HMCL223
Clinical Diagnostic Techniques

Session 3: *Glucose* / *Insulin Regulation*
Session Objectives

Glucose / Insulin Regulation

- HbA1c
- Serum Glucose
- Glucose/Insulin Tolerance Test (GITT)
- Glucose/Insulin Tolerance Test + Cortisol (GITT + Cortisol)
- Glucagon
- HOMA-IR
Glucose / Insulin Regulation
Clinical Presentation

- A client may present with the following likely presenting complaints:
  - Weight gain/loss
  - Fatigue
  - General concerns for health
  - Sores that don’t heal
  - Difficulty sleeping
  - Irregular menstrual cycles, anovulation Polycystic Ovarian Disorder (PCOS)
  - Eye disease, heart disease, kidney disease, nerve damage, past history of stroke
Glucose/Insulin Regulation

- Diabetes is a disease caused by glucose/insulin regulation. It is a chronic, potentially life threatening disease, changing the lives of patients and challenging our health system.

- According to the World Health Organisation, 1 in 25 Australians has diabetes. Many of these cases are type 2 diabetes, linked to obesity and diet.

- Australia also has one of the highest rates of type 1 diabetes in the world, which has doubled in the past 20 years and is still rising.

  (Australian Institute of Health & Welfare, 2015)
Glucose/Insulin Regulation

Without treatment, high sugar levels in the blood are associated with:

- heart disease
- kidney failure
- eye damage
- infertility
- inflammatory disorders

Finding a way to cure or prevent diabetes from developing would have an enormous impact on global health. Holistic approaches provide valuable preventative support.
Glucose/Insulin Regulation

Recapping on what diabetes is:

Sugar (glucose) is an essential energy source for our body. The hormone insulin is required for cells to absorb glucose and convert it into energy.

- Diabetes develops when the body can’t produce or use insulin effectively, leading to damaging high glucose levels in the bloodstream and depriving the body of its key energy source.

Pagana & Pagana, 2014
Glucose/Insulin Regulation

- Type 1 diabetes is an autoimmune disease in which the immune system attacks and kills insulin-producing cells in the pancreas. It requires daily, lifelong injections of insulin.

- In type 2 diabetes, insulin production decreases and the body’s cells become resistant to insulin.

- There is currently no cure for type 1 or type 2 diabetes, and no allopathic means to prevent type 1 diabetes developing.

(Pagana & Pagana, 2014)
Glucose/Insulin Regulation

- Type 2 diabetes is not caused by an immune attack on insulin-producing cells, however the immune system still plays a significant role.

- Obesity puts the body under stress, increasing base levels of inflammation.

- The body internally signals inflammation by building a structure called the inflammasome, which activates other inflammatory signalling molecules.
Glucose/Insulin Regulation

- One of these signalling molecules, IL1-beta, can be toxic to insulin-producing cells in the pancreas.

- This doesn’t affect insulin production in the short term, but over time inflammation associated with obesity can destroy these cells and contribute to type 2 diabetes.
Glucose/Insulin Regulation

- Researchers are investigating whether blocking IL-1 beta production could prevent type 2 diabetes.

- Widely recognised that the best prevention was a healthy lifestyle.

- Exercise and eating healthy foods are the best weapons we have to combat type 2 diabetes.

- Herbal and nutritional therapeutics provide important...
Glucose/Insulin Regulation

New research suggests the immune system could aid in regulating insulin in type 2 diabetes.

Acute metabolic stress triggers chronic systemic inflammation which triggers the development of type 2 diabetes.

The immune system has components that have the potential to provide a protective or beneficial role to patients with the disease.

Research identifies the complex interactions between endocrine cells and immune cells.

Immune cells are clearly significant for the maintenance of insulin release.

(Dalmas, 2017)
Glucose/Insulin Regulation

Several factors contribute to diabetes that are not commonly understood connections due to their influence on metabolic stress and Reactive Oxidation Species (ROS):

- inflammation
- toxic accumulation
- stress
- infection
- microbiome dysregulation
- sleep deprivation

Incorporating a holistic treatment strategy relies on clinical diagnostic techniques to isolate the underlying drivers.

(Dalmas, 2017, Halmos, 2016, Newsholme, 2016)
Discussion

Building on knowledge from lectures 1 & 2, what tests may you already find useful in identifying the underlying cause of Type 2 diabetes in a clinical situation?

How would you utilise these test results in a holistic patient management setting? What time frame would you suggest testing? Would retesting be necessary?
Glucose Regulation - Insulin

Let’s take a look at the key driver insulin. Insulin is a hormone that is produced and stored in the beta cells of the pancreas and can be tested by a blood sample.

- Insulin helps transport glucose from the blood to within cells
- It helps to regulate blood glucose levels
- It has a role in lipid metabolism

(Pagana, 2015)
Glucose/Insulin Resistance (IR)

Expanding on this, let’s now explore Insulin Resistance (IR). IR is the body's inability to respond to and use the insulin it produces.

- Insulin resistance may be linked to obesity, hypertension, and high levels of fat in the blood.

- In insulin resistance, muscle, fat, and liver cells do not respond properly to insulin and easily absorb glucose from the bloodstream.

As a result, the body needs higher levels of insulin to help glucose enter cells.

(Pagana, 2015)
Glucose/Insulin Resistance (IR)

This means, it is involved in key biomarkers involved with major body organs and endocrine glands such as the:

- Liver
- Pancreas
- Cardiovascular system
- Kidneys

Reviewing key biomarkers for disease states in other body systems is fundamental to the clinical diagnosis and effective holistic management of IR

(Pagana, 2015)
Glucose/Insulin Resistance (IR)

Left unmanaged a condition such as IR, perpetuates over time into hyperglycemia. This means the beta pancreatic beta cells try to keep up with this demand for insulin by producing more.

If the beta cells can produce enough insulin to overcome the insulin resistance, blood glucose levels stay in the healthy range.

Over time, without enough insulin, excess glucose can lead to type 2 diabetes and prediabetes as the beta cells fail to keep up with the body's increased need for insulin.

(Pagana, 2015)
Type II Diabetes

What’s important to remember is many different paths, driven by various genetic and environmental factors, result in the progressive loss of β-cell mass and/or function that manifests clinically as hyperglycaemia.

Naturopathic model of wellness supports a patient centred approach to diabetes management through holistic and vitalistic diagnosis and there may be a combination of different paths within the one clinical case.

- Diabetes is a chronic complex illness that requires continuing clinical care and intensive self care.

(Pagana, 2015)
Hyperglycaemia Measurement

- The measurement of prediabetes conditions such as hyperglycaemia can be performed in a clinical situation as part of a holistic health care setting by reviewing ketones.

- In simple words, when our body doesn’t have enough glucose, the liver breaks down fatty acid to produce ketones. There are ways of measuring and determining what level ketones are in our body and one of this is the ketone test strip.

(Pagana, 2015)
Hypoglycaemia Management

- Mistakes are often made between checking for ketones if you have diabetes and wanting to be on ketosis.

- It is important to know that they are completely different. When the cells in your body don’t have enough carbohydrates from food to burn energy, it burns fat instead; in the process of burning fat, it produces ketones.

(Pagana, 2015)
Hypoglycaemia Management

- A diabetic patient checks for ketones to know how much ketones he/she has in his/her urine or blood.

- Unlike checking for ketones, being in ketosis is a metabolic state whereby the body produces ketones, some organs make use of these ketones as fuel so that glycogen is only used by organs that depend on it.

- For people with diabetes, having high levels of ketones is considered to be dangerous, which is why it is important that they test for them to avoid and prevent getting into diabetic ketoacidosis (Pagana, 2015)
Gestational Diabetes

A type of diabetes that develops only during pregnancy and usually disappears upon delivery, but increases the mother's risk of developing diabetes later in life.

GDM is managed with meal planning, physical activity, and, in some cases, medication.

Consider different diagnostic testing you would utilize in a clinical situation to manage GDM in a naturopathic clinical setting?

(Pagana, 2015)
Glucose / Insulin Regulation

Clinical indications requiring further investigations or repeat investigations include:

- Impaired glucose tolerance: pre-diabetic levels need to be regularly monitored to track glucose tolerance

Routine examination for high risk individuals:

- Family history of Diabetes
- Overweight
- 45 years old+

Gestational diabetes screenings in pregnancy (24th-28th week), symptoms prior to pregnancy or previous gestational diabetes

(Pagana, 2015)
Glucose / Insulin Regulation

Differential diagnosis between Diabetes & Hyperglycaemia

Diabetes symptoms:
- Increased thirst, increased urination, tiredness, blurred vision, slow wound healing

Hypoglycaemia symptoms:
- Sweating, hunger, trembling, anxiety, confusion, blurred vision

Measuring Blood Glucose

The measurement of blood glucose can be performed by a number of different methods including the following:

1. Use of a glucose meter
2. HbA$_1$c blood cell measurement
3. Serum Glucose
4. Glucose Tolerance test
Discussion

Consider how you may interpret these results and how may these influence your management of:

- age related degenerative disease
- metabolic disorders
- reproductive disorders
- other?

What would be the possible differential diagnostic factors related to a 60yr old post menopausal female with fatigue?

What other clinical presentations would you look for in a patient to determine further investigative testing?
1. Use of a glucose meter
Measuring Blood Glucose

1. Use of Glucose meter
Glucose can be measured using a glucose meter and lance as follows:

- After washing your hands, insert a test strip into your meter.
- Use your lancing device on the side of your fingertip to get a drop of blood.
- Touch and hold the edge of the test strip to the drop of blood, and wait for the result.
- Your blood glucose level will appear on the meter's display.

(Pagana & Pagana, 2014)
2. HbA$_1$c blood cell measurement
HbA1c Measurement

2. Use of HbA₁c blood cell measurement.

HbA1c is a measurement of glucose & haemoglobin binding in the blood (HbA₁c).

During glycosylation, HbA₁c combines strongly with glucose. Higher serum glucose levels stimulates higher levels of HbA₁c.

As red blood cells have a 120 day life cycle, this measurement is indicative of serum glucose controls over the previous 3-4 months.

(Pagana & Pagana, 2014)
HBA\textsubscript{1C} FORMATION

Haemoglobin in the blood (red, rectangle) combines with glucose in the blood (green, circle) to form glycosylated haemoglobin. This reaction occurs over a 10 week period.

Controlled diabetes, not much glucose, not much glycosylated haemoglobin
Uncontrolled diabetes, more glucose, much more glycosylated haemoglobin

Source: www.medlineplus.com
HbA1c

A graph of glucose changes over 9 weeks. The glucose (green line) changes between 7-10. This results in an HbA1c level of 10% at the end of the 9 weeks (red line). Poorly controlled.

Here the glucose changes between 5-9. This results in an HbA1c level of 7% at the end of the 9 weeks. Well controlled.
## HbA1c

**Glycosylated Haemoglobin (HbA$_1$C)**

<table>
<thead>
<tr>
<th>Serum</th>
<th>HbA1c is a measurement glucose &amp; haemoglobin binding in the blood (HbA$_1$C). As red blood cells have a 120 day life cycle, this measurement is indicative of serum glucose controls over the previous 3-4 months.</th>
</tr>
</thead>
</table>
| **Reference Ranges (Adult)** | **Non-diabetic:** 4-5.9%  
**Good Diabetic Control:** <7%  
**Fair Diabetic control:** 8-9%  
**Poor diabetic control:** >9% |
| **Indicator** | Ordered for diagnosed diabetics (indicator of 3-4 month history of glucose control) & is tested every 3-6 months. Newly screened pre-diabetic clients. |

*(Pagana & Pagana, 2014, p. 266; Labtestsonline, 2015)*
# HbA1c: Interpreting the Results

<table>
<thead>
<tr>
<th>HIGH</th>
<th>LOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed DM</td>
<td>Haemolytic anaemia</td>
</tr>
<tr>
<td>Poorly controlled DM</td>
<td>Chronic blood loss</td>
</tr>
<tr>
<td>Non-diabetic hyperglycaemia</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Post-splenectomy</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
</tr>
</tbody>
</table>

The higher HbA$_1$C, the higher the risk of developing:
- Eye disease
- Heart disease
- Kidney disease
- Nerve damage
- Stroke

*(Pagana & Pagana, 2014, p. 268)*
HbA$_{1c}$

By a relatively simple calculation, GHb can be correlated accurately with the daily mean plasma glucose (MPG) level, the average glucose level throughout the day.

<table>
<thead>
<tr>
<th>A$_{1c}$ (%)</th>
<th>Approximate Mean Plasma Glucose (mg/dL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>65</td>
<td>Nondiabetic range</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>Nondiabetic range</td>
</tr>
<tr>
<td>6</td>
<td>135</td>
<td>Nondiabetic range</td>
</tr>
<tr>
<td>7</td>
<td>170</td>
<td>ADA target</td>
</tr>
<tr>
<td>8</td>
<td>205</td>
<td>Action suggested</td>
</tr>
</tbody>
</table>

(Pagana & Pagana, 2014, p. 267)
HbA1c

• Hemoglobinopathies can affect results, because the quantity of haemoglobin A (and, as a result, HbA₁) varies considerably in these diseases
• Falsely elevated values occur when the RBC lifespan is lengthened because the HbA₁ has a longer period available for glycosylation (e.g. post splenectomy)
• Ascorbic acid may cause falsely low levels of glycated fructosamine
• Gestational diabetes in pregnancy will cause persistent elevated blood glucose = elevated HbA1C. Usually resolves within 3 months post-partum.

(Pagana & Pagana, 2014, p. 268)
Discussion

Consider how you may interpret these results and how may these influence your management of:

- age related degenerative disease
- metabolic disorders
- reproductive disorders
- other?

What would be the possible differential diagnostic factors related to a 60yr old post menopausal female with fatigue?

What other clinical presentations would you look for in a patient to determine further investigative testing?
3. Serum Glucose
## Serum Glucose

<table>
<thead>
<tr>
<th>Serum Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum</strong></td>
</tr>
<tr>
<td>Serum Glucose is a direct measurement of the level of glucose in the blood.</td>
</tr>
<tr>
<td>Commonly performed in the assessment of diabetic patients.</td>
</tr>
<tr>
<td>Venous sample collected or a capillary sample collected by finger prick and</td>
</tr>
<tr>
<td>analyzed in a glucometer.</td>
</tr>
</tbody>
</table>

| Reference Ranges (Adult) | Fasting (3.6 - 6.1 mmol/L) | Normal Glucose Tolerance (6.0 – 6.9 mmol/L) | Impaired Glucose Tolerance (7.0 mmol/L +) | Probable Diabetes (7.0 mmol/L +) | Critical values (<3 or >25 mmol/L) |

| Indications               | Serum glucose (venous sample) measured after 8-10 hour fast is used to screen and diagnose diabetes. |

(Labtestsonline, 2015)
Serum Glucose

- Blood glucose levels may need to be measured several times a day, to determine how far above or below normal their glucose is and to determine what oral medications or insulin injections they may need.

- A drop of blood from a finger prick onto a plastic indicator strip and then inserting the strip into a glucose meter, will give an indication.

(www.medlineplus.gov, viewed 2/01/2010)
# Serum Glucose: Interpreting the Results

<table>
<thead>
<tr>
<th><strong>HIGH</strong></th>
<th><strong>LOW</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>Insulinoma</td>
</tr>
<tr>
<td>Acute stress response</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Cushings syndrome</td>
<td>Hypopituitarism</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Addisons disease</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>Chronic liver disease</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Insulin overdose</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>starvation</td>
</tr>
<tr>
<td>Diuretic therapy</td>
<td></td>
</tr>
<tr>
<td>Corticosteroid therapy</td>
<td></td>
</tr>
<tr>
<td>Acromegaly</td>
<td></td>
</tr>
</tbody>
</table>

(Pagana & Pagana, 2014, p. 265)
Glucose Tolerance Test (GTT)
Glucose Tolerance Test (GTT)

- Oral Glucose Tolerance Test (GTT) involves fasting glucose measurement, followed by the patient drinking a glucose drink to 'challenge' their system, followed by another glucose test two hours later.

- Pregnancy: glucose present in urine and routine screening between 24th-28th week (35yo+) includes a GGT to identify the presence of Gestational diabetes.

(LabtestsOnline, 2015)
Glucose Tolerance Test (GTT)

**Oral Glucose Tolerance Test**
- No food or drink 8 to 12 hours prior to test
- Drink glucose
- Blood is tested two hours later
- High glucose level = potential diabetes

**Fasting Plasma Glucose Tolerance Test**
- No food or drink 8 to 12 hours prior to test
- Blood is drawn and tested for the level of glucose in blood
- High glucose level = potential diabetes

(www.medlineplus.gov viewed 12/01/2010)
Glucose Tolerance Test (GTT)

<table>
<thead>
<tr>
<th>Serum</th>
<th>Serum glucose + oral glucose (50-75ml) intake measures blood glucose level 1 and 2 hours (up to 5 hours) after ingestion. This is compared to a baseline fasting sample. Commonly used to diagnose diabetes mellitus. In some cases a 1hr post-prandial Glucose Challenge Test (GCT) may be used in place of the full GTT.</th>
</tr>
</thead>
</table>
| Reference Ranges (Adult) | Fasting (6.1mmol/L) <110mg/dL  
1 hour (11.1mmol/L)<200mg/dL  
2 hours (7.8mmol/L) < 140mg/dL  
(7.8 – 11.0 mmol/L)  
(11.1+ mmol/L) | Normal  
Normal  
Normal  
Impaired GT  
Probable diabetes |

## GTT: Interpreting the Results

<table>
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<th>HIGH</th>
<th>LOW</th>
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</tr>
<tr>
<td>Gestational diabetes</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Hypopituitarism</td>
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<td>Addisons disease</td>
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<td></td>
</tr>
<tr>
<td>Myxeodema</td>
<td></td>
</tr>
</tbody>
</table>

(Pagana & Pagana, 2014, p. 265)
GTT: Interpreting the Results

Glucose tolerance (GT) test curve for a diabetic and a prediabetic patient. (Pagana & Pagana, 2014, Figure 2-17, p. 263)
Glucose/Insulin Tolerance Test + Cortisol (GITT + Cortisol)
Glucose/Insulin Tolerance Test + Cortisol (GITT + Cortisol)

- With the initial fasting blood taken at the start of the oral Glucose Tolerance test, additional 5ml of blood is drawn to measure insulin levels (GITT).
- Increased levels and insulin:glucose are indicative of pancreatic islet beta cell hyperplasia or tumour.
- Type II Diabetes + insulin therapy will also give a raised reading.
- An additional 5ml of blood (fasting) is taken to measure cortisol (required to be drawn at 8am).
- This measures adrenocortical function (RCPA manual, 2014)
Glucagon
Glucagon

- **Glucagon** is secreted in response to hypoglycaemia (to increase blood glucose) by the α-cells of the pancreatic islets of Langerhans.
- Glucagon stimulation in response to hypoglycaemia does not occur in Insulin-dependent diabetes and pancreatitis or pancreatic resection.
- To differentiate between these glucagon insufficiency causes arginine stimulation is performed as arginine is a potent of glucagon.
- In diabetes there are excessively high levels of glucagon with arginine stimulation.

(Pagana & Pagana, 2014, p. 472)
Glucagon

<table>
<thead>
<tr>
<th>Serum</th>
<th>Glucagon is a fasting test. Elevated levels (with arginine stimulation) occur in diabetes mellitus, acute illness.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>Fasting 25-250ug/dL Normal</td>
</tr>
<tr>
<td>Ranges</td>
<td></td>
</tr>
<tr>
<td>(Adult)</td>
<td></td>
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</tbody>
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<td>Diabetes Mellitus</td>
<td>Idiopathic glucagon deficiency</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Severe stress (infection,</td>
<td>Chronic pancreatitis</td>
</tr>
<tr>
<td>burns, surgery, acute</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>hypoglycaemia)</td>
<td></td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td></td>
</tr>
</tbody>
</table>

HOMA-IR
Homeostasis Model Assessment of Insulin Resistance (HOMA-IR)

- HOMA-IR stands for Homeostatic Model Assessment of Insulin Resistance.

- The meaningful part of the acronym is “insulin resistance”.

- It marks for both the presence and extent of any insulin resistance that you might currently express. It is a terrific way to reveal the dynamic between your baseline (fasting) blood sugar and the responsive hormone insulin. (Wallace, Levy & Matthews, 2004)
Homeostasis Model Assessment of Insulin Resistance (HOMA-IR)

HOMA-IR

- Homeostatic model assessment (HOMA) assesses β-cell function within the pancreas and insulin resistance (IR) from fasting GITT or **C-peptide concentrations**.

  (Wallace, Levy & Matthews, 2004, p. 1487)

- **C-peptide concentrations**: β-cells secrete C-peptide with insulin. Low levels indicate β-cell failure, high levels during fasting indicate hyperinsulinaemia, high levels of insulin with low C-peptide with fasting indicates hyperinsulinaemia (too high a level of insulin drug administered)

  (RCPA manual, 2015)
Discussion

Consider how you may interpret these results and how may these influence your management of:

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- metabolic disorders
- reproductive disorders
- other?

What would be the possible differential diagnostic factors related to a 60yr old post menopausal female with fatigue?

What other clinical presentations would you look for in a patient to determine further investigative testing?
References

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- Jay C. Jha, Florence Ho, Christopher Dan, Karin Jandeleit-Dahm A causal link between oxidative stress and inflammation in cardiovascular and renal complications of diabetes
- Lord, RS & Bralley, JA (eds) 2012, Laboratory evaluations for integrative and functional medicine. 2nd edn, Metametrix institute, Duluth, Georgia
Recommended Readings

- Medlineplus 2015, Diabetes Mellitus, viewed 09/07/2015

- Newsholme P, Cruzat V, Keane K, Carlessi R, de Bittencourt D Molecular mechanisms of ROS production and oxidative stress in diabetes Biochemical Journal Dec 2016, 473 (24) 4527-4550; DOI: 10.1042/BCJ20160503C


  http://care.diabetesjournals.org/content/25/2/275.long


  http://care.diabetesjournals.org/content/27/6/1487.full
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