Reversing the Rising Tide of Type 2 Diabetes in Nova Scotia with Therapeutic Nutrition

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Department of Internal Medicine
Dalhousie Fall Refresher
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Slide set for web-posting
### DISCLOSURES

<table>
<thead>
<tr>
<th>Position &amp; Organization</th>
<th>Details</th>
</tr>
</thead>
</table>
| Member of Expert Advisory Committee  
Institute for Personalized Therapeutic Nutrition (not-for-profit) | [https://www.therapeuticnutrition.org/](https://www.therapeuticnutrition.org/) |
| Medical Director  
Valley Metabolic Program | Utilizes carbohydrate restriction for patients with types 2 diabetes and metabolic disease. |
| Grant Money (2017)  
Valley Regional Hospital Foundation | Initiated a program for carbohydrate restriction for patients with type 2 diabetes. |
| Participant  
UBC/IPTN physician feasibility study | Testing an online platform, GroHealth, to deliver therapeutic carbohydrate restriction. |

No conflicts of interest with pharmaceutical companies or industry.

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Michael Mindrum, MD, FRCPC  
Assistant Professor, Dalhousie University
Objectives

Part 1: Setting the Stage

Epidemiology and natural history of type 2 diabetes

Limitations of our conventional approach to treatment
Objectives

Part 2: The Evidence

Physiologic models of type 2 diabetes remission

Review the evidence for therapeutic nutrition

Consider effectiveness of low carbohydrate diets
Type 2 diabetes prevalence: a rising tide

Adiposity and Type 2 DM

“personal fat threshold”

Healthy fat cells
Over-filled & inflamed somatic fat cells
Spill over of fat into visceral organs
Pre-DM
T2D

Natural History of Type 2 Diabetes
and our conventional approach to treatment

## Limitations to Conventional Approach: ACCORD TRIAL

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Event Rate (Annual)</th>
<th>RRR</th>
<th>ARR</th>
<th>Time (yrs)</th>
<th>NNH 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive</td>
<td>Standard</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>2.11%</td>
<td>2.29%</td>
<td>N/A</td>
<td>N/A</td>
<td>n/a</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.41%</td>
<td>1.14%</td>
<td>-23.6%</td>
<td>-0.24%</td>
<td>NNH of 95</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>10.5%</td>
<td>3.5%</td>
<td>-45%</td>
<td>-7%</td>
<td>NNH of 14</td>
</tr>
</tbody>
</table>

Limitations to Conventional Approach:
VADT Trial 15 yr follow up

“There was no evidence of a legacy effect or a mortality benefit with intensive glucose control.”

CADTH Network Meta-Analysis, comparative effectiveness

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>A1c</th>
<th>Weight (kg)</th>
<th>Systolic BP</th>
<th>OR of severe hypo-glycemia</th>
<th>OR of SAEs</th>
<th>OR of withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4 i</td>
<td>-0.58</td>
<td>0.18</td>
<td>-1.04</td>
<td>0.91</td>
<td>0.91</td>
<td>0.78</td>
</tr>
<tr>
<td>GLP-1a</td>
<td>-0.88</td>
<td>-1.44</td>
<td>-2.79</td>
<td>1.8</td>
<td>1.05</td>
<td>1.8</td>
</tr>
<tr>
<td>SGLT-2</td>
<td>-0.67</td>
<td>-2.21</td>
<td>-4.06</td>
<td>0.61</td>
<td>1.11</td>
<td>1</td>
</tr>
<tr>
<td>SUs</td>
<td>-0.7</td>
<td>2.11</td>
<td>0.28</td>
<td>6.4</td>
<td>0.96</td>
<td>0.74</td>
</tr>
<tr>
<td>Basal Insulin</td>
<td>-0.85</td>
<td>2.76</td>
<td>1</td>
<td>3</td>
<td>1.48</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Therapeutics Review Recommendations; 2017 (4): 1 - 20
Individualizing A1C Targets

A target A1C ≤6.5% may be considered in some patients with type 2 diabetes to further lower the risk of nephropathy and retinopathy which must be balanced against the risk of hypoglycemia.

Consider 7.1-8.5% if:
- Limited life expectancy
- High level of functional dependency
- Extensive coronary artery disease at high risk of ischemic events
- Multiple co-morbidities
- History of recurrent severe hypoglycemia
- Hypoglycemia unawareness
- Longstanding diabetes for whom it is difficult to achieve an A1C ≤7%, despite effective doses of multiple antihyperglycemic agents, including intensified basal-bolus insulin therapy.
“Current evidence supports that there is a potential epidemic in the overtreatment with antihyperglycemic therapies in diabetes.”


Limitations to Our Conventional Approach

Approach to Treatment

Vascular complications eventually occur unless glycemia is controlled

Insulin resistance provides defense against nutrient-induced injury of insulin-sensitive tissues

Elevated blood nutrients
- Glucose
- Lipids
- Amino acids

Nutrient off-loading
+/- low-dose insulin

- Lifestyle
  - Bariatric surgery
  - GLP-1R agonists
  - α-glucosidase inhibitors

- Metformin
- SGLT2 inhibitors
- Thiazolidinediones?
- DPP-4 inhibitors?

Reduced metabolic stress in ALL tissues
Reduced short- and long-term complications

Overriding insulin resistance in refractory patients

- High-dose insulin
- Sulfonylureas?

Insulin-induced metabolic stress
Short-term injury of insulin-sensitive tissues

Part 2: Diabetes Reversal & Remission


Therapeutic Nutrition

Individually tailored intervention designed to manage or reverse patient specific metabolic dysfunctions, medical conditions, or their associated symptoms.
Type 2 diabetes reversal

Dietary Trials
Natural history of type 2 diabetes

50% decline in beta-cell function

Macronutrients

carbohydrates

plant-based protein vs. animal based protein

fats

Saturated
Mono-unsaturated
Poly-unsaturated fats
Low Fat

- carbohydrates
- plant based protein > animal based
- fats
Mediterranean

- carbohydrates
- plant-based protein & high fish intake
- High MUFA fats
Low Carbohydrate

carbohydrates

animal based protein or plant based protein

fats
Low Energy

carbohydrates

Protein

fats
## Diabetes Remission

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial</td>
<td>A1c &lt; 6.5 off medications</td>
</tr>
<tr>
<td>Complete</td>
<td>A1c &lt; 5.7 off medications</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Complete remission &gt; 5 yrs (cure)</td>
</tr>
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<table>
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<tr>
<th>Alternate</th>
<th>Definition</th>
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<tr>
<td>Reversal</td>
<td>A1c &lt;6.5 without medication beside metformin (Virta)</td>
</tr>
<tr>
<td>Remission</td>
<td>A1c &lt; 6.5 off all medications for at least 2 months (DiRECT)</td>
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Look AHEAD

- Randomized 5145 patients with obesity & T2D to intensive lifestyle intervention or control designed to generate modest weight loss.

- Intensive Lifestyle Intervention utilizing meal replacement systems and healthy low fat diet (<30% fat).
  - Weekly group and individual counseling for 6 months
  - Then 3 sessions per month for 6 months
  - Then twice monthly for 4 yrs

- Control arm coached for healthy low fat diet and 3 group sessions per year

- Post hoc analysis looked at partial or complete remission of T2D defined as an A1c <6.5 without diabetes medications


Look AHEAD:
Prevalence of Complete or Partial Remission

Look AHEAD:
Durability of partial or complete remission

Look AHEAD
low durability of remission

Perhaps modest results are due to intervening too late or a different intervention is needed?
The 7 year cumulative incidence of achieving any remission was 1.6% among >100,000 patients.

Conclusion: Type 2 DM remission using dietary guidelines from the ADA with a calorie restricted <30% dietary fat can happen, but it is very rare.

Difference between efficacy (Look AHEAD) and effectiveness.

Could we do better with a different dietary strategy?
Direct Trial: A Low Energy Dietary Intervention

- Open label, cluster randomized trial, 49 primary care practices in Scotland & England
- 149 intervention participants age 20 to 65, T2D < 6 yrs
- Intervention with ~850 kcal/day formula for 3 to 5 months followed by stepped food reintroduction over 2 to 8 weeks & structured supports for weight loss maintenance (monthly visits) & “rescue plan” of 2 to 4 weeks partial meal replacement if weight regain occurs.
- Withdrawal of medications for blood sugar and blood pressure medications
- **Those on insulin were excluded**
- Primary outcome at one year
  - Weight loss >15 kg
  - A1c < 6.5 for 2 months off all anti-diabetes medications

DiRECT Trial T2D Remission

http://doi.org/10.1016/S0140-6736(17)33102-1
DiRECT Trial: T2D remission & weight loss

*Look Ahead at one year had 11% remission rate with 8 kg weight loss

Common Ground:
Limit Ultra-Processed Foods

Diets were presented in random order and matched for provided calories, sugar, fat, fiber, and macronutrients.

Key Points

Structured supports are key.

Modest changes lead to modest results.

If possible, act early.

Enthusiasm for remission can be tempered by duration of diabetes and intensity of lifestyle change.

Restricting fat or carbohydrates provides similar weight loss.
Carbohydrate Restriction
Glucose variability independent of weight loss

Gannon, M. C., Hoover, H., & Nuttall, F. Q. (2010). Further decrease in glycated hemoglobin following ingestion of a LoBAG30 diet for 10 weeks compared to 5 weeks in people with untreated type 2 diabetes. Nutrition & Metabolism,
Carbohydrate Restriction
Physiologic effects

# Carbohydrate Restriction

<table>
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<tr>
<th>Diet</th>
<th>Grams of CHO / day</th>
<th>Study</th>
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<td>&lt;30</td>
<td>VIRTA VMP</td>
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<td>JAMA</td>
</tr>
<tr>
<td>Liberal low carbohydrate diet</td>
<td>50 to 130</td>
<td>CSIRO</td>
</tr>
<tr>
<td>Moderate carbohydrate, calorie restricted</td>
<td>&gt;130 (&lt; 50% from CHO &amp; &gt; 30% from fat)</td>
<td>PREDIMED</td>
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Vegetables, whole grains, low in red meat, higher in poultry, fish, olive oil.

Photo courtesy of: www.dietdoctor.com
NEWLY diagnosed patients.

Randomized Mediterranean diet (108) or low fat diet (107)

Restrict energy to around 1500 kcal/day (women) and 1800 kcal/day (men)

### Carbohydrate Restriction

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Less red meat and butter → more fish and olive oil to keep saturated fat similar to low fat diet

Photo courtesy of: www.dietdoctor.com
CSIRO Trial

115 adults with T2D

Randomized to energy matched hypo-caloric diets for 2 yrs to LCHF vs low fat, each keeping saturated fat to <10%

CSIRO Trial

Weight

Hgb A1c
CSIRO Trial

Medication Reduction

Glucose Variability
# Carbohydrate Restriction

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<td>Mediterranean</td>
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Photo courtesy of: www.dietdoctor.com
263 veterans with T2D

Randomized to LCHF (<50 g/day) vs conventional treatment with group medical visits every 8 weeks.

Can intervention lead to non-inferior A1c with less medications?
Figure 3. Medication Dose Changes From Baseline for Each Diabetes Medication Class by Arm for Participants Who Attended Week 48

A Frequency of dose change in the WM/GMV arm

B Frequency of dose change in the GMV arm

DPP-4 indicates dipeptidyl peptidase 4 inhibitor; GLP-1, glucagon-like peptide-1 receptor agonist; GMV, group medical visit; SGLT-2, sodium-glucose co-transporter-2 inhibitors; and WM, weight management.
## Carbohydrate Restriction

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*Photo courtesy of: www.dietdoctor.com*
Virta Health Study

349 adults enrolled

Open label and non randomized comparing ketogenic diet versus usual care

Treatment arm also used remote monitoring and virtual care

Hallberg, S. et al. (2018). Effectiveness and Safety of a Novel Care Model for the Management of Type 2 Diabetes at 1 Year: An Open-Label, Non-Randomized, Controlled Study. Diabetes Therapy: Research, Treatment and Education of Diabetes and Related Disorders, 9(2), 583–612.
Virta Health Study
Insulin Dosing


[https://blog.virtahealth.com/2yr-t2d-trial-outcomes-virta-nutritional-ketosis/](https://blog.virtahealth.com/2yr-t2d-trial-outcomes-virta-nutritional-ketosis/)

Table from [https://blog.virtahealth.com/2yr-t2d-trial-outcomes-virta-nutritional-ketosis/](https://blog.virtahealth.com/2yr-t2d-trial-outcomes-virta-nutritional-ketosis/)
Key Points
Carbohydrate restriction

Act early if possible.

The less the carbohydrate the more effective (modest changes lead to modest results).

Can achieve similar to better glycemic control on less medications.

Leads to improved glucose variability and less hypoglycemia.

Improvement in blood pressure and dyslipidemia.*

Interventions via IT platform/virtual care or group medical visits have shown to be effective.
Valley Metabolic Program
VMP Intervention

- Offered teaching on why to consider carbohydrate restriction and how to do it
- Valley Metabolic Guide Book
- 5 Group sessions at 0, 2, 4, 8, 12 weeks
- Grocery store tours
- Health professional monitored FB page
- Follow patients clinically for one year.
- Can we improve A1c on less drug therapy with a low tech approach?
VMP Participants

- 35 patients
- Average age 60
- Average duration of T2D 12 years
- 11 of 35 patients were on insulin (average duration 10 yrs)
- Baseline A1c of 7.4
- 25 patients returned for 1 year follow up, all data included
Valley Metabolic Program
Quality Improvement
12 month Results

Data analysis courtesy
Dr. Jonathon Little (PhD), and Helena Neudorf PhD(c)
University of British Columbia
(unpublished)
VMP One Year Overview

- Hemoglobin A1c
- Waist Circumference
- Body Mass Index
- Systolic Blood Pressure
- Diastolic Blood Pressure
- Total Cholesterol
- LDL-C
- HDL-C
- Triglycerides
- WBC

Percent Change (%)
# Medication De-Prescribing

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Hypo Risk?</th>
<th>Suggestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Yes</td>
<td>Reduce/stop (if gradual CHO restriction wean by 50%)</td>
</tr>
<tr>
<td>Insulins</td>
<td>Yes</td>
<td>Typically wean by 30 to 50% successively depending on baseline glucose and CHO level*</td>
</tr>
<tr>
<td>SGLT2i</td>
<td>No</td>
<td>Stop. Risk of euglycemic DKA</td>
</tr>
<tr>
<td>Biguanides</td>
<td>No</td>
<td>Individualize, often maximize</td>
</tr>
<tr>
<td>DPP-4</td>
<td>No</td>
<td>Individualize, consider stopping</td>
</tr>
<tr>
<td>GLP1a</td>
<td>No</td>
<td>Individualize.</td>
</tr>
<tr>
<td>Thiazidolones</td>
<td>No</td>
<td>Usually stop</td>
</tr>
</tbody>
</table>

Suggest glucose target of 7 to 10 while weaning down on hypoglycemic agents of insulin or sulfonylurea. Consider diagnosis of LADA prior to de-prescribing insulin.

http://doi.org/10.3399/bjgp19X704525
A1c for Insulin Users
A1c
Key Point

Carbohydrate restriction is effective for patients in our community with achieving similar A1c with less drugs.

It is a refreshing clinical experience.
Guidelines

⚫ 2018: ADA and EASD approved use of low carbohydrate diets as medical nutrition therapy for adults with type 2 diabetes.

⚫ Guidelines in the UK and Australia are also inclusive of carbohydrate restriction.

⚫ The UK and ADA recognize remission as an appropriate aim for type 2 DM management (bariatric surgery, low calorie, carbohydrate restriction).

⚫ Diabetes Canada: Macronutrient distribution is flexible within recommended ranges (45 to 65% CHO) and will depend on individual treatment goals and preferences. 😩😩😩


T2D management with therapeutic nutrition: don’t forget the other guidelines

- **Vascular Protection**
  - **Smoking Cessation**
  - **Blood Pressure Control**
    - Often stop or decrease diuretics at start of diet
    - Liberalize salt intake
    - Reduce dosing if SBP <120 & hold if SBP <110. *Increase salt intake
  - **ACE/ARBs**
  - **Glycemic Control**
    - Relax glycemic control for de-prescribing hypoglycemic agents
    - Recognize improved glycemic variability
  - **Statins based on guideline targets**
  - **Diet, Exercise, Sleep,**
Discussion

Optimism