Type 2 Diabetes Remission; Internist Perspective

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Agenda

- Pathophysiology of T2DM ‘old and new concepts’
- Definition of T2DM remission
- Landmark studies
- Differences between Asians and Caucasians in terms of T2DM
- Studies of T2DM remission in Asians
- Who will get the remission?
- How to get the remission?
Conventional View of Diabetes
The Ominous Octet
The Twin-Cycle Hypothesis
Definition of T2D remission

- American Diabetes Association
- HbA1c <6.5% (48 mmol/mol)
- Remains at that level for at least 3 months
- Without continuation of the usual anti-hyperglycaemic agents

Table 1—Interventions and temporal factors in determining remission of T2D

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Interval before testing of HbA1c to reliably evaluate the response</th>
<th>Subsequent measurements of HbA1c to document continuation of a remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacotherapy</td>
<td>At least 3 months after cessation of this intervention</td>
<td>Not more often than every 3 months or less frequent than yearly</td>
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<tr>
<td>Surgery</td>
<td>At least 3 months after the procedure and 3 months after cessation of any pharmacotherapy</td>
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<tr>
<td>Lifestyle</td>
<td>At least 6 months after beginning this intervention and 3 months after cessation of any pharmacotherapy</td>
<td></td>
</tr>
</tbody>
</table>

Riddle M.C. et al. Diabetes Care 2021;44:2438–2444
The Look AHEAD Study

• 5,145 overweight or obese patients with type 2 diabetes

• An intensive lifestyle intervention (intervention group) or to receive diabetes support and education (control group)

• Median follow-up was 9.6 years

• Weight loss was greater in the intervention group than in the control group throughout the study
  • 8.6% vs. 0.7% at 1 year
  • 6.0% vs. 3.5% at study end

T2D remission rate in intervention group
  • 11.5% at 1 year
  • 7.3% at 4 years
  • Modest weight loss achieved
  • Wide range of T2D duration

The Diabetes Remission Clinical Trial (DiRECT)

- 49 primary care practices in Scotland
- Weight management programme (intervention) or best-practice care by guidelines (control)
  - Individuals aged 20–65 years
  - Diagnosed with T2D within the past 6 years
  - BMI of 27–45 kg/m²
  - Not receiving insulin

Mean weight loss:
- Intervention group 10 ± 8 kg
- Control group 1 ± 3.7 kg

Figure 3: Change in weight of participants who remained in the trial and those who dropped out during each phase of the intervention.
Error bars represent 95% CIs.
Figure 2: Primary outcomes and remission of diabetes in relation to weight loss at 12 months
(A) First co-primary outcome: achievement of at least 15 kg weight loss at 12 months. (B) Second co-primary outcome: remission of diabetes (glycated haemoglobin <6.5% [48 mmol/mol], off antidiabetic medication for 2 months). (C) Remission of diabetes, in relation to weight loss achieved at 12 months (both groups combined).

T2D remission rate
• At 1 year: 46%
• At 2 years: 36%
Different people have different fat thresholds

The Twin-Cycle Hypothesis

Isocaloric balance after substantial weight loss

Pre-existing muscle insulin resistance

Normal liver fat

1 VLDL glyceride

Subcutaneous fat storage capacity

Decreased islet triglyceride

Normal insulin response to ingested glucose

Pancreas cycle

Normal post-prandial glucose

Normal plasma glucose

Normal basal insulin secretion

Normal insulin sensitivity and control of glucose production

Liver cycle
What Asians differ from Caucasians in terms of T2DM?
India and China account for nearly half of the global number of people with T2DM

Compared with European people, Indian and Chinese people seem to be:

- Generally younger ages at diagnosis
- Lower β-cell function
- Lower insulin resistance
- Lower BMI
Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States

Ronald C.W. Ma and Juliana C.N. Chan

- East Asians develop T2DM at much lower BMI than Caucasians
- Obesity associated T2DM risk
  - a 2.5- to 3-fold in Asians
  - A 6- to 8-fold in a U.S. population
- Younger onset (3 years lower)
- Beta-cell dysfunction
- Visceral fat
- More insulin resistance
- White rice consumption

Figure 1. Relationship between BMI and diabetes prevalence in different ethnicities from the DECODA Study compared to a European population. Adapted with permission.
White rice consumption and risk of type 2 diabetes: meta-analysis and systematic review

Emily A Hu research assistant\textsuperscript{1}, An Pan research fellow\textsuperscript{1}, Vasanti Malik research fellow\textsuperscript{1}, Qi Sun instructor in medicine\textsuperscript{1,2}

White rice consumption:
- Asians: 3 - 4 servings/day
- Western: 1 - 2 servings/week

The pooled relative risk:
- **Asians: 1.55** (95% CI 1.20 - 2.01)
- Western: 1.12 (0.94 - 1.33)
For each serving per day increment of white rice intake, the relative risk of T2DM was **1.11** (1.08 to 1.14)
The Global Nutrient Database: availability of macronutrients and micronutrients in 195 countries from 1980 to 2013

Josef Schmidhuber, Patrick Sur, Kairsten Fay, Bethany Huntley, Joseph Salama, Alexander Lee, Leslie Comaby, Masako Horino, Christopher Murray, Ashkan Afshin
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What Asians differ from Caucasians in terms of T2DM?

- Younger ages at diagnosis
- Lower BMI
- More impaired β-cell function
- Different fat distribution
  - Higher visceral fat

Dietary pattern
- Lower energy
- Higher CHO consumption
  - White rice
- Lower protein
Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an open-label, parallel-group, randomised controlled trial

Shahrad Taheri, Hadeel Zaghloul*, Odette Chagoury*, Sara Elkadad, Salma Hayder Ahmed, Neda El Khatib, Rasha Abou Amona, Katie El Nahas, Noor Suleiman, Abdulla Alnnaama, Abdulla Al-Hamaq, Mary Charlson, Martin T Wells, Samya Al-Abdulla, Abdul Badi Abou-Samra

18 – 50 years, Middle East and north Africa region
Diabetes duration ≤3 years (mean 21 months)
BMI ≥27 kg/m² (mean 35 kg/m²)

Intensive lifestyle intervention
• A 12-week total diet replacement phase (800 kcal/day)
• Followed by a 12-week food reintroduction phase
• All diabetes medications were discontinued

Intensive lifestyle
n = 79

Usual care
n = 79

Lancet Diabetes Endocrinol 2020; 8: 477–489
Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an open-label, parallel-group, randomised controlled trial

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Average weight loss
• Intervention 12 kg
• Control 4 kg

T2D remission rate
• Intervention 61%
• Control 12%
Immediate and long-term effects of a very-low-calorie diet on diabetes remission and glycemic control in obese Thai patients with type 2 diabetes mellitus

Age was 48 ± 1.7 years (range, 33–59)
DM duration <10 years (median 2.0)
BMI 23–30 kg/m² (BMI 27.7 kg/m²)
At 12 months, DM remission was achieved in approximately 30%.
Diabetes remission after a lifestyle-medicine intervention on type 2 diabetes in lean and obese Chinese subjects: a prospective study

Wenying Zou1^, Kunyuan Luo2^, Zhiyong Hu1, Xiongchou Zhang2, Cuiping Feng3, Dingkang Ye3, Shenghao Liu3, Qiwei Zhang3, Rongshao Tan4, Chengbin Fu1^, 2^

<20 years after T2DM diagnosis
≥6 months treatment with oral anti-diabetic drugs without serious complications
no history of insulin use.

Lifestyle-medicine intervention
• Withdrawal of anti-diabetic drugs
• 1st month, a low-carbohydrate diet (35–40% carbohydrate, 20–30% protein, and 30–45% fat);
  • 1,800 kcal/day for the lean group
  • 700–900 kcal/day for the obese group
• 2nd – 6th month, stepped normal construction diet
  50–55% carbohydrate, 15–20% protein, and 20–30% fat; 30–35 kcal/kg/day

Obesity group
(BMI ≥25 kg/m²)

n = 31

Lean group
(BMI <25 kg/m²)

n = 77

Ann Palliat Med 2022;11(4):1462-1472
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Wenyong Zou\textsuperscript{1\*\#}, Kunyuan Luo\textsuperscript{2\#}, Zhiyong Hu\textsuperscript{1}, Xionghou Zhang\textsuperscript{2}, Cuiping Feng\textsuperscript{2}, Dingkang Ye\textsuperscript{3}, Shenghao Liu\textsuperscript{2}, Qiwei Zhang\textsuperscript{4}, Rongshao Tan\textsuperscript{4}, Chengbin Fu\textsuperscript{1\*\#}

A reduced \textit{visceral fat} was strongly associated with decreases in A1C levels
The national Acceptable Macronutrient Distribution Range (AMDR) for adults:
- Carbohydrates 45–65% of total calories
- Protein 5–15%
- Fat 15–35%

For remission/prevention of T2D:
- A lower range of carbohydrate intake (49–56%E)
- A higher range of protein (14–20%E)
- A narrower range of fat intake (21–27%E)
Who will get T2DM remission?

- Young age
- Short duration of T2DM
- Preserved beta-cell function
- Fewer anti-hyperglycemic agents
- No insulin
How to get T2DM remission?

- Significant weight loss
- Weight loss maintenance
- Low carbohydrates, high protein diet?

T2DM remission
Thank you very much.