



How sweet it is!

Steroid Induced Hyperglycemia

April Mills, Primary Care Nurse WRHA &
Mark Kristjanson, Medical Lead, Primary
Care, Community oncology Program



Disclosures

- **Faculty / Speaker's name: April Mills and Mark Kristjanson**
- **Relationships with commercial interests:**
 - **Grants/Research Support: None**
 - **Speakers Bureau/Honoraria: None**
 - **Consulting Fees: None**
 - **Other: None**

Mitigating Potential Bias

- Not applicable

Learning Objectives

At the end of the presentation the learner will be able to:

1. Describe the impact of steroid-related hyperglycemia on hard outcomes pertaining to chemotherapy.
2. Explain the steps clinicians can take to anticipate and manage steroid-related hyperglycemia during chemotherapy.
3. Explain to other colleagues when and how to access other resources (diabetes educators, endocrinologists, dieticians, etc.) in the management of steroid-related hyperglycemia

Clinical Importance

- Cancer is now the leading cause of death and premature loss of life in Canada
- Nearly half of all Canadians will develop cancer in their lifetimes; about half of whom will die of their disease*
- An estimated 202,400 new cases of cancer were anticipated in Canada in 2016

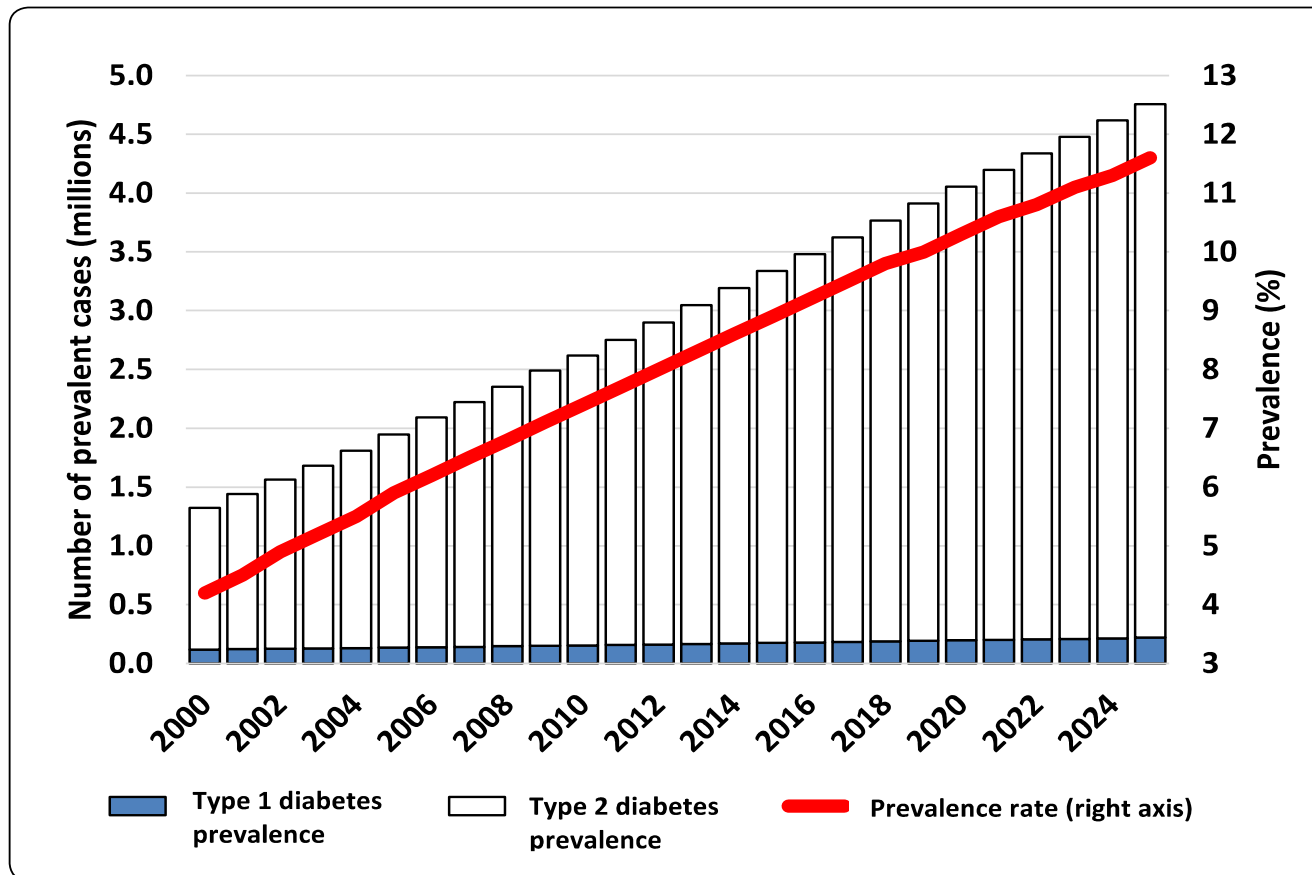
**Canadian Cancer Statistics, 2016*

Clinical Importance

- Diabetes and pre-diabetes affect over 10 million Canadians
- Diabetes prevalence has more than doubled since 2000
- The prevalence of diabetes will grow by 40% in the next ten years

Canadian Diabetes Association, 2015

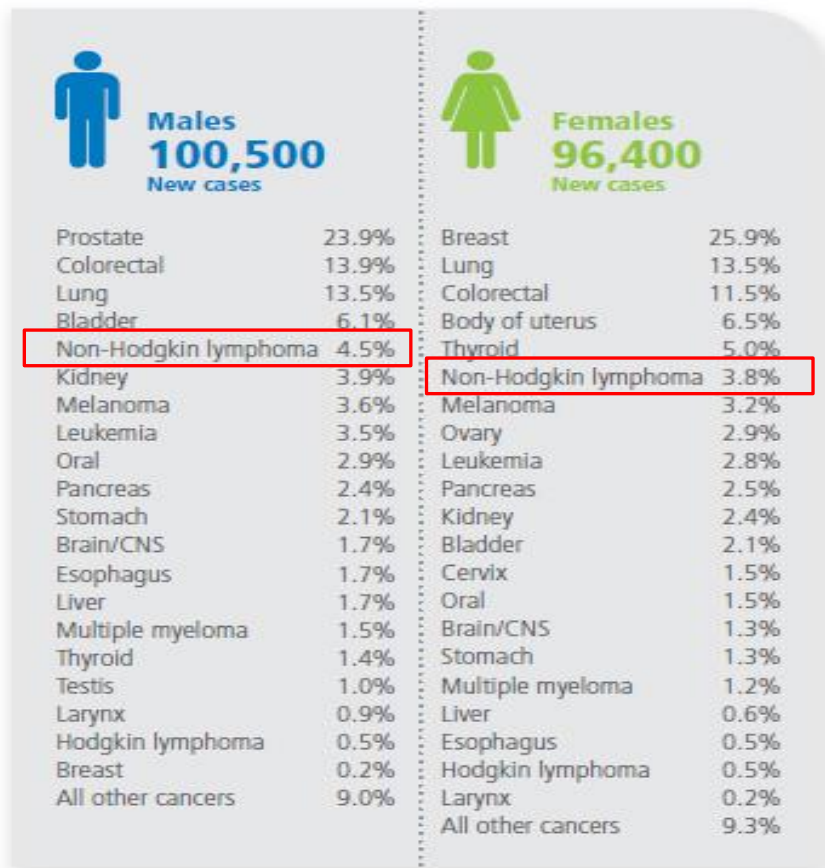
Diabetes Prevalence in Canada, 2000-2025



Note. The graph presents crude prevalence rates.

Source: Canadian Diabetes Cost Model, 2015.

Present Distribution of Estimated New Cancer Cases in Canada, 2015



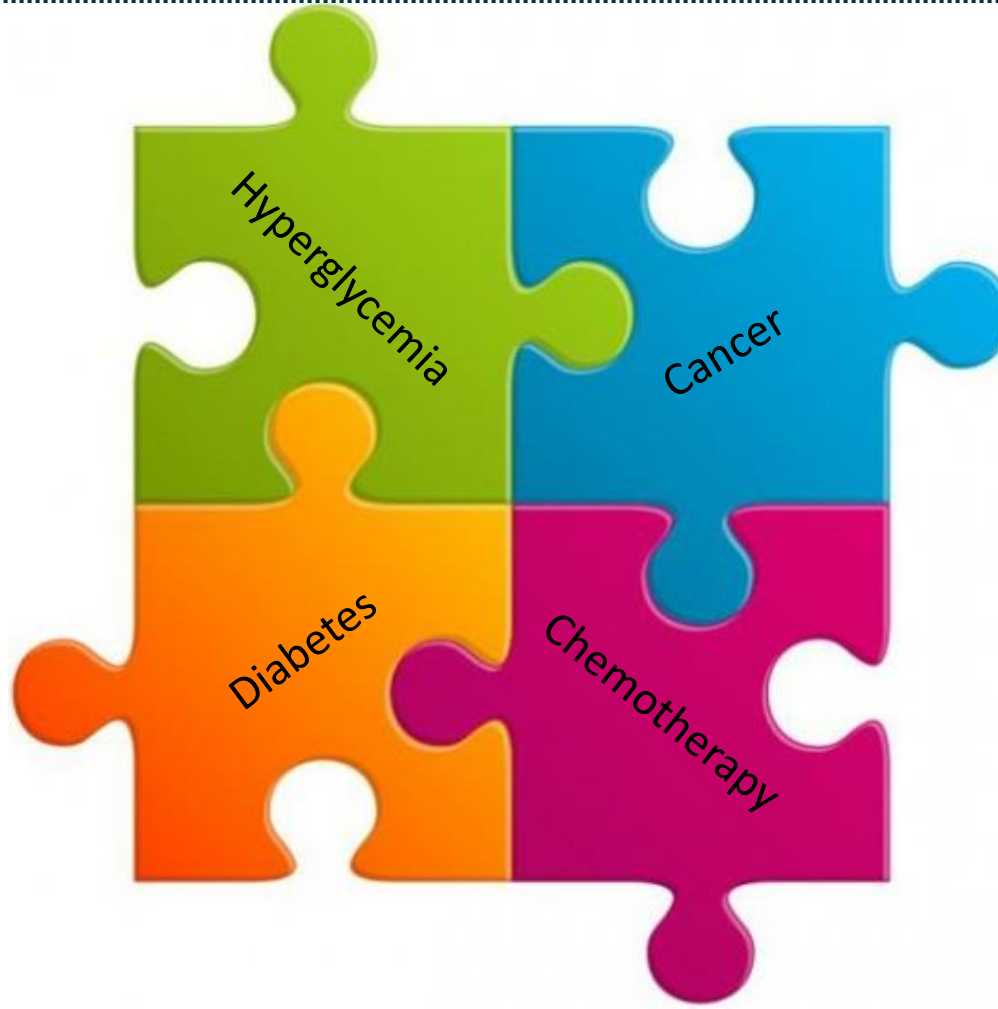
CNS=central nervous system

Note: The complete definition of the specific cancers listed here can be found in Table A10.

Analysis by: Surveillance and Epidemiology Division, CCDP, Public Health Agency of Canada

Data sources: Canadian Cancer Registry database at Statistics Canada and Quebec Cancer Registry (2008–2010)

What is the connection?



What is the connection?

- Prevalence of both diabetes and cancer is increasing in Canada
- Diabetics are at a higher risk for many types of cancer
- Chemotherapy regimes often include high doses of steroids
- High dose steroids induce hyperglycemia in non-diabetic patients and make glycemic control for diabetics more challenging

What is research telling us?

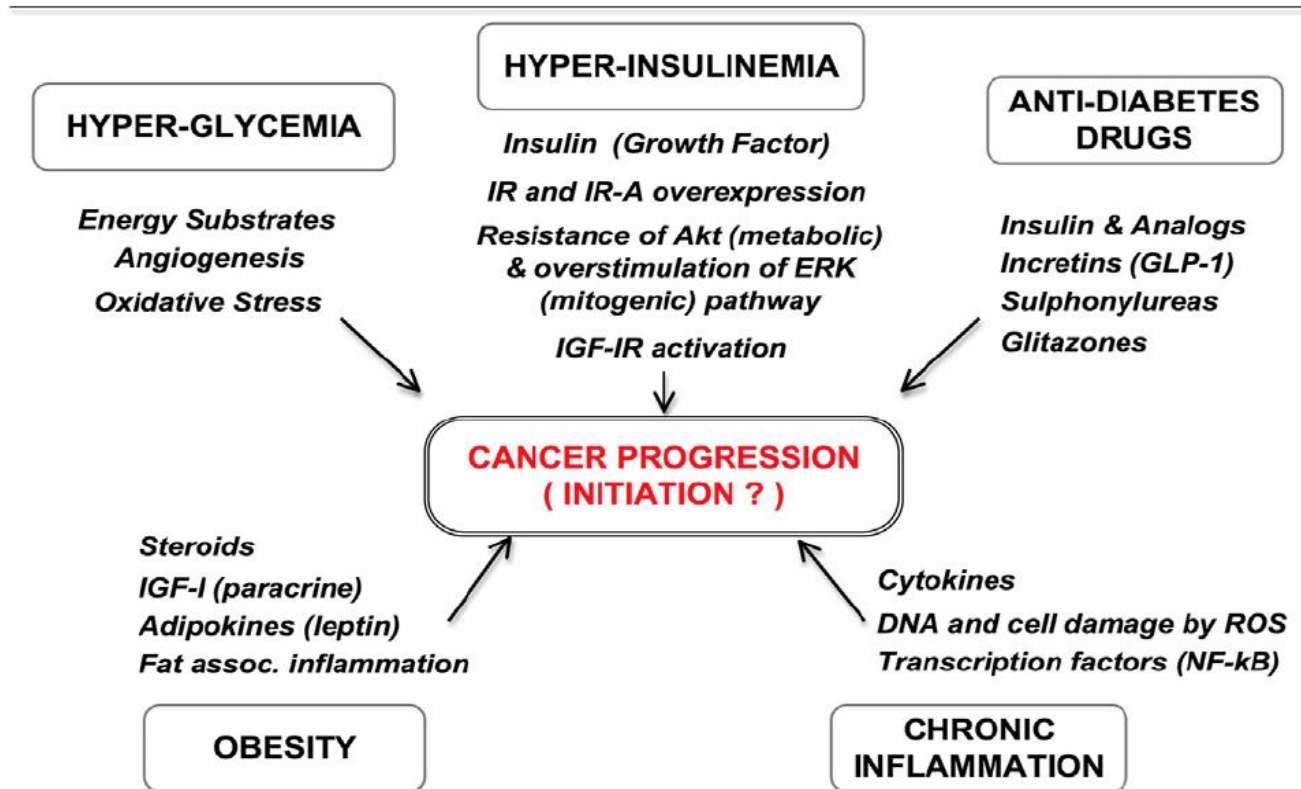
- Warburg Hypothesis
 - The dependence of many cancers on glycolysis for energy
 - Cancer cells have high glucose requirement for ATP generation by glycolysis rather than oxidative phosphorylation

What is research telling us?

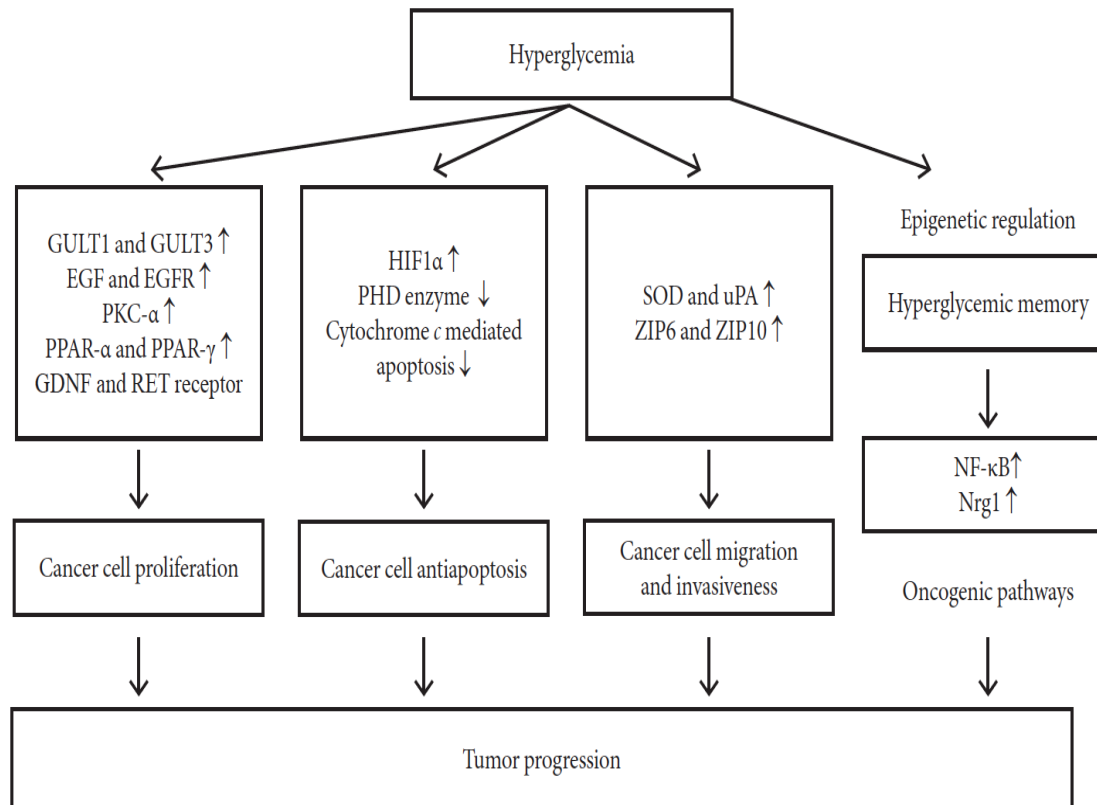
- Diabetes and Cancer Initiation and Progression
 - Hyperglycemia and hyperinsulinemia can promote cancer via both independent and synergic mechanisms

What is research telling us?

DIABETES-RELATED FACTORS AND MECHANISMS POTENTIALLY INVOLVED IN CANCEROGENESIS



What is research telling us?



What has already been done?

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL
ARTICLES

Hyperglycemia during Induction Therapy is Associated with Poorer Survival in Children with Acute Lymphocytic Leukemia

Rona Y. Sonabend, MD, Siripoom V. McKay, MD, M. Fatih Okcu, MD, MPH, Jinrong Yan, MD, Morey W. Haymond, MD, and Judith F. Margolin, MD

- Retrospective review
- 167 children with ALL between 1999 and 2002 at Texas Children's Hospital
- Hyperglycemia during induction and RFS and OS
- Overt hyperglycemia was seen in 34% of patients
- Overt hyperglycemia = poorer RFS and OS at 5 years
- Only 16 patient were treated with insulin therapy
- **Demonstrated the effect of hyperglycemia on survival outcome and the need for better blood glucose surveillance and control**

What has already been done?



March 15, 2004, V100 pg 1179-1185

Relation between the Duration of Remission and Hyperglycemia during Induction Chemotherapy for Acute Lymphocytic Leukemia with a Hyperfractionated Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone/Methotrexate–Cytarabine Regimen

Weiser MA, Cabanillas ME, Konopleva M, Thomas DA, Pierce, SA, Escalante CP, Kantarjian HM, and O'Brien SM

- Prospective review
- 275 adults with previously untreated ALL who achieved complete remission with hyper-CVAD were evaluated.
- 103 patients were hyperglycemic; only 20 had a previous diagnosis of DM
- Hyperglycemic patients had shorter CRD and OS
- Hyperglycemic patients were more likely to develop infection and sepsis
- **Demonstrated that hyperglycemia was associated with greater complications during chemotherapy treatment and greater chance of disease recurrence**

What has already been done?

Curr Oncol, Vol. 20, pp. e532-538; doi: <http://dx.doi.org/10.3747/co.20.1499>

ORIGINAL ARTICLE



Glucocorticoid-induced hyperglycemia is prevalent and unpredictable for patients undergoing cancer therapy: an observational cohort study

D. Harris MD,^a A. Barts MD,*^a J. Connors,[†]
M. Dahl MD PhD,* T. Elliott MBBS,* J. Kong MD,*
T. Keane MD,[‡] D. Thompson MD,* S. Stafford MD,*
E. Ur MBBS,* and S. Sirrs MD**

- Observational cohort study
- 90 patients receiving glucocorticoids as part of their chemotherapy were screened with random glucose measurements
- Hyperglycemia was found in 58% with DM range in 18.9%
- Presence of hyperglycemia did not correlate with traditional DM risk factors
- **GC induced hyperglycemia is common in patients undergoing chemotherapy and cannot be predicted by traditional DM risk factors**

What has already been done?

Hyperglycemia During Chemotherapy for Hematologic and Solid Tumors Is Correlated With Increased Toxicity

Antonella Brunello, MD, Rachna Kapoor, MBBS, MPH,† and Martine Extermann, MD, PhD‡*

American Journal of Clinical Oncology

- Retrospective review
- 349 patients (162 NHL and 187 PC) between Jan 1999 and Nov 2007
- All patients were receiving R-CHOP chemotherapy regime
- Primary endpoint assessed if glycemia correlated with toxicity
- Secondary endpoint PFS and OS
- G4 HemT was 47% in NHL and 5% in PC
- G3-4 NHemT was 48.8% in NHL and 48.1% in PC
- Early interruption of chemotherapy was 22% in NHL and 84% in PC
- **A positive correlation with higher toxicity rates for patients with uncontrolled glycemia while receiving chemotherapy**
- **Did not determine if this translates to poorer long-term outcomes**

Impact of Diabetes Mellitus on Outcomes in Patients With Colon Cancer

Meffrey A. Meyerhardt, Paul J. Catalano, Daniel G. Holler, Robert J. Mayer, John. S. Macdonald, Al B. Benson III, and Charles S. Fuchs
Journal of Clinical Oncology, Vol 21, No 3 (February 1), 2003:pp 433-440

- 3,759 patients with high-risk Stage II or Stage III colon cancer in a prospective trial of 4 different chemo regimens
- Median survival 6.0 years for diabetics vs. 11.3% for non-diabetics
- Disease-free survival 48% for diabetics vs 59%
- Overall survival 57% vs 66%
- Recurrence-free survival 56% vs 64%
- Diabetics had more treatment-related diarrhea

Case Scenario: Special Patients Unit

- All characters appearing in this work are fictitious. Any resemblance to real persons, living or dead, is purely coincidental.



Case Scenario: Special Patients Unit

- 71 year old man with Hodgkin's lymphoma and NIDDM presents to SPU with complaints of weakness and postural light headedness
 - BP 88/52, P104, T36.5 C, RR 22, O2 sats 96%
 - Dry mucous membranes, nil else acute on exam
 - RBS 30 mmol/L, BOHB normal
-
- How to treat?

Case Scenario: Special Patients Unit

- 1 L normal saline, 10 units of Novo rapid subcut
- 1H later, still weak but postural Sx resolved
- BP 98/64, P96, RBS 24 mmol/L
- Novo rapid 10 units repeated; 0.5 L normal saline
- 1H later RBS 17, BP 100/68, P 84
- Patient discharged with instructions to follow up with family doc regarding blood sugars and with hematologist as scheduled pre-chemo

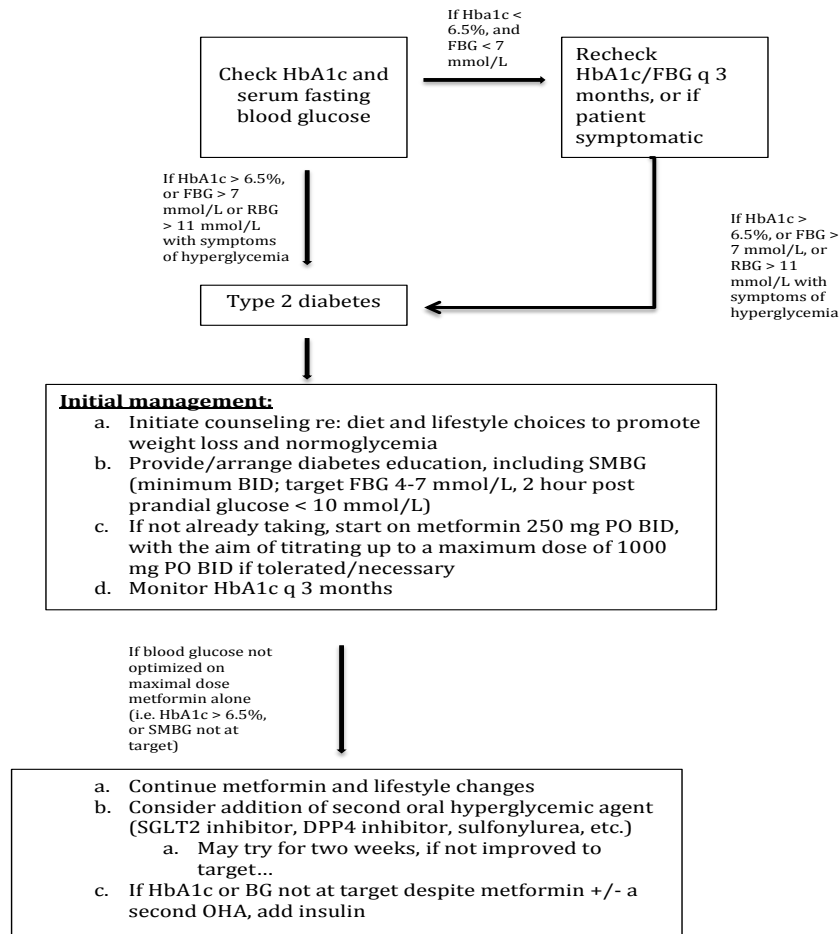
Case Scenario: Special Patients Unit

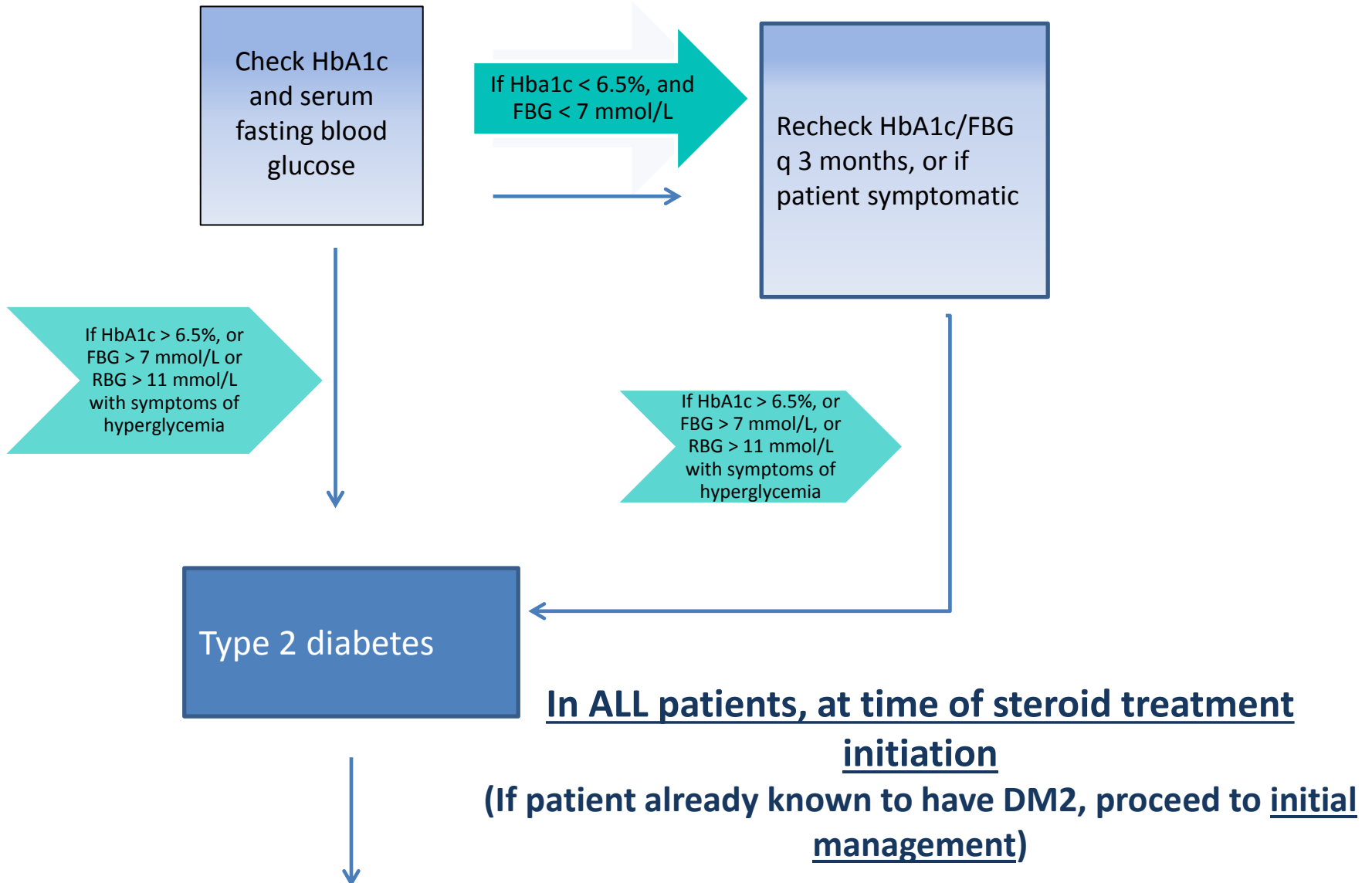
- Next cycle, same patient presents with same problem
- Patient treated in similar fashion with similar results
- Telephone call made to HSC DER* nurse clinician
- Request made to teach patient to self administer 7 units of Novo rapid ac T1D while on steroids
- And it worked.....kinda, sorta.....

What to do?

- Dr. Isanne Schacter (Endocrinology, WRHA) has developed an algorithm based on CDA guidelines
- Surveillance for and management of hyperglycemia related to the use of steroids in chemotherapy
- With input from Dr. Schacter and April Mills (Diabetes Educator & Primary Care Nurse, WHRA), basic algorithm adapted to various chemotherapy regimens
- Approval in principle from Hematology Department at CCMB for pilot of algorithms in DSG clinics
- Primary Care: your turn

In ALL patients, at time of steroid treatment initiation
(If patient already known to have DM2, proceed to initial management)





Type 2 diabetes

Initial management:

- Initiate counseling re: diet and lifestyle choices to promote weight loss and normoglycemia
- Provide/arrange diabetes education, including SMBG (minimum BID; target FBG 4-7 mmol/L, 2 hour post prandial glucose < 10 mmol/L)
- If not already taking, start on metformin 250 mg PO BID, with the aim of titrating up to a maximum dose of 1000 mg PO BID if tolerated/necessary
- Monitor HbA1c q 3 months

Type 2 diabetes

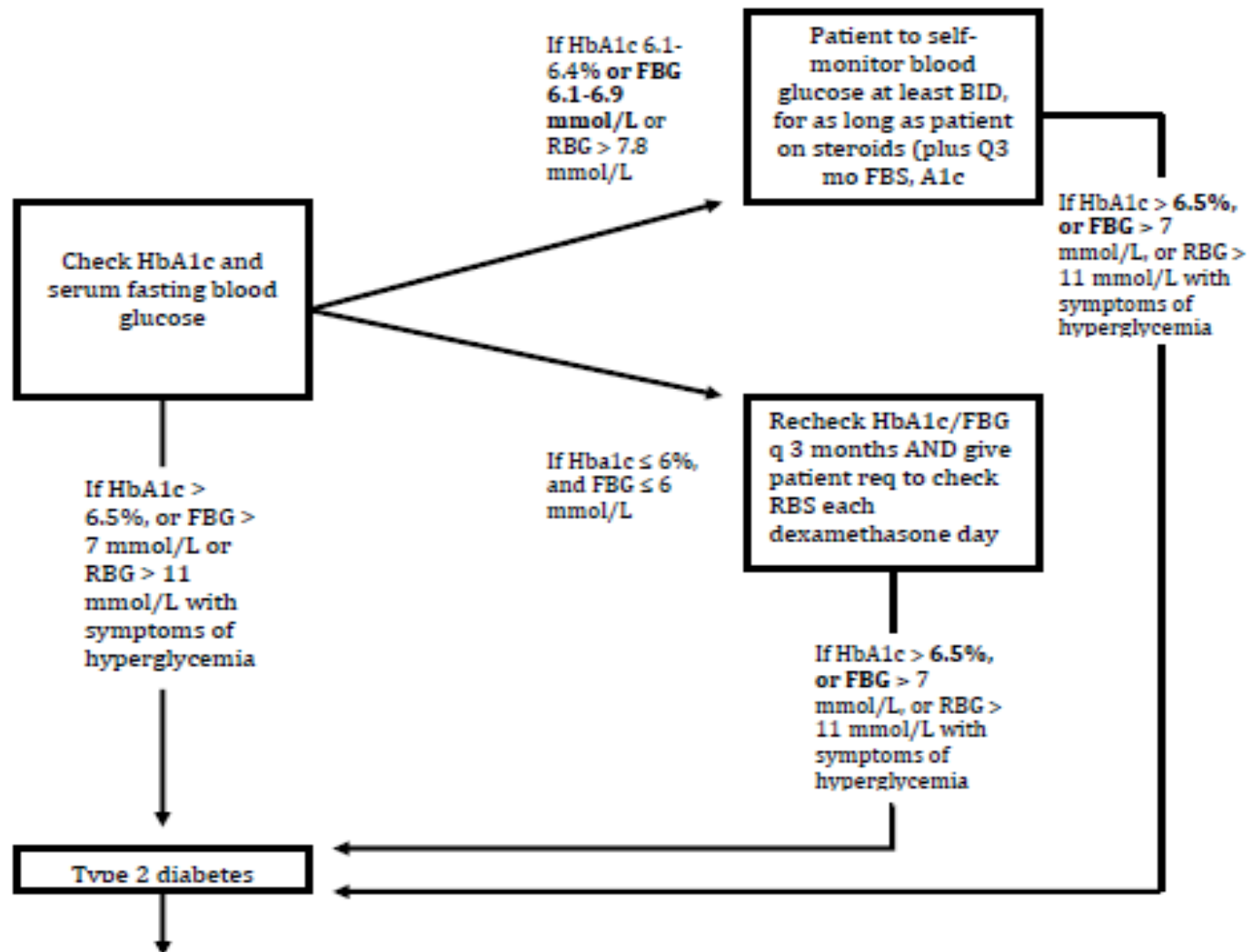
If blood glucose not optimized on maximal dose metformin alone (i.e. HbA1c > 6.5%, or SMBG not at target)

- Continue metformin and lifestyle changes
- Consider addition of second oral hyperglycemic agent (SGLT2 inhibitor, DPP4 inhibitor, sulfonylurea, etc.)
- May try for two weeks, if not improved to target...
- If HbA1c or BG not at target despite metformin +/- a second OHA, add insulin

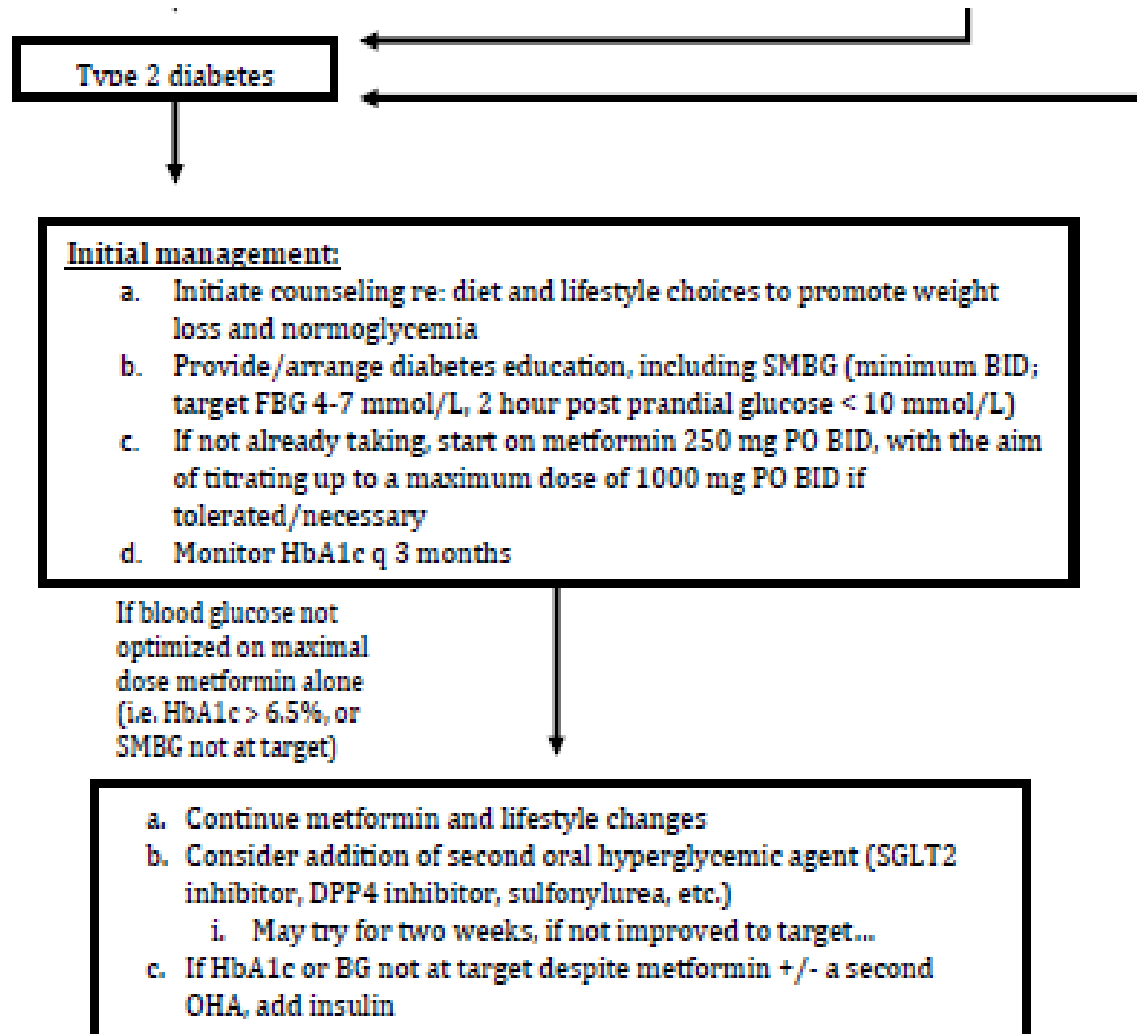
Blood glucose management algorithm

for

Lenalidomide/Dexamethasone regimens



Blood glucose management algorithm
for
Lenalidomide/Dexamethasone regimens



Insulin

Insulin Preparations

<u>Rapid-acting</u> Vial and cartridge	Aspart (NovoRapid®) Lispro (Humalog®/or/U200)	Start < 15 min. Peak 2hr
Short-acting (regular) Vial and cartridge	Novolin®ge Toronto Humulin® R	Start 30-60 min. Peak 4 hr
<u>Intermediate</u> Vial and cartridge	Novolin®ge NPH Humulin® N	Start 1.5 hrs Peak 7-8 hr
<u>Prolonged action</u>	Lantus (Glargine) Solostar/cartridge Toujeo (U300) Solostar only Levemir (Detemir) Quickpen/cartridge Basaglar (Glargine) Quickpen/cartridge	Start 3-4 hrs. Peakless

Insulin Initiation — Diabetes Canada Guideline Appendix

The screenshot shows a web browser window with the following details:

- Address bar: `guidelines.diabetes.ca/ciacpg_resources/appendices/Appendix_3.pdf`
- Page number: 1 of 2
- Page title: **Appendix 3**
Examples of Insulin Initiation and Titration Regimens in People with Type 2 Diabetes
- Text content:

All people starting insulin should be counseled about the recognition, prevention and treatment of hypoglycemia. Consider a change in type or timing of insulin administration if glycemic targets are not being reached.

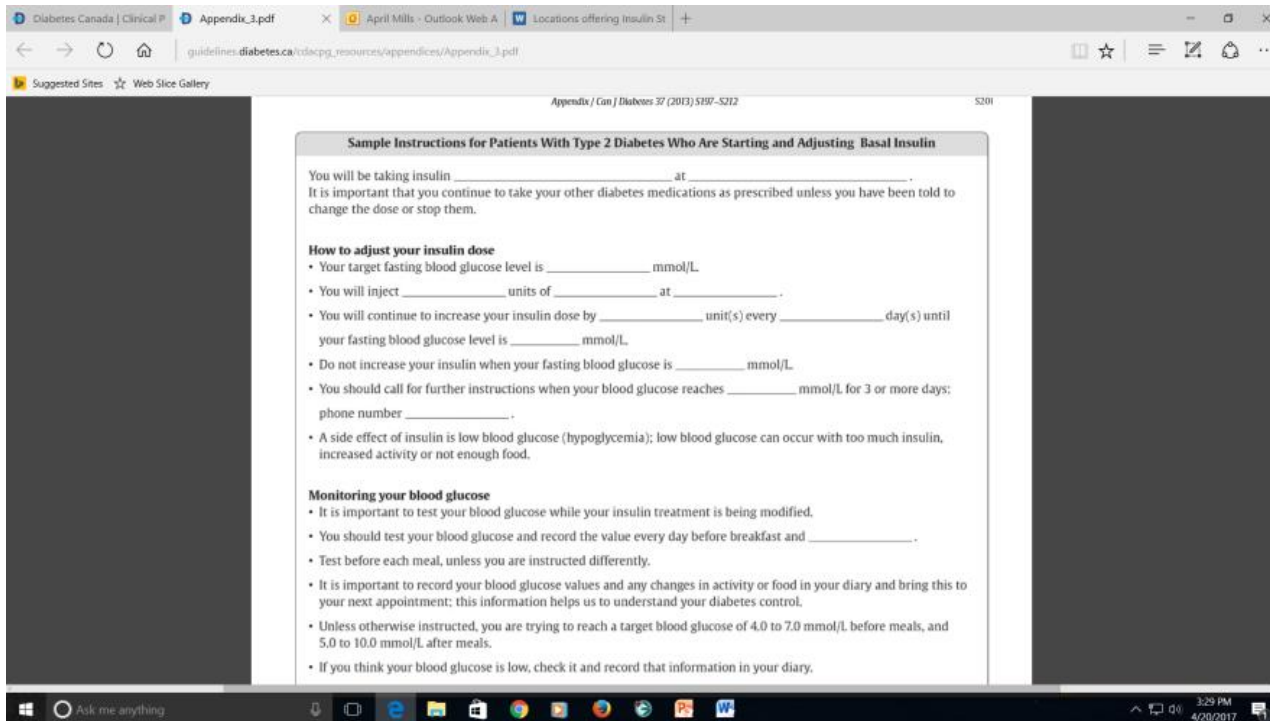
Example A: Basal insulin (Humulin®-N, Lantus®, Levemir®, Novolin®ge NPH) added to oral antihyperglycemic agents

 - Insulin should be titrated to achieve target fasting BG levels of 4.0 to 7.0 mmol/L.
 - Individuals can be taught self-titration, or titration may be done in conjunction with a healthcare provider.
 - Suggested starting dose is 10 units once daily at bedtime.
 - Suggested titration is 1 unit per day until target is reached.
 - A lower starting dose, slower titration and higher targets may be considered for elderly or normal weight subjects.
 - In order to safely titrate insulin, patients must perform SMBG at least once a day fasting.
 - Insulin dose should not be increased if the individual experiences 2 episodes of hypoglycemia (BG <4.0 mmol/L) in 1 week or any episode of nocturnal hypoglycemia.
 - For fasting BG levels consistently <5.5 mmol/L, a reduction of 1 to 2 units of insulin may be considered to avoid nocturnal hypoglycemia.
 - Oral antihyperglycemic agents (especially secretagogues) may need to be reduced if daytime hypoglycemia occurs.

Example B: Basal Plus Strategy - Adding bolus (prandial) insulin (Apidra®, Humalog®, NovoRapid®) once daily to optimized basal insulin therapy

 - When intensification of insulin therapy is necessary, start one injection of meal time insulin to either main meal or breakfast.
 - Starting dose is 2 to 4 units and patient can be taught self titration or dose increase can be done by HCP.

Instruction Sheet for Patients



The screenshot shows a web browser window with the following content:

- Address bar: guidelines.diabetes.ca/rdacpg_resources/appendices/Appendix_3.pdf
- Page Title: Appendix / Can J Diabetes 37 (2013) S197–S212
- Page Number: S201
- Section Header: **Sample Instructions for Patients With Type 2 Diabetes Who Are Starting and Adjusting Basal Insulin**
- Text: You will be taking insulin _____ at _____.
It is important that you continue to take your other diabetes medications as prescribed unless you have been told to change the dose or stop them.
- Section Header: **How to adjust your insulin dose**
- List-Group:
 - Your target fasting blood glucose level is _____ mmol/L.
 - You will inject _____ units of _____ at _____.
 - You will continue to increase your insulin dose by _____ unit(s) every _____ day(s) until your fasting blood glucose level is _____ mmol/L.
 - Do not increase your insulin when your fasting blood glucose is _____ mmol/L.
 - You should call for further instructions when your blood glucose reaches _____ mmol/L for 3 or more days; phone number _____.
 - A side effect of insulin is low blood glucose (hypoglycemia); low blood glucose can occur with too much insulin, increased activity or not enough food.
- Section Header: **Monitoring your blood glucose**
- List-Group:
 - It is important to test your blood glucose while your insulin treatment is being modified.
 - You should test your blood glucose and record the value every day before breakfast and _____.
 - Test before each meal, unless you are instructed differently.
 - It is important to record your blood glucose values and any changes in activity or food in your diary and bring this to your next appointment; this information helps us to understand your diabetes control.
 - Unless otherwise instructed, you are trying to reach a target blood glucose of 4.0 to 7.0 mmol/L before meals, and 5.0 to 10.0 mmol/L after meals.
 - If you think your blood glucose is low, check it and record that information in your diary.

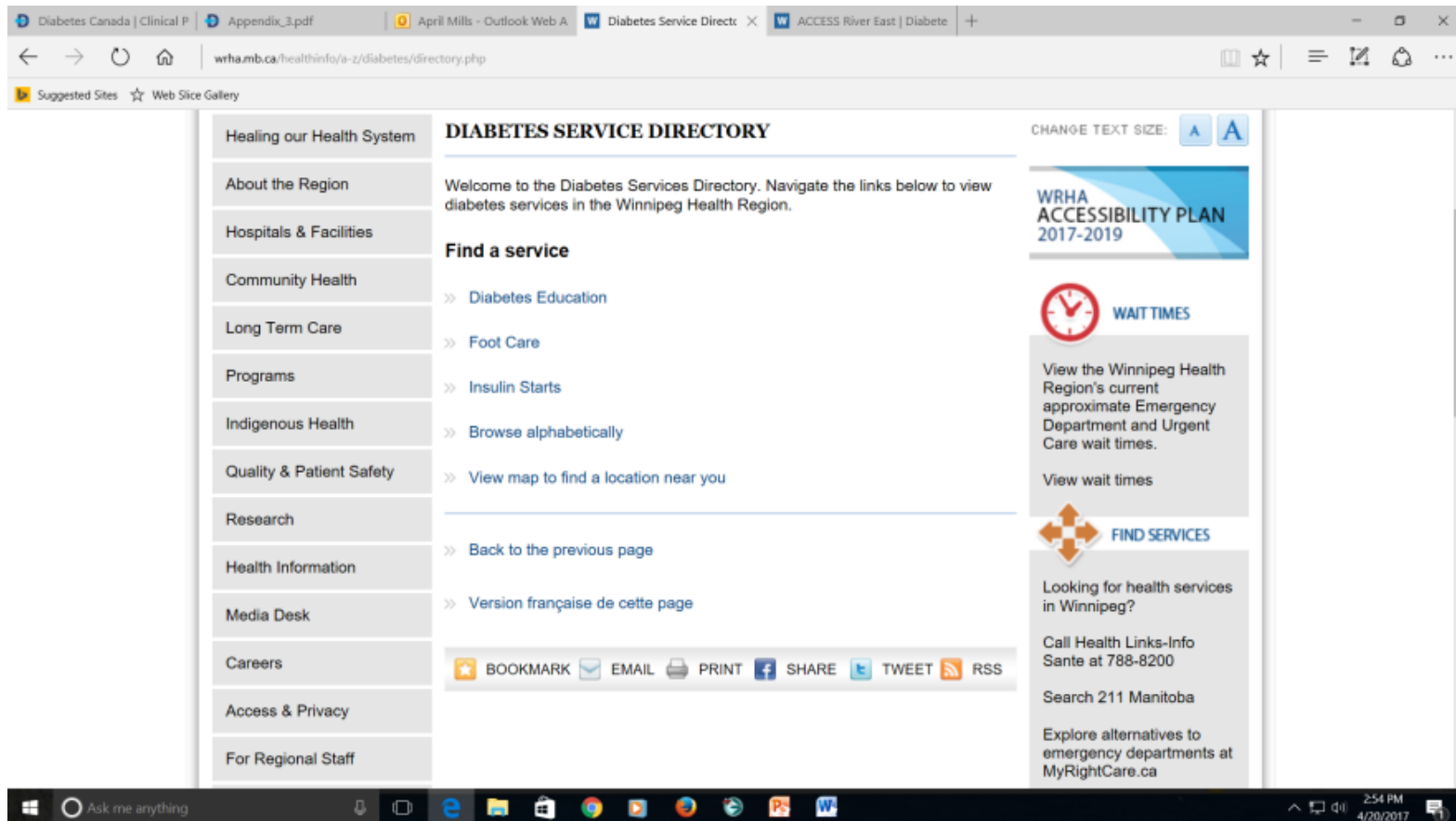
WRHA Primary Care Type 2 Diabetes Care Map

<http://www.wrha.mb.ca/healthinfo/a-z/diabetes/caremap.php>

The screenshot shows a web browser window displaying the WRHA Primary Care Type 2 Diabetes Care Map System. The page has a navigation menu on the left with categories like 'Healing our Health System', 'About the Region', 'Hospitals & Facilities', 'Community Health', 'Long Term Care', 'Programs', 'Indigenous Health', 'Quality & Patient Safety', 'Research', 'Health Information', 'Media Desk', 'Careers', 'Access & Privacy', 'For Regional Staff', 'For Health Professionals', 'Community Calendar', 'Contact Us', and 'Search this site'. The main content area is titled 'DIABETES' and 'WRHA Primary Care Type 2 Diabetes Care Map System'. It includes a description: 'The WRHA Primary Care Type 2 Diabetes Care Map System is available in PDF format and require Adobe Acrobat Reader to view.' Below this is a numbered list of 13 items: 1. Primary Care Type 2 Diabetes Utilization Guidelines; 2. Primary Care Type 2 Diabetes Assessment; 3. Diabetes Care Record; 4. Type 2 Diabetes Learning Package (Envelope) *; 5. What is Type 2 Diabetes? What Does it Mean to Me? *; 6. What Can I Do About Type 2 Diabetes? *; 7. How Do I Live with Type 2 Diabetes *; 8. What if I Don't Do Anything About Type 2 Diabetes? *; 9. Where Can I Go for Help with Type 2 Diabetes? *; 10. How to Treat Hypoglycemia (Low Blood Sugar) *; 11. Foot Care Guide for Diabetes *; 12. Just the Basics – Tips for Healthy Eating, Diabetes Management and Prevention *; 13. Diabetes Service Directory. On the right side, there are several utility boxes: 'CHANGE TEXT SIZE' with up/down arrows; 'WRHA ACCESSIBILITY PLAN 2017-2019'; 'WAIT TIMES' with a clock icon and a link to 'View the Winnipeg Health Region's current approximate Emergency Department and Urgent Care wait times'; 'FIND SERVICES' with a magnifying glass icon and a link to 'Looking for health services in Winnipeg?'; 'MOBILE APP' with a smartphone icon and a link to 'Use your phone to find information about wait times and health services in Winnipeg. Download the Connected Care mobile app for iPhone/Android.' The browser's address bar shows 'wrha.mb.ca/healthinfo/a-z/diabetes/caremap.php'. The Windows taskbar at the bottom shows the time as 2:53 PM on 4/26/2017.

Diabetes Service Directory

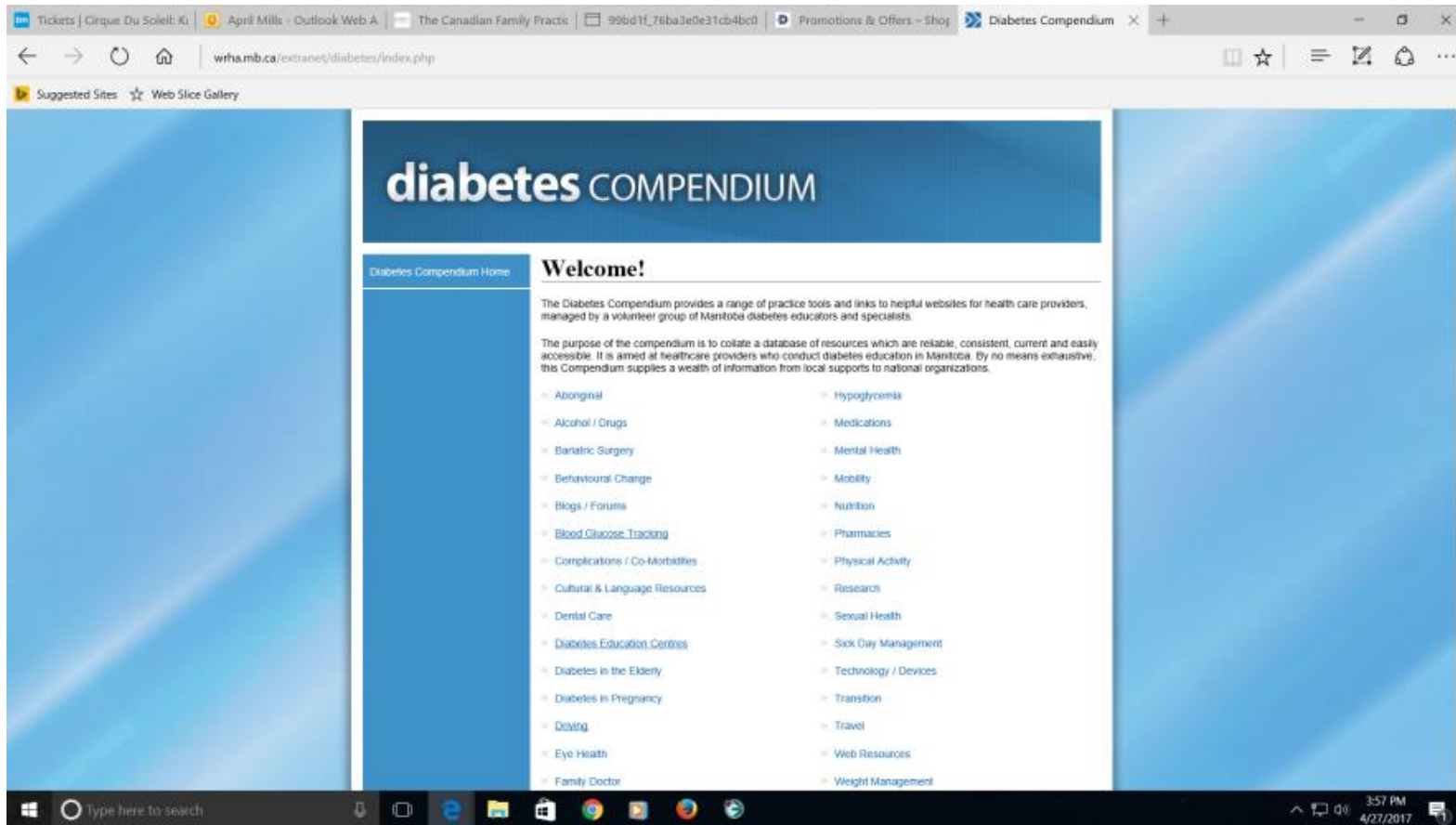
<http://www.wrha.mb.ca/healthinfo/a-z/diabetes/directory.php>



The screenshot shows a web browser window displaying the Diabetes Service Directory page. The browser's address bar shows the URL www.wrha.mb.ca/healthinfo/a-z/diabetes/directory.php. The page features a navigation menu on the left with categories such as "Healing our Health System", "About the Region", "Hospitals & Facilities", "Community Health", "Long Term Care", "Programs", "Indigenous Health", "Quality & Patient Safety", "Research", "Health Information", "Media Desk", "Careers", "Access & Privacy", and "For Regional Staff". The main content area is titled "DIABETES SERVICE DIRECTORY" and includes a welcome message, a "Find a service" section with links to "Diabetes Education", "Foot Care", "Insulin Starts", "Browse alphabetically", and "View map to find a location near you", and a "Back to the previous page" link. A "Version française de cette page" link is also present. At the bottom of the main content area, there are social media and utility icons for "BOOKMARK", "EMAIL", "PRINT", "SHARE", "TWEET", and "RSS". On the right side of the page, there is a "CHANGE TEXT SIZE" control, a "WRHA ACCESSIBILITY PLAN 2017-2019" banner, a "WAITTIMES" section with a clock icon and text about emergency department and urgent care wait times, and a "FIND SERVICES" section with a crosshair icon and text about health services in Winnipeg, including a phone number (788-8200) and a search function for 211 Manitoba. The Windows taskbar at the bottom shows the time as 2:54 PM on 4/20/2017.

Diabetes Compendium

<https://wrha.mb.ca/extranet/diabetes/index.php>



The screenshot shows a web browser window displaying the Diabetes Compendium website. The browser's address bar shows the URL wrha.mb.ca/extranet/diabetes/index.php. The website has a blue header with the text "diabetes COMPENDIUM". Below the header, there is a "Welcome!" section with a brief description of the compendium's purpose and a list of topics. The topics are organized into two columns:

- Aboriginal
- Alcohol / Drugs
- Bariatric Surgery
- Behavioural Change
- Blogs / Forums
- Blood Glucose Tracking
- Complications / Co-Morbidities
- Cultural & Language Resources
- Dental Care
- Diabetes Education Centres
- Diabetes in the Elderly
- Diabetes in Pregnancy
- Diving
- Eye Health
- Family Doctor
- Hypoglycemia
- Medications
- Mental Health
- Mobility
- Nutrition
- Pharmacies
- Physical Activity
- Research
- Sexual Health
- Sick Day Management
- Technology / Devices
- Transition
- Travel
- Web Resources
- Weight Management

The Windows taskbar at the bottom shows the time as 3:57 PM on 4/27/2017.

Diabetes Compendium

- Youville Diabetes Centre - 33 Marion Street
- Certified Diabetes Educators (nurses, pharmacists, dietitians)
- Community Pharmacies – will do insulin starts
- Home Care Nursing
- Access Centre's, Mount Carmel, Klinik, Teaching clinics
- “My Health Team”
- Healthy Aging Resource Team (HART)
Downtown/Point Douglas
- Endocrinologists

Endocrinology Consult Services

WRHA Endocrinology consult services are located at

- *HSC
- St. Boniface General Hospital
- Grace Hospital
- Victoria General Hospital

TAKE HOME

1. Patients with uncontrolled hyperglycemia during chemotherapy
 - have more side effects from chemo
 - Are less likely to be cured
2. You already treat diabetes & collaboration is your forte
3. Resources are available
 - <http://www.wrha.mb.ca/healthinfo/a-z/diabetes/directory.php>
 - Endocrinology
 - Algorithms coming to a theatre near you

References

- Brunello A, Kapoor R, Exterman M. Hyperglycemia during chemotherapy for hematologic and solid tumors is correlated with increased toxicity. *American Journal of Clinical Oncology*. 2011; 34, 292-296.
- Canadian Diabetes Association. *2015 Report on Diabetes: Driving Change*. Toronto, ON: CDA; 2015.
- Giovannucci E, Harlan DM, Archer MC et al. Diabetes and Cancer: A Consensus Report. *Ca Cancer J Clin*. 2010; 60: 207-221.
- Harris D, Barts A, Connors J, et al. Glucocorticosteroid-induced hyperglycemia is prevalent and unpredictable for patients undergoing cancer therapy: and observational cohort study. *Current Oncology*. 2013; 20(6):532-538.

References

- Meffrey A. Meyerhardt, Paul J. Catalano, Daniel G. Holler, Robert J. Mayer, John. S. Macdonald, Al B. Benson III, and Charles S. Fuchs
Journal of Clinical Oncology, Vol 21, No 3 (February 1), 2003:pp 433-440
- Sciacca L, Vigneri R, Tumminia A, et al. Clinical and molecular mechanisms favoring cancer initiation and progression in diabetic patients. *Nutrition, Metabolism & Cardiovascular Diseases*. 2013; 23; 808-815.
- Sonabend RY, McKay SV, Okcu MF, et al. Hyperglycemia during induction therapy is associated with poorer survival in children with acute lymphocytic leukemia. *The Journal of Pediatrics*. 2009; 155:73-78.
- Xu CX, Zhu, HH, Zhu YM. Diabetes and cancer: Associations, mechanisms, and implications for medical practice. *World Journal of Diabetes*. 2014; 5(3): 372-380.

- Ryu TY, Park J, Scherer PE. Hyperglycemia as a risk factor for cancer progression. *Diabetes & Metabolism Journal*. 2014;38: 330-336.
- Impact of Diabetes Mellitus on Outcomes in Patients With Colon Cancer
Meffrey A. Meyerhardt, Paul J. Catalano, Daniel G. Holler, Robert J. Mayer, John. S. Macdonald, Al B. Benson III, and Charles S. Fuchs
Journal of Clinical Oncology, Vol 21, No 3 (February 1), 2003:pp 433-440

Your Turn



QUESTIONS?

email@emailaddress.com

