GESTATIONAL DIABETES: An Overview

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Brief overview of Insulin

• Insulin is a protein hormone synthesized in beta cells of Islets of Langerhans in Pancreas;

• Metabolic functions enhanced by Insulin include:
  • Uptake of glucose in muscle and adipose tissue,
  • Glycogenesis,
  • Glycolysis,
  • Protein synthesis,
  • Cellular uptake of Potassium and Phosphate ions;

• Insulin stimulates synthesis of: Glycogen, Fats & Proteins,

• Insulin inhibits degradation of: Glycogen, Fat & Proteins
• Insulin regulates uptake of Glucose into tissues with GLUT 4 Transporter, Examples:
  • Muscle cells, Adipose tissue, Connective tissues, White blood cells;
• Insulin DOES NOT regulate Glucose uptake into tissue with GLUT 2 Transporter, Examples:
  • Brain, Liver, Kidneys,
• **BUT** Insulin regulates biosynthesis of Glycogen in Liver cells (Glycogen Synthetase reaction);
• Insulin counter regulatory hormones oppose the actions of Insulin; these hormones include: Glucagon, Epinephrine, Glucocorticoids, Growth hormone;
Brief overview of Glucagon

- Glucagon is produced in Alpha cells in Pancreas
- Glucagon causes increase in blood glucose level;
- Glucagon acts on hepatocytes, stimulating breakdown of Glycogen to Glucose, which is then released in blood;
- Glucagon stimulate breakdown of Fat and conversion of fatty acids to glucose (Gluconeogenesis);
- Secretion of Glucagon is stimulated by low glucose level or by increasing amino acid levels (as arise after a protein-rich meal) in blood,
- Increasing blood glucose reduces release of Glucagon;
- Glucagon is one of the Insulin Counter Regulatory Hormones;
What is the Insulin feedback loop?

Insulin feedback loop is:

• Action of Insulin and Insulin Counter Regulatory Hormones in regulating blood glucose level;

• Homeostatic regulation of blood glucose is the balance between actions of Insulin and Insulin Counter-regulatory Hormones: **INSULIN FEEDBACK LOOP**;

• Failure of the feedback loop affects regulation of blood glucose;

• Failure of part of the loop causes increase in blood glucose level;
  • Glucose cannot get into cells that use or store it;
  • Excess Glucose may be dumped in urine resulting in “Sweet Urine” (**Diabetes Mellitus**)
What is Diabetes Mellitus (DM)?

Precise definition of DM is very difficult;

Diabetes Mellitus:
- Disease characterized by derangements in Carbohydrate, Fat and Protein metabolism;

Diabetes Mellitus:
- Syndrome characterized by Hyperglycemia due to:
  - An absolute or relative lack of Insulin and/or Insulin Resistance
What are the major types of Diabetes Mellitus?

- **Primary DM** is generally sub-classified into:
  - Type I DM: Insulin Dependent Diabetes Mellitus (IDDM);
  - Type 2 DM: Non-Insulin Dependent Diabetes Mellitus (NIDDM)
• **Secondary DM**: may be due to:
  • Pancreatic disease,
  • Endocrine disease (Cushing’s syndrome),
  • Adrenal diabetes,
  • Drug therapy,
  • Insulin receptor abnormalities,
  • Gestational diabetes,
What are some of the causes of Type 1 DM?

- Type 1 DM, (Juvenile-Onset DM),
- Type 1 DM is **not** limited to juvenile patients;
- Causes of Type 1 DM include the inability to produce Insulin, due to either:
  - Defective Beta cells in Pancreatic Islets,
  - Absent of Beta cells in Pancreatic Islets;
  - Autoimmune process causing destruction of Beta cells in Pancreatic Islets,
• Presence of Islet cell antibodies in Serum may predicts future development of Type 1 DM;
• Islet-cell antibodies act against Glutamic Acid Decarboxylase (GAD);
• Environmental precipitating factors of DM:
  • Viral infections,
  • Dietary factors (presence of anti-metabolites in some foodstuffs);
What are some of the characteristics of Type 1 DM?

• Type 1 DM is usually characterized by:
  • Deficiency in Insulin and consequent Hyperglycemia,
  • Hyperglycemia causes blood glucose level to exceed
    Renal Threshold of 200mg/dl or 11mmol/L, Resulting
    in Glucosuria,

• Following sequence of events occur:
  • Sugar is excreted in urine (Glucosuria),
  • Water follows the sugar due to osmosis (Osmotic
    diuresis),
  • Large volume of urine is passed out (Polyuria),
• Patient becomes thirsty, drinks lots of water (Polydipsia),
• There is Lack of Insulin:
  • Thus, Muscles, Adipose tissue, Connective tissues and White Blood Cells cannot utilize Glucose present in blood (Starvation in the midst of plenty),
• Patient become hungry and eats a lot (Polyphagia),
• Due to continuous lack of Insulin, Glucose cannot enter Muscle and other tissues, thus patient may start to loose weight (Wasting),
• Patient may develop Ketoacidosis (Why?)
What are the consequences if Type 1 DM is not controlled?

- **Hyperglycemia**:  
  - Partly due to inability of Insulin-dependent tissues to use blood glucose (Starvation in the midst of plenty, *(Why?)*)  
  - Increased Hepatic Gluconeogenesis,  
  - Depressed Glycolysis due low glucose levels in cells;

- **Hyper-Lipoproteinemia (Chylomicrons and VLDL)**:  
  - Due to low Lipoprotein Lipase activity in Adipose tissue,  
  - Insulin is required for biosynthesis of Lipoprotein Lipase,  

- **Ketoacidosis: Increased production of Ketone bodies**:  
  - Acetone,  
  - Acetoacetic acid,  
  - β-Hydroxybutyric acid;
General occurrence of Type 2 DM

• **Type 2 DM:** accounts for 85% cases of DM in PNG
• Formally called:
  • Non-Insulin Dependent Diabetes Mellitus (NIDDM);
  • Maturity-onset diabetes mellitus,
• Common in middle-age obese individuals,
• Can occur in non-obese middle-age individuals,
• Can occur in any age group;
What are some of the possible causes of Type 2 DM?

• May be due to any of the following:
  • Resistance of peripheral tissues to Insulin, despite normal or high Insulin level in blood,
  • Deficiency or defect in Insulin Receptors in target tissues (Relative Insulin deficiency),
  • Obesity, (may have clinical features of Type 2 DM),
  • Defect in Insulin Receptors is related to increased levels of Tumor Necrosis Factor-α (TNF-α) in Adipocytes,
  • Increase adipose tissue mass causes increase TNF-α, which then blocks Insulin Receptors,
• Diet can control Type 2 DM in Obese patient,
• Obese patients that are motivated to lose weight:
  • Insulin receptors will increase in number,
  • Post-receptor abnormalities will improve, resulting in tissue sensitivity to insulin and Glucose tolerance;
• Defects occurring within Insulin-responsive cells at sites beyond Insulin receptors,
• In non-obese individuals:
  • Type 2 DM may be cause not only by Insulin Resistance, but also by Impaired Pancreatic β-cell function resulting in Relative Insulin Deficiency;
What are some consequences of uncontrolled Type 2 DM?

• Uncontrolled Type 2 DM is characterized by:
  • Hyperglycemia,
  • Hyper-Triglyceridemia,
• Hyperglycemia causes accumulation of glucose in:
  • Eyes (Lens epithelium, Retinal capillaries),
  • Peripheral Nerve cells (Schwann cells),
  • Kidneys (Papillae, Glomerulus),
• Aldose Reductase and Sorbitol Dehydrogenase in these tissues converts:
  • Glucose to Fructose, Dulcitol and Sorbitol;
• Sorbitol accumulates and crystallizes causing damage to tissues by causing them to swell;
• Resulting in conditions such as:
  • Cataract formation in eyes (diabetic cataract),
  • Diabetic Neuropathy and loss of sensation,
  • Retinopathy (damage to retina),
  • Damage to blood vessels (Vascular disease),
  • Damage to kidneys causing renal failure,
  • Damage to Cardiac tissue (Ischemic heart disease),
• Type 2 DM does not cause Ketoacidosis (WHY?)
GESTATIONAL DIABETES (GDM)

What is gestational diabetes mellitus (GDM)?

• **GDM** is not easily and clearly defined;
• **GDM**: Carbohydrate Intolerance causing Hyperglycemia of variable severity with onset or first recognition during Pregnancy;
• **GDM**: Condition in which blood glucose level is elevated and other diabetic symptoms may appear during pregnancy in a female who has not previously been diagnosed with DM;
• In these women all diabetic symptoms usually disappear after delivery;
IMPORTANT TO NOTE

• Women with DM before pregnancy do NOT have GDM they have “DM and Pregnancy” such women should be treated accordingly before, during, and after the pregnancy;

• In some women, during early part of pregnancy (e.g. First trimester and first half of second trimester) Fasting and Post-Prandial Glucose levels may be lower than in normal, non-pregnant women;
• In some women, High Fasting or Post-prandial Glucose levels during the First trimester and First half of second trimester of pregnancy may reflect presence of DM before pregnancy;

• Normal Glucose Tolerance during the early part of pregnancy does not rule out the possibility that the patient may develop GDM later;
What group of women can be considered at high risk for developing GDM?

• High Risk Groups for GDM include:
  • Women with history of Glucose Intolerance,
  • Women who previously gave birth to larger for gestational age babies,
  • Older women,
  • Women with High Fasting or Random Blood Glucose Levels
DIAGNOSIS OF DIABETES MELLITUS

Is diagnosis of DM the same as monitoring of DM?

• Diagnosis of DM is not the same as monitoring of DM,
• Diagnosis:
  • To clinically establish a condition in a patient,
• Monitor:
  • To follow progress on a condition already diagnosed,
• Specific Biochemical tests and Guidelines are used for diagnosis of DM,
• Specific Biochemical tests and Guideline are used for monitoring DM,
Some Biochemical tests for diagnosis of DM

Glucosuria (Glycosuria):

• Good first-line screening test for DM,
• Glucose appears in urine when plasma glucose level rises above renal threshold (11mmol/L or 200mg/dL);
• Glucosuria may occur in patients with low renal threshold for glucose;
  • Individuals are said to have Glucosuria without DM,
• Renal threshold increases with age, thus some patients may have DM without Glucosuria,
• Glucosuria indicates Hyperglycemia over the period of formation of the urine, it does not reflect the exact level of blood glucose at the time of testing;
Fasting Blood Glucose (FBG):

- FBG is measured after overnight fast (8 to 10hrs),
- FBG is better than RBG for diagnostic purposes,
- FBG above **8.0mmol/L** on **two different occasions** may be diagnostic of DM,
- FBG between **6.0 to 8.0mmol/L** is borderline,
- *(Note: to convert mmol/L to mg/dl multiply by 18.0)*
Random Blood Glucose (RBG):

• RBG: one of major tests required in emergency,
• RBG less than 8.0mmol/L is usually expected in non-diabetics,
• RBG higher than 11.0mmol/L in more than one occasion indicates that the individual be investigated more thoroughly for DM;
• Measurement of RBG on Whole blood, Plasma or Capillary blood have different cut-off points;
• Table 1: WHO guideline for diagnosis
Table 1: WHO Guideline for diagnosis of DM

<table>
<thead>
<tr>
<th>RANDOM GLUCOSE SAMPLE (mmol/L)</th>
<th>Diabetes likely</th>
<th>Diabetes uncertain</th>
<th>Diabetes unlikely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous plasma</td>
<td>$\geq 11.1$</td>
<td>$5.5 - &lt; 11.1$</td>
<td>$&lt; 5.5$</td>
</tr>
<tr>
<td>Venous blood</td>
<td>$\geq 10.0$</td>
<td>$4.4 - &lt; 10.0$</td>
<td>$&lt; 4.4$</td>
</tr>
<tr>
<td>Capillary plasma</td>
<td>$\geq 12.2$</td>
<td>$5.5 - &lt; 12.2$</td>
<td>$&lt; 5.5$</td>
</tr>
<tr>
<td>Capillary blood</td>
<td>$\geq 11.1$</td>
<td>$4.4 - &lt; 11.1$</td>
<td>$&lt; 4.4$</td>
</tr>
</tbody>
</table>
Two Hours Post-Prandial blood glucose:

• Measure blood glucose level 2-hours after consumption of a meal,
• It is a better indicator that FBG and RBG,
• Individuals with blood glucose above 11.0mmol/L should be investigated more thoroughly for DM;
How is Oral Glucose Tolerance Test (OGTT) performed in a patient, when requested?

• OGTT is recommended only if RBG and FBG tests cannot be interpreted clearly to justify DM;
• OGTT must be carried out under proper clinical supervision;
• Patient should be sitting comfortably throughout test, should not smoke or exercise and should be on normal diet for at least 3 days prior to the test;
• Patient should be properly briefed before starting the procedure;
• Patient should fast overnight (8 to 10 hrs),
PROCEDURE FOR OGTT:

- Measure FBG and Urine Glucose of patient after an overnight fast;
- Record both results;
- Prepare solution containing **75.0g of Glucose in 300ml water**;
- Patient should drink all the solution within 5 min,
- Measure blood glucose level every 30 min for 2 hrs,
- Measure glucose in urine after 2 hrs,
- Record all the results;
How are OGTT results interpreted?

• WHO Guidelines in Table 2 may be used, or
• Results used to draw Graph: Time vs. Blood Glucose,
• In Asymptomatic patients, OGTT should be interpreted as diagnostic of DM only when:
  • There is an increased 2-hrs Glucose level, and
  • Blood Glucose is equal to or greater than 11.0mmol/L (200.0 mg/dL) at some other point during the test;
• If patient has normal FBG, but the 2hrs value is in the diabetic range, test should be repeated after 6wks;
• Impaired Glucose Tolerance (IGT) is considered abnormal; it is an intermediate stage between normal and DM;
• IGT indicates risk of developing DM;
<table>
<thead>
<tr>
<th></th>
<th></th>
<th><strong>DM (mmol/L)</strong></th>
<th><strong>IGT (mmol/L)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Venous plasma</strong></td>
<td><strong>Fasting</strong></td>
<td>≥ 7.8</td>
<td>&lt; 7.8</td>
</tr>
<tr>
<td></td>
<td><strong>2 hours</strong></td>
<td>≥ 11.1</td>
<td>7.8 - &lt; 11.1</td>
</tr>
<tr>
<td><strong>Venous blood</strong></td>
<td><strong>Fasting</strong></td>
<td>≥ 6.7</td>
<td>&lt; 6.7</td>
</tr>
<tr>
<td></td>
<td><strong>2 hours</strong></td>
<td>≥ 10.0</td>
<td>6.7 - &lt; 10.0</td>
</tr>
<tr>
<td><strong>Capillary plasma</strong></td>
<td><strong>Fasting</strong></td>
<td>≥ 7.8</td>
<td>&lt; 7.8</td>
</tr>
<tr>
<td></td>
<td><strong>2 hours</strong></td>
<td>≥ 12.2</td>
<td>8.9 - &lt; 12.2</td>
</tr>
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Graph of Time against Concentration of Blood Glucose in the OGTT test.
How can GDM be diagnosed?

- Screening for GDM can be carried out between 24 and 28 weeks of gestation:
- Two or three separate measurements of FBG and RBG should be done on the patient;
- **OGTT is recommended only if RBG and FBG tests cannot be interpreted clearly to justify DM**;
- In such cases to diagnose GDM in the patient the OGTT can be performed under proper clinical supervision;
- **OGTT should not be carried out in a diabetic patient!!**
• Pregnant women having results that meet the WHO criteria for DM or Impaired Glucose Tolerance (IGT) are classified as having GDM;
• It is recommended that the patient be tested (repeat OGTT) again about six or more weeks after delivery;
• This is to enable reclassification of the patient as having either DM, IGT, or normal glucose tolerance;
• Patient must be put into the high-risk group for DM, regardless of the outcome of the test results;
What are the possible causes of GDM?

• Actual causes of GDM are not fully known, but some Theories have been suggested:
  • GDM is related to Insulin Resistance cause by actions of Insulin Counter-Regulatory Hormones produced in the Placenta;
    • Placenta provides Nutrients and other components required for normal fetal growth and development;
  • Placenta also releases hormones (Cortisol, Estrogen, Human Placental Lactogen) whose metabolic functions are to ensure normal progression of pregnancy;
• High plasma levels of these hormones tend to block the action of Insulin;
• Effects of these hormones are usually more apparent during 20 to 24 weeks of Gestation;
• As pregnancy progresses the placenta produces increase amounts of these hormones, thus increasing their actions against Insulin, which then leads to Insulin resistance;
• Effects of these hormones are more intense from the 20\textsuperscript{th} to 24\textsuperscript{th} week of gestation;
• Normally, pancreas is able to make additional insulin to overcome Insulin Resistance, but when production of Insulin is not enough to overcome the effect of the Placental hormones, Gestational Diabetes results;
• Some women who have GDM may develop Type 2 DM (NIDDM) years later;
• Gestational diabetes and Type 2 DM involve Insulin Resistance
• Lifestyle changes may help prevent DM after Gestational diabetes
What are some of the complications of GDM?

• Imbalance in some biochemical parameters is a common feature of neonates of GDM mothers;
• Examples of such imbalances include:
  • Hypocalcaemia,
  • Low serum Magnesium,
  • Macrosomia (Fat babies),
  • Hypoglycemia;
What is Macrosomia and what causes it?

- **Macrosomia**: baby considerably larger than normal,
- Placenta is major source of nutrients for fetus,
- Maternal Insulin does not cross the placenta, but glucose easily crosses the placenta,
- Hyperglycemia in a mother with GDM will result in Hyperglycemia in Fetus causing the Pancreas in the fetus to produce more insulin in an attempt to clear the extra glucose in circulation,
• Since the fetus is getting more glucose and thus more energy that it needs to grow and develop, the extra glucose will be converted to fat for storage,

• Thus, even when the mother has GDM, the fetus is able to produce all the insulin it needs;

• Combination of high blood glucose levels from the mother and high insulin levels in the fetus results in large deposits of fat in the adipose tissue of fetus;

• This leads to Macrosomia, or excessively “Fat” baby;
Why can Hypoglycemia develop in neonates from GDM mothers?

- Hypoglycemia may occur if the mother's blood glucose level (mother with GDM) have been consistently high, causing the fetus to have a high level of insulin in circulation;

- After delivery, the neonate continues to have high insulin level, but no longer has the high level of glucose from the mother, resulting in the neonate becoming hypoglycemic;
How can a patient with DM be monitored? (Long-term indices of diabetic control)

What is Glycosylated Hemoglobin (HbA\(_{1c}\))?

- About 98% of Hb in RBC is HbA\(_{1}\)
- HbA\(_{1}\) is made up of HbA\(_{1a}\), HbA\(_{1b}\), HbA\(_{1c}\)
- HbA\(_{1c}\) is highest in amount, and is the component that strongly undergoes Glycosylation with Glucose;
- HbA\(_{1}\) combines with blood glucose in a non-enzymatic reaction to form Glycosylated Hb (HbA\(_{1c}\)),
- Amount of HbA\(_{1c}\) formed is dependent on amount of Glucose in blood over 120-days life span of RBC;
• HbA$_{1c}$ level reflects the average blood sugar level for the 100- to 120-day period before the test;
• Elevation of HbA$_{1c}$ occurs about 3 weeks after sustained elevation in blood glucose;
• It takes about 4 weeks for HbA$_{1c}$ to decrease after a sustained reduction in blood glucose,
• Measurement of HbA$_{1c}$ is a good Clinical indicator of Glycemic control in a patient on DM medication,
• In healthy person HbA$_{1c}$ is 4% to 6% of total HbA,
• In prolonged Hyperglycemia the level of HbA$_{1c}$ may rise to as much 12% of Total HbA;
What are some of the uses of Test for HbA$_{1c}$?

- HbA1c is a good index of diabetic control, it is used to complement results from single blood glucose level, or as patient’s log of own blood glucose measurements;
- Used to evaluate DM treatment and compliance;
- Use to compare past and new diabetic therapy,
- Used to estimate duration of hyperglycemia in patients with newly diagnosed DM,
What is Microalbuminuria (MAU)?

- **MAU** is increase in urinary albumin that cannot be detected during urinalysis with Albustick, Clinistick, Dipstick or Multistick;
- MAU is urinary albumin level between 25 to 250mg/day,
- MAU is may lead to progressive increase in proteinuria resulting in clinical Albuminuria (Macroalbuminuria) and declining Glomerular Filtration Rate,
- Macroalbuminuria may be associated with renal damage leading to end stage renal failure and increased coronary mortality among diabetic and hypertensive patients;
- For a diabetic patient MAU indicates early (Sub-clinical), reversible renal damage;
What is Hypoglycemia?

- **Hypoglycemia** is a laboratory “diagnosis” that means blood glucose level below 2.2mmol/L (40.0 mg/dl);

- Hypoglycemia may be due to:
  - Endocrine disorders,
  - Liver disease,
  - Inborn errors of metabolism,
  - Gastrointestinal surgery,
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