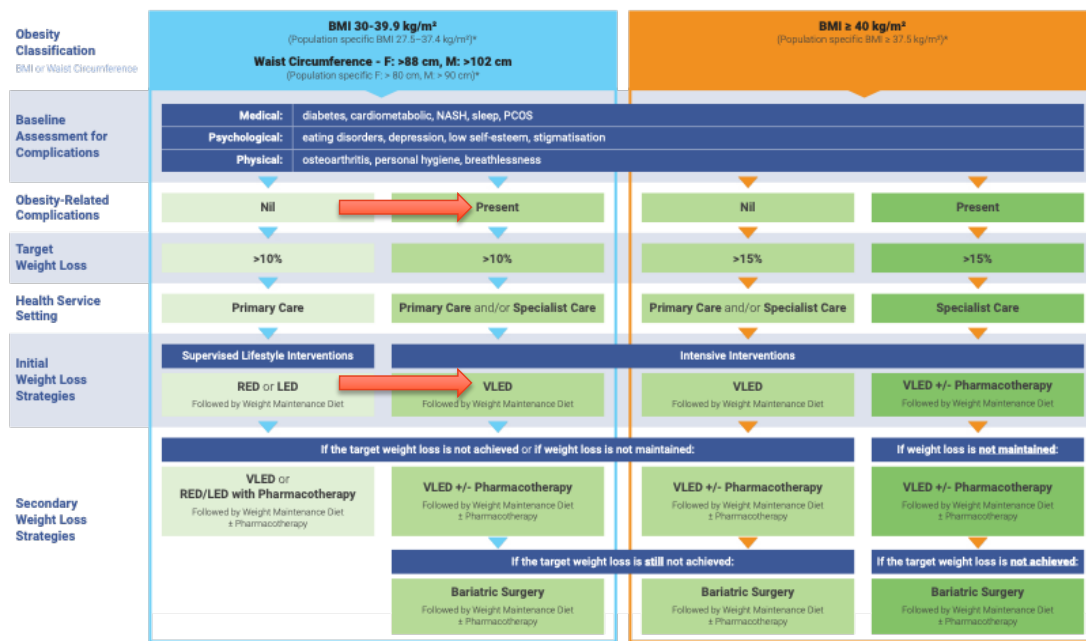[f] HealthCarePlus Medical Centre, Carindale, QLD 4152, Australia
[g] Monash University, Clayton, VIC 3800, Australia
[h] Medical School, University of Western Australia, Crawley, WA 6009, Australia
[i] Australian Diabetes Society, 145 Macquarie St, Sydney, NSW 2000, Australia

AUSTRALIAN OBESITY MANAGEMENT ALGORITHM

	BMI 30-39.9 kg/m² (Population specific BMI 27.5–37.4 kg/m²)* Waist Circumference - F: >88 cm, M: >102 cm (Population specific F: > 80 cm, M: > 90 cm)*		BMI ≥ 40 kg/m² (Population specific BMI ≥ 37.5 kg/m²)*	
Obesity Classification BMI or Waist Circumference				
Baseline Assessment for Complications	**Medical:** diabetes, cardiometabolic, NASH, sleep, PCOS **Psychological:** eating disorders, depression, low self-esteem, stigmatisation **Physical:** osteoarthritis, personal hygiene, breathlessness			
Obesity-Related Complications	Nil	Present	Nil	Present
Target Weight Loss	>10%	>10%	>15%	>15%
Health Service Setting	Primary Care	Primary Care and/or Specialist Care	Primary Care and/or Specialist Care	Specialist Care
Initial Weight Loss Strategies	Supervised Lifestyle Interventions — RED or LED Followed by Weight Maintenance Diet	VLED Followed by Weight Maintenance Diet	Intensive Interventions — VLED Followed by Weight Maintenance Diet	VLED +/- Pharmacotherapy Followed by Weight Maintenance Diet
Secondary Weight Loss Strategies	If the target weight loss is not achieved or if weight loss is not maintained: VLED or RED/LED with Pharmacotherapy Followed by Weight Maintenance Diet ± Pharmacotherapy	VLED +/- Pharmacotherapy Followed by Weight Maintenance Diet ± Pharmacotherapy	VLED +/- Pharmacotherapy Followed by Weight Maintenance Diet ± Pharmacotherapy	If weight loss is not maintained: VLED +/- Pharmacotherapy Followed by Weight Maintenance Diet ± Pharmacotherapy
		If the target weight loss is still not achieved: Bariatric Surgery Followed by Weight Maintenance Diet ± Pharmacotherapy	Bariatric Surgery Followed by Weight Maintenance Diet ± Pharmacotherapy	If the target weight loss is not achieved: Bariatric Surgery Followed by Weight Maintenance Diet ± Pharmacotherapy

BMI = body mass index, LED = low energy diet, NASH = non-alcoholic steatohepatitis, PCOS = polycystic ovary syndrome, RED = reduced energy diet, VLED = very low energy diet
*Cut-offs apply to Asian population and recommended for Australian indigenous population.

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Obesity is the leading risk factor for Type 2 diabetes

Table 3. Ten-Year Risk (1986-1996) of Developing an Obesity-Related Morbidity Among 77 690 Female Nurses and 46 060 Male Health Professionals in the United States

	Adjusted Odds Ratios (95% CI)*						
	Diabetes	Gallstones	Hypertension	High Cholesterol Level	Colon Cancer	Heart Disease	Stroke
Women							
10-y risk of developing disease, %†	5	6	14	58	0.6	3	0.5
Body mass index, kg/m²							
<25.0	Referent	Referent	Referent	Referent	Referent	Referent	Referent
25.0-29.9	4.6 (3.9-5.4)	1.9 (1.7-2.0)	1.7 (1.6-1.8)	1.1 (1.1-1.2)	1.2 (1.0-1.5)	1.4 (1.2-1.5)	.2 (1.0-1.4)
30.0-34.9	10.0 (8.4-11.8)	2.5 (2.3-2.7)	2.1 (1.9-2.2)	0.9 (0.9-1.0)	1.3 (1.0-1.7)	1.5 (1.3-1.7)	.0 (0.8-1.4)
≥35.0	17.0 (14.2-20.5)	3.0 (2.7-3.3)	2.3 (2.1-2.6)	0.7 (0.6-0.7)	1.8 (1.3-2.6)	1.5 (1.3-1.8)	.1 (0.8-1.7)
Men							
10-y risk of developing disease, %†	8	13	13	46	0.5	4	1
Body mass index, kg/m²							
<25.0	Referent	Referent	Referent	Referent	Referent	Referent	Referent
25.0-29.9	3.5 (2.9-4.1)	1.4 (1.3-1.6)	1.7 (1.6-1.8)	1.3 (1.2-1.3)	1.2 (1.0-1.5)	1.5 (1.4-1.7)	.2 (1.0-1.5)
30.0-34.9	11.2 (9.3-13.6)	2.3 (1.9-2.7)	2.7 (2.4-3.0)	1.2 (1.1-1.3)	1.7 (1.2-2.4)	2.0 (1.7-2.3)	.0 (1.5-2.7)
≥35.0	23.4 (19.4-33.2)	2.9 (2.1-4.1)	3.0 (2.3-3.9)	1.3 (1.1-1.6)	1.3 (0.5-3.2)	2.2 (1.5-3.1)	.3 (1.2-4.4)

*Adjusted for age, smoking status, and race. CI indicates confidence interval.
†Risk, estimated from a logistic regression model, for a 50- to 59-year-old woman or man who is white, never smoked, and has a body mass index less than 25.

Obesity is the leading risk factor for Type 2 diabetes

In Australia in 2011
53% of diabetes burden was due to overweight and obesity

References: Australian Institute of Health and Welfare 2017. Australian Burden of Disease Study series no.11. Cat. no. BOD 12. BOD. Canberra: AIHW.

Cell Metabolism

Effects of Moderate and Subsequent Progressive Weight Loss on Metabolic Function and Adipose Tissue Biology in Humans with Obesity

Graphical Abstract
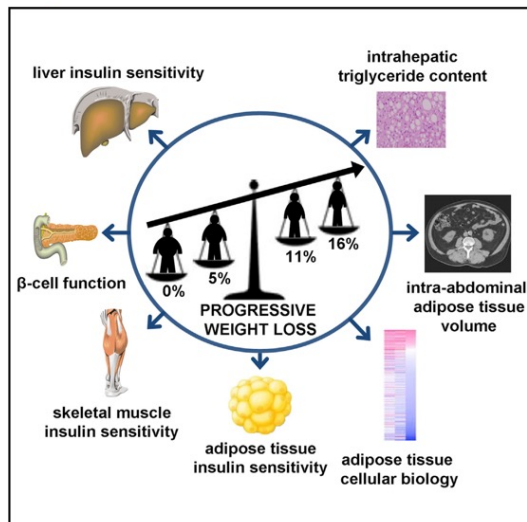
Authors

Faidon Magkos, Gemma Fraterrigo, Jun Yoshino, ..., Adewole L. Okunade, Bruce W. Patterson, Samuel Klein
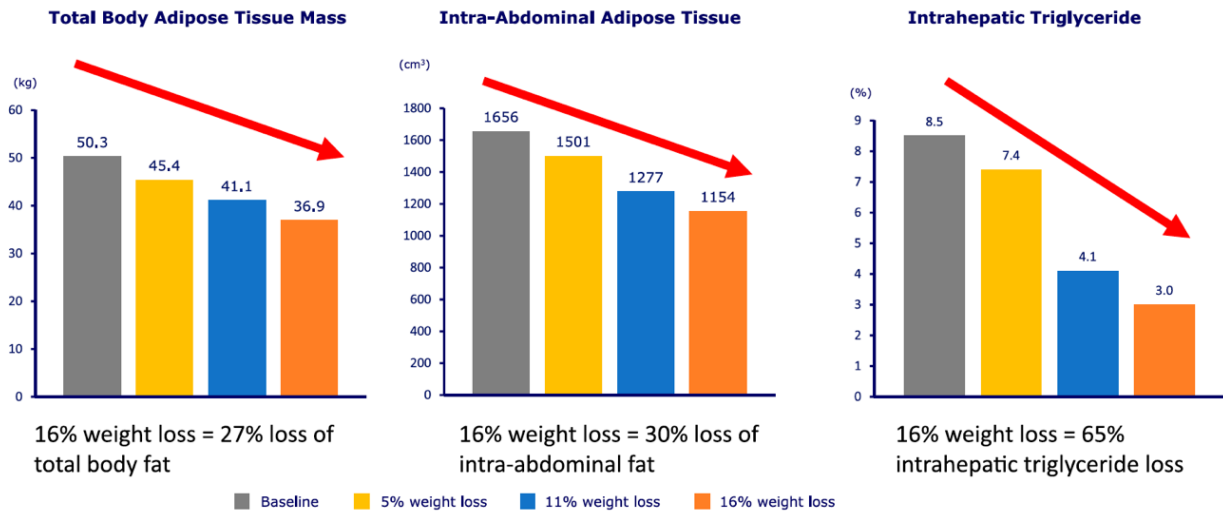
Correspondence

sklein@dom.wustl.edu

In Brief

Magkos et al. demonstrate the profound therapeutic effects of weight loss on metabolic function in subjects with obesity. Even a moderate 5% weight loss has considerable health benefits, including decreased intra-abdominal and intra-hepatic fat and increased multi-organ insulin sensitivity and β cell function. Additional weight loss further improves many cardiometabolic outcomes.

Magkos f et al. Cell Metabolism 2016;23:591 - 601

Weight loss produces disproportionately greater loss of intra-abdominal and liver adipose tissue

**Total Body Adipose Tissue Mass**

(kg)

50.3, 45.4, 41.1, 36.9

16% weight loss = 27% loss of total body fat

Intra-Abdominal Adipose Tissue

(cm³)

1656, 1501, 1277, 1154

16% weight loss = 30% loss of intra-abdominal fat

Intrahepatic Triglyceride

(%)

8.5, 7.4, 4.1, 3.0

16% weight loss = 65% intrahepatic triglyceride loss

■ Baseline ■ 5% weight loss ■ 11% weight loss ■ 16% weight loss

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Weight loss has dose-dependent and tissue-dependent biological effects

Effects of moderate and subsequent progressive weight loss

	5% weight loss	11% weight loss	16% weight loss
Adipose tissue insulin sensitivity	✓	✓	✓
Liver insulin sensitivity	✓	✓	✓
Muscle insulin sensitivity	✓	✓ ✓	✓ ✓ ✓
β cell function	✓	✓ ✓	✓ ✓ ✓
Intra-abdominal adipose tissue volume	✓	✓ ✓	✓ ✓ ✓
Intrahepatic triglyceride content	✓	✓ ✓	✓ ✓ ✓
Adipose tissue biology*		✓	✓ ✓
Inflammatory markers		✓	✓ ✓

*Upregulation of genes involved in cholesterol flux, downregulation of genes involved in lipid synthesis, extracellular matrix remodelling and oxidative stress.

A new weight-centric approach for diabetes
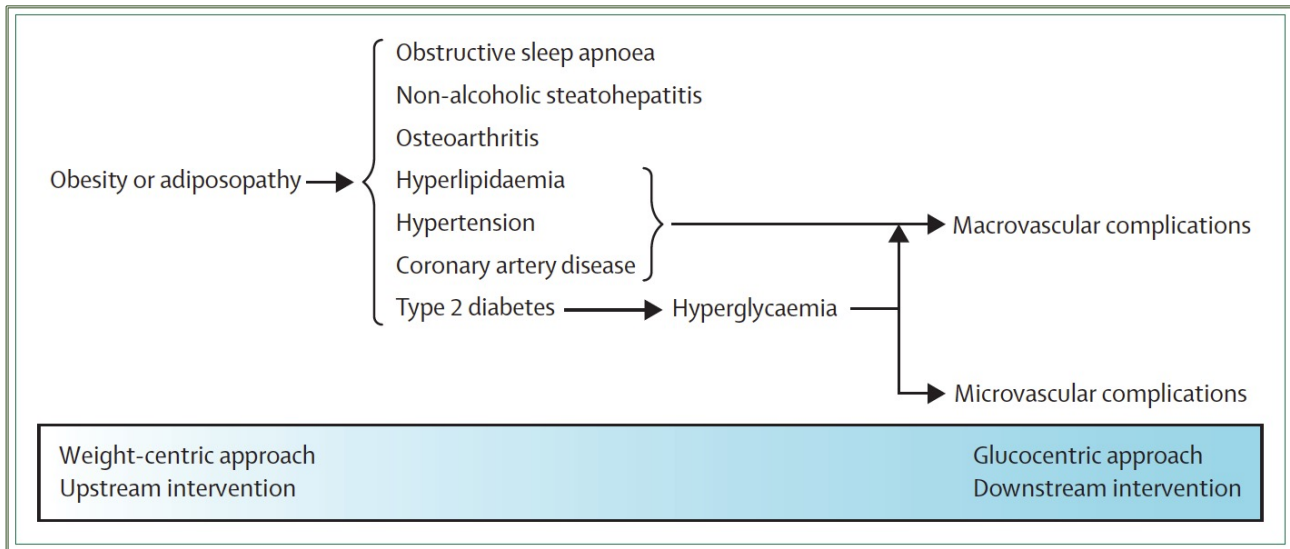
What is a Very Low Energy Diet (VLED)?

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What is a VLED, SERD and MRP?

- Definition Very Low Energy Diet (VLED)

  - $\leq$ 3.4 MJ (800 kCal) per day

- Definition Severely Energy Restricted Diet (SERD)

  - A diet that provides less than 35% of total energy requirements

- Definition Meal Replacement Product (MRP)

  - Product that replaces usual food intake

What might this look like?

3x MRP daily and 2L water

3x MRP daily, 2L water, 1 teaspoon oil, 2 cups+ low carb vegetables

+/- additional protein

Resources for health care practitioners

What dietary interventions using VLEDs have been successful for diabetes remission?

Diabetes Remission Clinical Trial (DiRECT)

Diabetes Intervention Accentuating Diet and Enhancing Metabolism (Diadem)

DiRECT-Aus clinical trial

NEW

Diabetes Remission Clinical Trial (DiRECT)

Weight Management within routine Primary Care

Design: Open-label, cluster-randomised by GP practices

Typical T2D patients: Duration <6 years, age <65 years, HbA1c <10%

Co-primary outcomes:
– Numbers maintaining ≥15kg weight loss at 12 months

– Numbers with <u>remission of diabetes at 12 months</u>
  (HbA1c <6.5%, off anti-diabetes drugs for >2 months)

DiRECT Intervention: Counterweight-Plus Protocol

1. Total Diet Replacement
   Nutritionally complete (vitamins & minerals)
   830 kcal: 61%E carb, 13% fat, 26% protein

2. Stepped Food Reintroduction
   Add a ~400kcal meal every 2-3 weeks
   Step-counters: gradually increase PA

3. Weight Loss Maintenance
   Food-based diet +/- meal replacements
   50%E carbohydrate, 35% fat, 15% protein
   Offer Relapse Management (regain >2kg)

Visits 2-4 weekly at own primary care centres
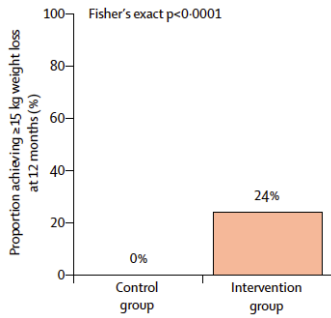**Programme delivered by usual primary care staff**
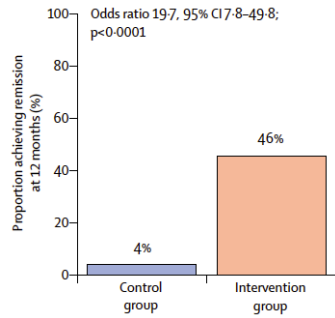
**Maintain PA** ~30mins/ day
STOP all diabetes meds
STOP all BP meds

Diabetes Remission Clinical Trial (DiRECT)

Fisher's exact p<0·0001

Proportion achieving ≥15 kg weight loss at 12 months (%)

Control group: 0%
Intervention group: 24%

Odds ratio 19·7, 95% CI 7·8–49·8; p<0·0001

Proportion achieving remission at 12 months (%)

Control group: 4%
Intervention group: 46%

Odds ratio per kg weight loss 1·32, 95% CI 1·23–1·41; p<0·0001

Proportion achieving remission at 12 months (%)

Weight loss at 12 months (kg)
0: 0%
<5: 7%
5–10: 34%
10–15: 57%
≥15: 86%

≥10 kg loss: 73% are in remission

Achievement of at least 15 kg weight loss at 12 months
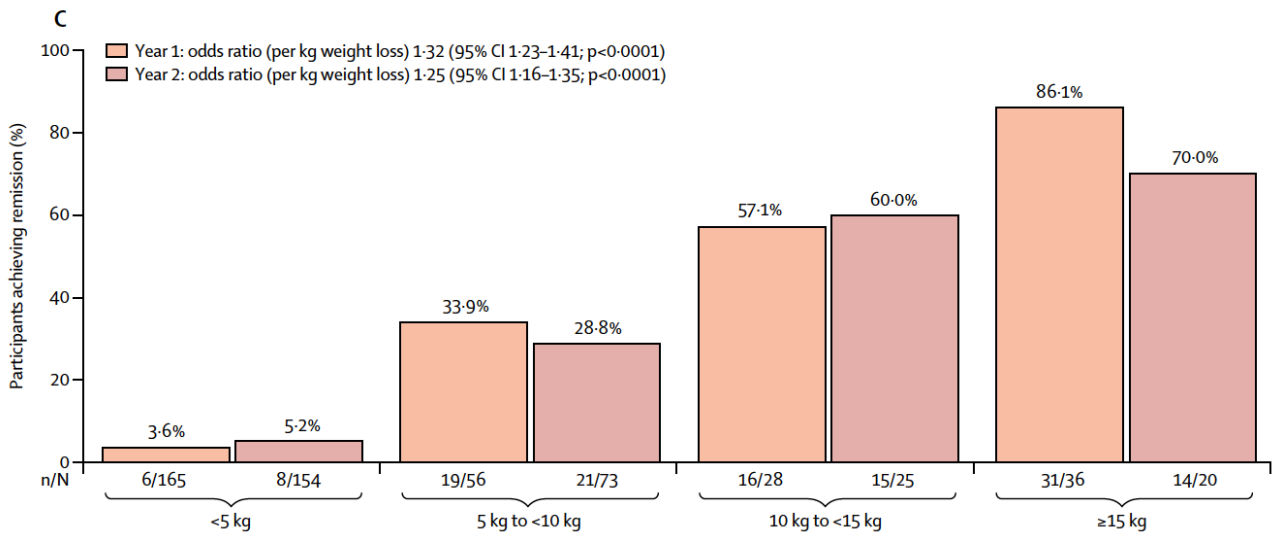
Achievement of remission of diabetes
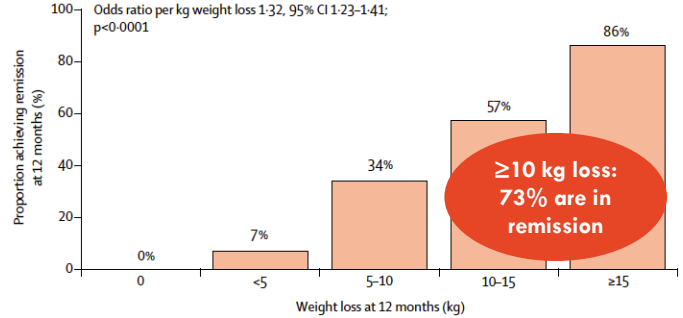
Remission of diabetes, in relation to weight loss achieved at 12 months (both groups combined).

Lean ME et al. Lancet. 2018; 391:541–51.

Diabetes Remission Clinical Trial (DiRECT) – 2 year outcomes

C

Participants achieving remission (%)

- Year 1: odds ratio (per kg weight loss) 1·32 (95% CI 1·23–1·41; p<0·0001)
- Year 2: odds ratio (per kg weight loss) 1·25 (95% CI 1·16–1·35; p<0·0001)

n/N	<5 kg		5 kg to <10 kg		10 kg to <15 kg		≥15 kg	
	6/165	8/154	19/56	21/73	16/28	15/25	31/36	14/20
	3·6%	5·2%	33·9%	28·8%	57·1%	60·0%	86·1%	70·0%

Remission of type 2 diabetes in relation to weight loss achieved (both randomised groups combined).

References: 1. Lean ME et al. Lancet. 2018; 391:541–51. 2. Lean ME et al.Lancet Diab Endocrinol. 2019 May; 7(5):344-355

Remission of Type 2 Diabetes Is Dependent upon β-Cell Recovery
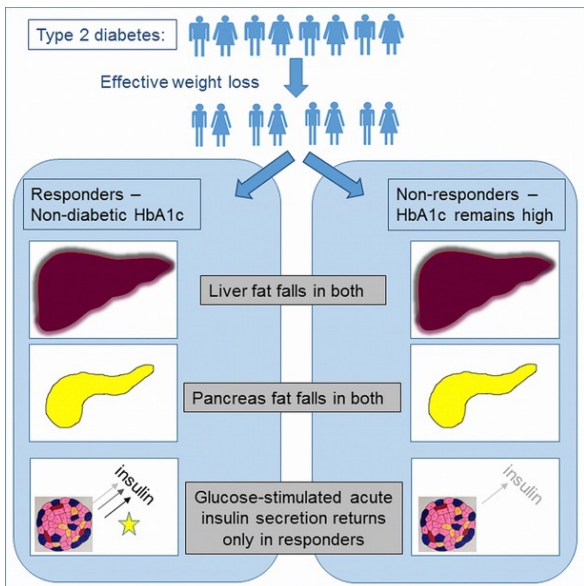
Responders and non-responders were similar at baseline:

- Age
- Weight & adipose tissue volumes
- Sex
- Liver fat
- Plasma triglycerides

Non-responders:

- Higher baseline HbA1c
- Longer duration of T2D
- Lower fasting insulin
- lower plasma ALT

References: 1. Taylor R et al. Cell Metabolism 2018;18(4):547-556

Diabetes Intervention Accentuating Diet and Enhancing Metabolism (Diadem-1)

Achievement of weight loss targets at 12 months

Achievement of remission of diabetes
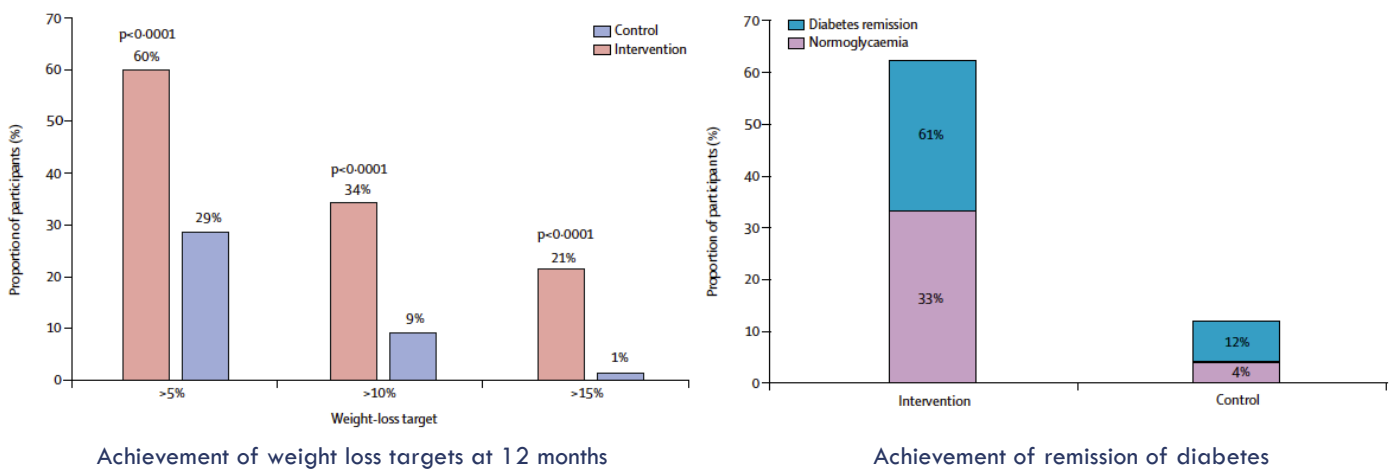
Taheri S et al. Lancet Diab Endocrinol. 2020; 8:477-489

Intensive Lifestyle Intervention for Remission of Early Type 2 Diabetes in Primary Care in Australia: DiRECT-Aus

Samantha L. Hocking, Tania P. Markovic, Crystal M.Y. Lee, Tegan J. Picone, Kate E. Gudorf, and Stephen Colagiuri

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Acknowledgements

Study design

Key inclusion criteria

- Age 20 – 65 years
- T2D diagnosed within the previous 6 years
- HbA1c ≥ 6.5% (48 mmol/mol) or between 6.0 – 6.5% (42- 48 mmol/mol) if using glucose lowering medication
- BMI > 27 kg/m^2

- **Key exclusion criteria**
- Type 1 diabetes
- currently using insulin
- HbA1c ≥ 10% (86mmol/mol)
- had experienced weight loss ≥ 5kg within the last 6 months
- had significant cardiovascular, renal or psychiatric disease or substance misuse

Total diet replacement 13 weeks	→	**Food Reintroduction** 8 weeks	→	**Weight loss maintenance** 31 weeks

52 week intervention

A single-arm, open-label intervention study conducted in 25 primary care practices

All oral antidiabetic drugs were discontinued on commencement of the dietary intervention

Total diet replacement: Optifast (Nestlé Health Science)

    3 meal replacement products/day*

    ≥2L low energy fluids

    2 cups of low starch vegetables with one teaspoon of oil daily

    * if BMI >40 kg/m^2 4 meal replacement products /day

Outcomes

Primary outcome
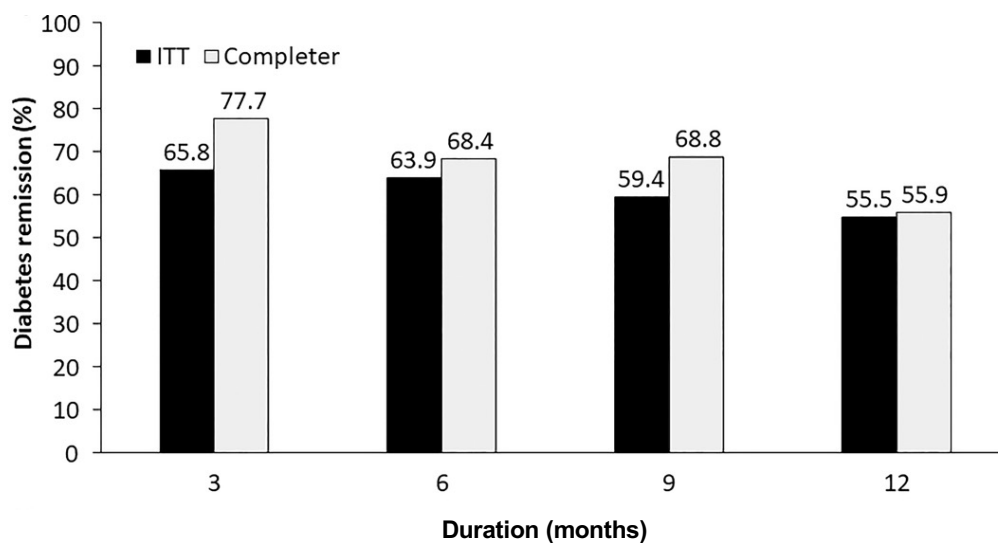
- Remission of T2D* at 12 months.

Secondary outcomes

- Weight change at 12 months
- T2D remission and weight change at 3, 6, and 9 months

*Type 2 Diabetes remission was defined as HbA1c < 6.5% (< 48 mmol/mol) and cessation of glucose-lowering medications for at least 2-months±7 days
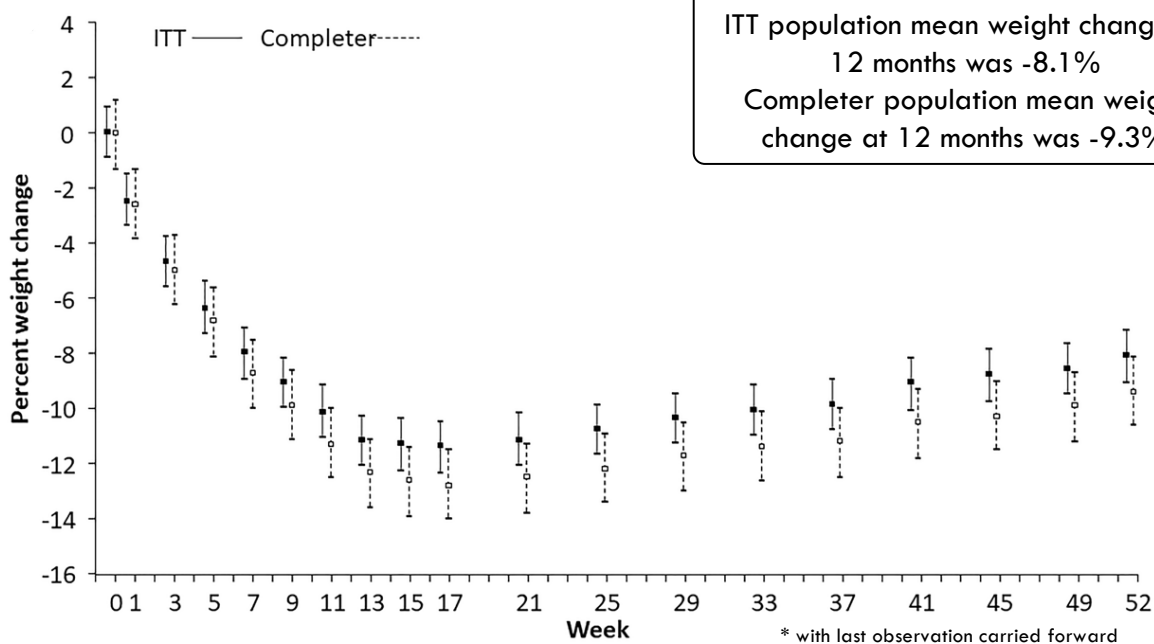
Primary Outcome – Diabetes Remission

Weight change over 52 weeks

ITT population mean weight change at 12 months was -8.1%
Completer population mean weight change at 12 months was -9.3%

* with last observation carried forward

Diabetes remission according to weight loss
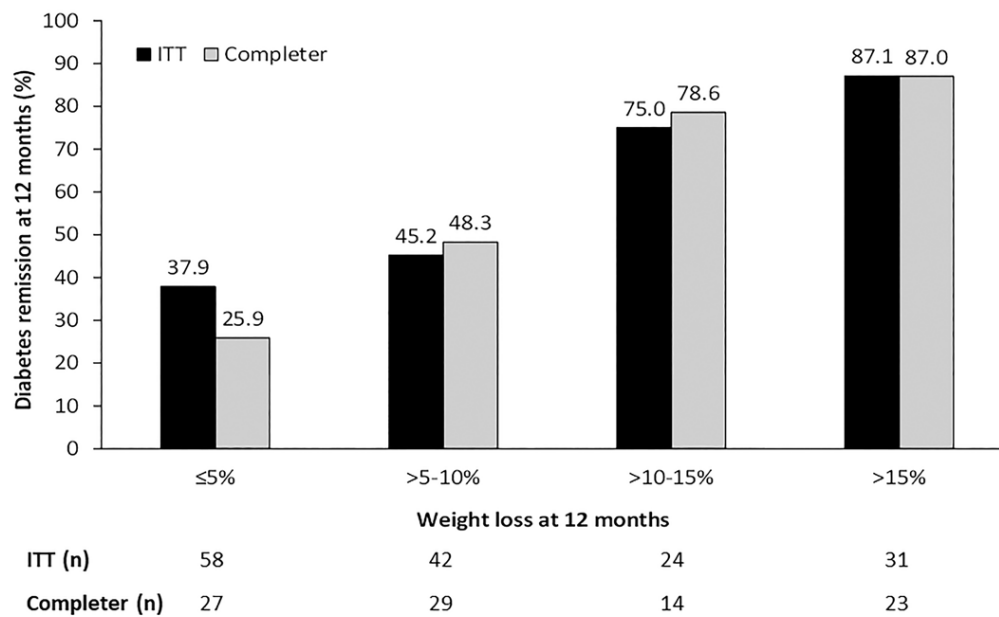
What are the key elements for diabetes remission?

Weight reduction?
- ~15% of individuals that lost >15 kg did not achieve T2D remission

Duration of diabetes?
- Non-responders have a longer duration of diabetes

Age of individual?
- Non-responders are older than responders

Beta cell function?
- Non-responders have poorer beta cell function

Durability of diabetes remission from VLEDs remains unknown

Let's review Pauline's progress

Pauline has been following VLED – using 3 meal replacements per day
- "everything is really good"
- Lost 6 kg weight over first 4 weeks
- Found shakes easy to use
- Enjoyed additional vegetables and salads

After 12 weeks
- Weight loss has slowed
- Lost 12 kg in weight
- Reintroduced 1 food-based meal per day
- Diabetes remission - HbA1c 6.3%

After 24 weeks
- Lost 16 kg in total
- Maintains diabetes remission – HbA1c 6.2%
- Remains on 1 meal replacement product per day at breakfast

Conclusions

Type 2 diabetes is not a permanent disease

One in two individual with Type 2 diabetes can achieve remission with weight loss

The likelihood of diabetes remission is proportional to weight loss with remission achieved by ~85% of people who can reduce their weight by >15%.

Total diet replacements are easy to follow and well-tolerated

REMISSION SHOULD BE AN AIM OF DIABETES CARE AT THE TIME OF DIAGNOSIS

Thanks for your attention

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