Glycemic Challenges in Patients with Cancer and Diabetes
Denise Hershey PhD, FNP-BC
Sue Storey PhD, RN, AOCNS
Veronica Brady, PhD, BC-ADM, CDE
Jill Olausson PhD, RN, CDE

Overview
Sue Storey, PhD, RN, AOCNS
Indiana University, School of Nursing

Objective 1
• Overview of pathophysiologic processes shared between diabetes, malglycemia and cancer.
• Impact of chemotherapy on glycemic control in cancer patients
• Impact of glycemic control on outcomes in cancer patients.

Relationship Between Diabetes and Cancer
• Excess weight at younger ages had a strong association with increased risk of pancreatic cancer (Li, 2009)
• Overweight (BMI ≥ 25) and obesity (BMI ≥ 30) are risk factors for T2DM and is also a well established risk factor for colon/rectum, endometrial, breast, kidney, pancreas, gallbladder, liver and esophageal cancers (Giovannucci, et al, 2010)
• Diabetes is an independent risk factor for cancers of the liver, pancreas, colon, kidney and endometrial cancer (Habo, 2013)

• Gestational diabetes as a risk factor for pancreatic cancer (Perrin, et al, 2007)
• Prevalence of diabetes among newly diagnosed cancer patients is estimated to be 8-18% (Ko & Chaudry, 2002)
• Having diabetes when given a cancer diagnosis increases the risk of death by 40% (Brancati, 2008)

• Fasting serum glucose >125 mg/dL = increased risk of cancer (Jee, et al., 2005)
• Elevated insulin levels create a biochemical environment conducive to cancer growth (Flood, 2007)
• Both cancer and diabetes occur more frequently in males than females (Giovannucci, et al. 2010)
Overview of Physiologic Processes Associated with Malglycemia, Cancer and Outcomes

**Malglycemia**
- Insulin Resistance
- Hyperinsulinemia
- Glucose Metabolism
- Pro-inflammatory Cytokines

**Shared Pathologic Pathways of Malglycemia and Cancer**
- ↑ Oxidative Stress
- ↑ ROS
- ↑ Inflammation
- ↑ Pro-inflammatory Cytokines
- Compromised Immune System
- Altered Cell Signaling

Outcomes

**Impact of Glycemic Control on Outcomes of Patients with Cancer**
- Cellular changes resulting in progression/metastasis (Biernacka et al., 2013; Ryu et al., 2014)
- Impact imaging studies (Rabkin et al., 2010)
- Alter response to treatment (Duan et al., 2014)
- Prolong immune suppression (Butler et al., 2005)

**Pharmacologic Agents in Oncology that May Affect Blood Glucose**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Side Effect</th>
<th>Possible Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>Hypoglycemia</td>
<td>Increased hepatic glucose; decreased insulin effectiveness; decreased insulin secretion</td>
</tr>
<tr>
<td>Interferon -2</td>
<td>Hypoglycemia</td>
<td>Immune mediated</td>
</tr>
<tr>
<td>L-Asparaginase</td>
<td>Hypoglycemia</td>
<td>Inhibition of insulin or insulin receptor synthesis</td>
</tr>
<tr>
<td>Omacetaxine</td>
<td>Hypoglycemia</td>
<td>Inhibition of insulin secretion</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>Hypoglycemia</td>
<td>Inhibition of insulin secretion; antagonizes insulin resistance</td>
</tr>
</tbody>
</table>

**Impact of Glycemic Control on Outcomes of Patients with Cancer**
- Health outcomes:
  - Increased risk of venous thromboembolism (Mraovic, B., et al., 2010)
  - Increased utilization of blood products (Sheean et al., 2006)
  - Infection, toxicities, morbidity, mortality (Storey & Von Ah, 2012; Olausson et al., 2014, Storey & Von Ah, 2015)
Diabetes & Cancer: Challenges and Barriers to Glycemic Control

Denise Soltow Hershey PhD, FNP-BC
Michigan State University – College of Nursing

Objective 2

- Discuss the impact of cancer treatment on diabetes self-management
- Discuss predictors of poor diabetes self-management in patients with cancer
- Discuss identified challenges and barriers to managing diabetes from:
  - Patient perspective
  - Nursing Perspective
  - Oncology Provider Perspectives

Results from 2 Studies

- Older Adults with Diabetes and Cancer: Impact on Diabetes Self-Management
  - Funded by: Alpha Pi STT Chapter Research Award, and a Nurse Corp Initiative Scholarship, provided by the Michigan Department of Community Health and Michigan Department of Labor and Economic Growth.

- A multi-perspective view of care issues and challenges encountered by patients with diabetes and cancer
  - Funded by an MSU - College of Nursing Internal Grant Award

Changes in Diabetes Self-Management & Symptoms Overtime (Study1)

<table>
<thead>
<tr>
<th>Paired Variables</th>
<th>Paired differences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (sd)</td>
</tr>
<tr>
<td>DM Self-Management Baseline</td>
<td>30.64 (5.1)</td>
</tr>
<tr>
<td>DM Self-Management 4 weeks</td>
<td>35.46 (5.4)</td>
</tr>
<tr>
<td>Symptom Severity Baseline</td>
<td>35.43 (7.9)</td>
</tr>
<tr>
<td>Symptom Severity 8 weeks</td>
<td>52.56 (27)</td>
</tr>
</tbody>
</table>

Cancer Impact on Diabetes Self-Management

Impact on Specific Self-Management Activities
Impact on Specific Self-Management Activities

Impact on Performing Self-Management Activities

Factors Correlated with Diabetes Self-Management

- Significant correlations (p ≤.05) between diabetes self-management after a minimum of 8 weeks on Chemotherapy
  - Years with Diabetes: r = .52
  - Total number of medications: r = .38
  - Diabetes Self-Efficacy: r = .67
  - Diabetes Outcome Expectancies: r = .41
  - Baseline Diabetes Self-management: r = .75

Predictors of Diabetes Self-Management

Linear regression model indicating significant predictors for diabetes self-management at 8 weeks

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Beta</th>
<th>Standard Error</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-4.187</td>
<td>8.513</td>
<td>-.492</td>
<td>.627</td>
</tr>
<tr>
<td>Living Arrangements</td>
<td>-5.465</td>
<td>2.438</td>
<td>-.219</td>
<td>-2.241</td>
</tr>
<tr>
<td>Years with Diabetes</td>
<td>.689</td>
<td>.323</td>
<td>.240</td>
<td>2.133</td>
</tr>
<tr>
<td>Total Number of Medications</td>
<td>1.289</td>
<td>.401</td>
<td>.367</td>
<td>3.214</td>
</tr>
<tr>
<td>Baseline DM behaviors</td>
<td>.423</td>
<td>.138</td>
<td>.401</td>
<td>3.057</td>
</tr>
<tr>
<td>Diabetes Self-efficacy</td>
<td>.305</td>
<td>.132</td>
<td>.305</td>
<td>2.312</td>
</tr>
<tr>
<td>Baseline Symptom Severity</td>
<td>.286</td>
<td>.088</td>
<td>.452</td>
<td>3.242</td>
</tr>
<tr>
<td>8 week Symptom Severity</td>
<td>-2.22</td>
<td>.086</td>
<td>.402</td>
<td>-2.596</td>
</tr>
</tbody>
</table>

Identified Challenges and Barriers

Focus Group Results (Study 2)

- Three Over Arching Themes
  - Impact on Health/Self-management
  - Prioritization/Responsibility
  - Communication/Care-Management

Impact on Health/Self-Management

Symptoms are not exclusive to one disease and cause confusion to both patients and providers; and they also impact diabetes self-management.

Patient Quotes
- The chemo and the diabetes side-effects were the same.
- I would question everybody. Is this from the diabetes or the chemo? And they couldn’t answer.
- I don’t think you can exercise; you can’t do the stuff you did before.
- Foods don’t always taste good... finding foods that were acceptable that you wanted to eat were all the things that you’re not supposed to have with your diabetes

Nurse Quotes
- Well their symptoms. There was one patient who was having horrendous hot flashes and thought it was the blood sugar, but it was the hormones. So he’s popping sugar, and it ended up 400.
- Eating and exercise is a big thing for diabetics. And they often don’t feel like doing anything. We’re telling them to eat whatever and they’re on Decadron so their appetite is just ravensous.

Provider Quotes
- Any symptoms they get is due to their cancer treatment. Even if they are having sugar problems and they feel or pass out they think it is from the cancer treatment.
- One thing is their eating, especially if they are on chemo. They can’t eat or they are not eating because of their nausea and vomiting so maintaining their weight, their glucose levels, and their insulin can be a huge issue.
Impact on Health/Self-Management

Issues with overall health status, including glycemic control, were identified by both patients and providers.

<table>
<thead>
<tr>
<th>Patient Quotes</th>
<th>Nurse Quotes</th>
<th>Provider Quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The hardest part was trying to keep my sugar down</td>
<td>• You push the envelope, and we push the cancer line and everything, well if they're diabetic you just screwed them all up, but they go to eat</td>
<td>• It's very difficult that we make it go sky high</td>
</tr>
<tr>
<td>• My cancer would go up to 500 but it also dropped to 54</td>
<td>• They do worse, they feel worse, they don't recover as fast, they tend to have to be held more in the hospital. They don't get optimal treatment, which means their chances are really severely decreased.</td>
<td>• Once they get an infection, they get woefer infections they are less likely to show response to antibiotics so that is probably part of it too.</td>
</tr>
<tr>
<td>• I gained twenty pounds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• The pain was my neuropathy I didn't have that before. Until I started the chemo. and it didn't start until after the second treatment, then it really got bad.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prioritization/Responsibility

Cancer care is prioritized over diabetes management – by both patients and providers.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Nurse</th>
<th>Provider</th>
</tr>
</thead>
<tbody>
<tr>
<td>• I wasn't too, not concerned about the diabetes</td>
<td>• They can't multi focus they all at the same time. They focus on their cancer or they focus on their blood sugars, but they can't combine. It's too overwhelming.</td>
<td>• Well, I think one of the challenges is when they get the diagnosis, they are overwhelmed too, and they are kind of feeling overwhelmed too, and kind of pushing it away to the specialist</td>
</tr>
<tr>
<td>• Most chemo doctors I run into don't care about your sugar, the only thing they care about is the chemo</td>
<td>• Well, and then who's gonna manage it, I mean to always who should manage it</td>
<td>• I think this is somebody else's problem.</td>
</tr>
<tr>
<td>• My pain, the neuropathy I didn't have that before. Until I started the chemo</td>
<td>• It's a lot more and it's like pushing it away to the specialist</td>
<td>• The family doctor essentially to talk to your oncologist. I think this is somebody else's problem. Primary care physicians are kind of feeling overwhelmed too, and kind of pushing it away to the specialist.</td>
</tr>
</tbody>
</table>

Communication/Care Management

All identified a gray area regarding who was managing the diabetes.

<table>
<thead>
<tr>
<th>Patient Quotes</th>
<th>Nurse Quotes</th>
<th>Provider Quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• They don't get confused and they get mixed messages from their other care providers</td>
<td>• They get confused and they get mixed messages from their other care providers</td>
<td>• They do worse, they feel worse, they don't recover as fast, they tend to have to be held more in the hospital. They don't get optimal treatment, which means their chances are really severely decreased.</td>
</tr>
<tr>
<td>• My subjective being relin or doing a favor will write for one of the patients other meds, like cardiac meds because they didn't have a refill... they tend to not go to their primary care</td>
<td></td>
<td>• Once they get an infection, they get woefer infections they are less likely to show response to antibiotics so that is probably part of it too.</td>
</tr>
<tr>
<td>• They can't multi focus, they all at the same time. They focus on their cancer or they focus on their blood sugars, but they can't combine. It's too overwhelming.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• They do worse, they feel worse, they don't recover as fast, they tend to have to be held more in the hospital. They don't get optimal treatment, which means their chances are really severely decreased.</td>
<td></td>
</tr>
</tbody>
</table>

Summary/Implications

- **Research**
  - Interventions need to be developed and tested based on suggested interventions/solutions
  - Targeted Diabetes Education Program
  - Informational brochures re. managing and differentiating between symptoms associated with your diabetes and cancer
  - Provider targeted interventions
- **Practice**
  - Identify and implement strategies to improve communication
  - Provider - Provider
  - Provider - Patient
  - Identify ways to use current resources more effectively
  - Diabetes Educators
  - Clinicians

Glycemic Challenges in Patients with Cancer and Diabetes

Veronica Brady, PhD, BC-ADM, CDE
University of Nevada-Reno
Objective 3

- Discuss the prevalence of hyperglycemia among patients with cancer
- Discuss the impact of hyperglycemia on clinical outcomes –
  - Infection
  - Relapse
  - Progression free & overall survival

Prevalence of Hyperglycemia

- Hyperglycemia occurs in 32-60% of cancer patients with and without previous history of diabetes (Harris et al., 2013; Lee et al., 2014; Weiser et al., 2004; Wu et al., 2014).
- Steroid induced hyperglycemia can often go undetected (Baldwin & Apel, 2013).

Impact of Hyperglycemia on Clinical Outcomes

- Patients with ALL: Age >60 with serum glucose > 180mg/dL had poorer overall survival and were more likely to develop complicated infections (Weiser et al., 2004)

Length of stay for colorectal cancer surgery patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DM N=72</th>
<th>No DM N=447</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long LOS:</td>
<td>31(43%)</td>
<td>121(27%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Complications:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>11(15.2)</td>
<td>47(10.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac</td>
<td>2(2.8)</td>
<td>2(1.6)</td>
<td>NS</td>
</tr>
<tr>
<td>GI</td>
<td>4(5.6)</td>
<td>24(5.4)</td>
<td>NS</td>
</tr>
<tr>
<td>GU</td>
<td>1(1.4)</td>
<td>0(0.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Infections</td>
<td>5(6.9)</td>
<td>12(2.7)</td>
<td>0.07</td>
</tr>
<tr>
<td>Respiratory</td>
<td>1(1.4)</td>
<td>3(0.7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Diabetes was an independent risk factor for longer length of stay

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-op complication</td>
<td>3.9</td>
<td>2.1, 7.0</td>
</tr>
<tr>
<td>Electrolyte disorder</td>
<td>2.6</td>
<td>1.3, 5.3</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.1</td>
<td>1.1, 4.0</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1.9</td>
<td>1.1, 3.3</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>1.8</td>
<td>1.2, 2.8</td>
</tr>
<tr>
<td>Metastases</td>
<td>1.5</td>
<td>1.0, 2.3</td>
</tr>
</tbody>
</table>

*LOS=length of stay, OR=Odds ratio, CI=confidence interval

C-statistic=0.69

Geraci, Busaidy et al. MDACC unpublished
Hyperglycemia associated with shorter survival in patients with ALL receiving hyper-CVAD

Survival and glucose levels

Hyperglycemia Median Survival (mo)
Yes 29
No 88
P < 0.001

Hypercglycemia associated with shorter survival in patients with ALL receiving hyper-CVAD

Weiser MA et al. Cancer 2004

Patients with diabetes and colon cancer have poorer overall survival

Definitions

Euglycemia
-glucose 00:00 to 06:00: <126 mg/dL, and glucose any other time: <200 mg/dL.

Intermediate glycemia
-Between the two criteria.

Sustained significant hyperglycemia
-glucose >200 mg/dL on at least two different days.

Diabetes is associated with shorter overall survival in patients with pancreatic cancer

Diabetic 19.5 mos
NonDM 29.4 mos
p=0.001 N=298

Summary

• At least one out of 3 to 4 admissions have diabetes mellitus/ hyperglycemia

• Hyperglycemia is associated with
  - ~1.5-3 x hospital stay
  - ~2-3.5 x transfer to ICU
  - ~1.5-2 x bacterial fungal infection & iv antibiotic use
  - ~3-5 x hospital mortality
  - ~50% higher overall mortality

• This was true for all cancer stages, all ages, “steroid induced diabetes”, & other confounders including possible anticipated death.
Roles for Diabetes Educators

- Identification of patients at risk for hyperglycemia
- Participation in discharge planning
- Teaching survival skills

Objectives

- Describe the importance of controlling hyperglycemia before, during, and after cancer therapies
- Identify special circumstances that occur with diabetes and cancer
- Describe diabetes treatment of special circumstance

Importance of Appropriate Management of Hyperglycemia in the Oncology Setting

- Prevent infection
- Maximize effectiveness of cancer treatments
- Decrease symptoms
- Improve quality of life

Nutrition

- Malnutrition and Cancer Cachexia
  - Improving nutrition allows for
    - better metabolic control
    - Improved treatment outcomes
    - Reduction in inflammation
    - Improvement in immune response to cancer (August & Huhmann, 2009).
  - Malnutrition and weight loss can limit dosing of cancer therapies

Managing Diabetes and Cancer

Jill Olausson PhD, RN, CDE
**Nutritional Support**

- High glycemic load often causes hyperglycemia
  - Oral supplements
  - Parenteral feedings to avoid weight loss frequently cause hyperglycemia
- Insulin to match feeding patterns
  - Check BGs q 4-6 if delivered over 24 hours (not ac)
  - 24 hour support needs 24 hour insulin coverage (i.e. insulin in TPN)
  - Nocturnal feedings only need long-acting basal insulin (consider NPH)
  - Bolus feedings need bolus insulin

**End of Life Management**

- Both hyperglycemia and hypoglycemia can decrease quality of end of life
- Goal of diabetic therapy is to maintain patient comfort and quality of life

**Nausea and Vomiting**

- Similar to sick day rules
- Prophylactic treatments before meals
- Small frequent meals
- For post prandial control, avoid medications that are long acting (Psarakis, 2006)
  - Consider shorter acting secretagogue over sulfonylurea
  - Use rapid acting insulin
  - Dose after meals, when PWD feels they will be able to tolerate food
- Remember PWD with type 1 diabetes will always need some basal insulin to prevent ketosis

**Setting Glycemic Targets**

**Special Considerations**

- Impaired cognition
  - Provide written material
  - Include caregiver/partner in education
- Glucocorticoids
  - Provide medication information
  - Instructions that as GCs are tapered, antidiabetic agents must also be titrated

**Prevention of Symptoms of Hyperglycemia**

- Goal-prevent symptoms of frequent urination, dehydration, unintentional weight loss, and infection
- Maximize comfort
- Presentation of symptoms when BGs > 200 mg/dL
- Acidosis can occur when BGs > 300 mg/dL
Suggested glycemic targets and actions according to life expectancy

<table>
<thead>
<tr>
<th>Life expectancy</th>
<th>Glycemic target (mg/dL)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>120–270</td>
<td>Reduce blood sampling and avoid hypoglycemia</td>
</tr>
<tr>
<td>Weeks</td>
<td>180–360 (reduce blood sampling and avoid hypoglycemia)</td>
<td>Stop glucose monitoring and consider to stop antidiabetic therapy</td>
</tr>
<tr>
<td>Days or hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

McCoubrie, Jeffrey, Paton, & Dawes (2005)

Table 1. Suggested Management of Diabetes at End of Life

<table>
<thead>
<tr>
<th>Life expectancy</th>
<th>Type 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable nutritional status</td>
<td>Monitor current therapy.</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Reduce current dose if not on diet. Consider other therapies. Monitor for hypoglycemia.</td>
</tr>
<tr>
<td>Severe nausea and vomiting</td>
<td>Change to parenteral route. Onset of symptoms, reduce insulin dose.</td>
</tr>
<tr>
<td>Bowel obstruction</td>
<td>Add nasogastric feeding. Monitor for hyperglycemia.</td>
</tr>
<tr>
<td>Anxiety and delirium</td>
<td>Consider reduction. Monitor if incontinence.</td>
</tr>
</tbody>
</table>

Tice, 2006

Case Study

The case of D.M.

- 38 yo Hispanic male with 5 year history of type 2 diabetes now with newly diagnosed leukemia. Admitted for EPOCH chemotherapy which contains prednisone 140mg x 5 days. Note: blood glucose prior to admission 75mg/dL
- PMH: T2DM, HTN, Obesity
- Home medications: Glimepiride 4mg qam, Metformin 1 gm bid
- Labs: 8/12: BUN 11, Cr 0.75, glucose 96, A1c 7.2 %
- 8/20: BUN 29, Cr 2.19, glucose 39, LDH 18662, alk phos 376, phos 5.3, Calcium 10.7, uric acid 14.3
- 8/21: BUN 33, Cr 1.98, glucose <30mg/dL

Recommendations for End-of-Life Diabetes Care

- Taper medications in response to:
  - Nausea and vomiting
  - Decreased oral intake
  - Decreased exercise
  - Weight loss
- Reduce SMBG

ADA, 2016
Sulfonylurea induced hypoglycemia

The case of D.M (cont)

- At the time of discharge blood glucose ranging 100-180mg/dL, cr-1.7, & GFR-60
- Dietary intake is good.
- He is planned for his next cycle of chemo in 10 days.
  - What medications would you consider discharging the patient on?
  - When would you see him in clinic?
  - What antidiabetic medications would you consider using with his next chemotherapy containing steroids?

The Case of D.M.

- D.M. has completed 6 cycles of chemotherapy. Since the last treatment he has been on MDI therapy at 0.6 units/kg/day (basal/bolus). His blood glucose levels have ranged 140-200mg/dL. Due to the recent need for RBC transfusions he has not had an A1c.
  - Thoughts?

Recommendations for Home Blood Glucose Management

Check blood sugar before meals and at bedtime and record. Bring record to all appointments.

Inject Detemir/Glargine/Degludec units at bedtime
Inject Novolog/Humalog/Apidra units prior to meal or 15 minutes after meals as follows:

<table>
<thead>
<tr>
<th>Blood sugar</th>
<th>Units of insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 80mg/dL</td>
<td>units</td>
</tr>
<tr>
<td>80-100mg/dL</td>
<td>units</td>
</tr>
<tr>
<td>101-150mg/dL</td>
<td>units</td>
</tr>
<tr>
<td>151-200mg/dL</td>
<td>units</td>
</tr>
<tr>
<td>201/250mg/dL</td>
<td>units</td>
</tr>
</tbody>
</table>

Do not inject unless you are eating a meal. Do not inject at bedtime. Please notify your diabetes team if steroid dose is changed or if blood sugar persistently less than 70 or greater than 300mg/dL.

Return to clinic in weeks/months.

PANEL DISCUSSION