Carbohydrate metabolism

- Carbohydrates are made up of carbon, hydrogen and oxygen
- Carbohydrates are found in sugar, jam, fruits etc
- There are three major groups of carbohydrates.

(1) Monosaccharides
- ✓ These are simple sugars that can be absorbed directly from the intestines
- ✓ They include hexoses such as glucose, fructose and galactose
- ✓ They also include pentoses such as xylose, ribose and arabinose

(2) Disacccharides
- ✓ They are not directly absorbed from the intestines
- ✓ On hydrolysis with enzymes, they yield two molecules of monosaccharides
- ✓ Disaccharides include sucrose, maltose and lactose.

(3) Polysaccharides
- ✓ They are more complex and are easily absorbed in the body
- ✓ They include starch and glycogen
- ✓ They are hydrolysed by amylase to mainly maltose and glucose

Enzyme	**Disaccharides**	**Monosaccharides**
Lactase	Lactose	Glucose + Galactose
Sucrase	Sucrose	Glucose + Fructose
Maltase	Maltose	Glucose + Glucose

- There are three ways in which the glucose is either utilized or stored in the body

(1) Glycolysis
- ✓ This is breakdown of glucose to pyruvic acid or lactic acid for the production of energy inform of ATP
- ✓ It is used to control the level of glucose in the blood

(2) Glycogenesis
- ✓ This is the process of glycogen formation
- ✓ Glycogenolysis is breakdown of glycogen
- ✓ Glucose is converted to glycogen and stored in the liver and skeletal muscles

(3) Conversion to fat
- ✓ Excess glucose not immediately needed is oxidized to fatty acids and stored as fat in tissues.

Hormones that affects blood glucose level

(1) Insulin
- ✓ Produced and secret by beta cells of islets of langerhans in the pancreas
- ✓ Regulates the rate of glucose absorption and its conversion to glycogen
- ✓ Its production is stimulated by a rise in blood glucose level
- ✓ In absence of insulin, the blood glucose level rises

(2) Glucagon
- ✓ Produced and secret by alpha cells of islets of langerhans in the pancreas
- ✓ It stimulates: breakdown of stored glycogen, liver gluconeogenesis, hepatic lipolysis
- ✓ When glucagon is secreted, blood glucose level rises

(3) Adrenalin

- ✓ Also known as epinephrine produced by adrenal medulla
- ✓ It increases glycogenolyosis and inhibits uptake of glucose in the tissues
- ✓ Presence of adrenalin results in rise in blood glucose level

(4) Growth hormone

- ✓ Also known as somatotrophic hormone synthesized in the anterior pituitary
- ✓ It inhibits uptake of glucose in the tissues and increases liver glucose output.
- ✓ It helps in gluconeogenesis of fat there increasing the overall blood glucose level

(5) Adrenocorticotrophic hormone

- ✓ A hormone produced by the anterior pituitary
- ✓ It inhibits uptake of glucose in the tissues and increases liver glucose output.
- ✓ It helps in gluconeogenesis of fat there increasing the overall blood glucose level

(6) Corticosteroid hormone

- ✓ Also known as glucoccorticoids and are secreted by adrenal cortex
- ✓ They inhibit the action of insulin thus blocking glucose utilization by the tissues
- ✓ This hormone promotes use of protein instead of glucose for the production of heat and energy

(7) Thyroxine

- ✓ A hormone produced by the thyroid gland
- ✓ It increases absorption of glucose from the GIT and stimulates glycogenolysis
- ✓ It promotes an increase in blood glucose level.

NB:

- ➢ A raised blood sugar (glucose) level is known as hyperglycaemia
- ➢ Low blood glucose level is known as hypoglycaemia
- ➢ A false raised blood sugar levels may result if blood sample is collected from an arm receiving I.V infusion
- ➢ Icteric samples (jaundiced) can likewise give falsely low glucose levels
- ➢ Various sugars found in urine under certain circumstances both pathological and physiological
- ➢ Glucose is the most common; others are lactose, fructose, xylose etc
- ➢ They are also known as reducing sugars since they reduce cupric sulphate to cuprous oxide (red in color)
- ➢ Reduction takes place in alkaline media
- ➢ Reducing substances that are non-sugars are;
  - o Drugs (salicylates)
  - o Uric acid
  - o Creatinine
  - o Gluconic acid
- ➢ Presence of glucose in urine is known as glycosuria and indicated diabetes mellitus
- ➢ Lactose appears in urine in late pregnancy and during lactation (lactosuria)
- ➢ Fructose appears after ingesting large quantities of fruits
- ➢ Salicylates appears after taking pain relieving drugs such as aspirins
- ➢ All reducing sugars can be detected using benedict's alkaline copper reduction method.

Causes of abnormal glucose levels

Hyperglycaemia

- Diabetes mellitus

- Acromegaly
- Obesity
- Severe liver disease
- Pancreatic disorder
- Pituitary disorder
- Steroid therapy
- Shock, convulsion and acute stress reaction.
- Adrenal cortical hyperactivity (Cushing's syndrome) –metabolic disorder caused by overproduction of corticosteroid hormones by adrenal cortex often leading to obesity and high blood pressure

Hypoglycaemia

- Insulinoma
- Hypopituitarism
- Adrenal cortical insufficiency
- Ectopic insulin production from tumors
- Acute alcohol ingestion
- Severe liver disease
- Glycogen storage disorder
- Kwashiorkor (malnutrition)
- Addison disease – disease caused by inadequate secretion of hormones by adrenal cortex characterized by anaemia and bronze discoloration of the skin

False glucose levels

- May result if blood sample is collected from an arm receiving intravenous infusion
- Icteric samples can likewise give falsely low glucose level

NB:

- **Insulin** is produced by beta cells of islets of langerhans in the pancreas
- Unregulated excess insulin secretion is seen in Insulinomas –insulin secretin tumors
- Excess insulin causes hypoglycemia

✓ **Glucagon** is produced by alpha cells of islets of langerhans in the pancreas
✓ Unregulated excess glucagon secretion is seen in glucagomas –a rare islet tumors
✓ Excess glucagon causes hyperglycaemia

➢ **Somatostatin** is produced by delta cell of the islets of langerhans
➢ This inhibits glucagon and insulin secretion amoung other hormones such as pituitary & GIT hormones
➢ Unregulated excess somatostatin secretion is seen in somatostatinomas – a rare islet tumor

- **Pancreatic peptide** is produced by F-cells or PP cells
- Significance of pancreatic peptide is not clear but can reduce appetite & food intake
- Unregulated excess pancreatic peptide secretion is seen in hyperplasia – a rare islet tumor
- Some patients are asymptomatic others produce watery diarrhea syndrome

Glucose estimation

✓ Glucose is analyzed with point of care devises at home or physician's office
✓ Whole blood gives 10-15% lower glucose reading than plasma

- ✓ Capillary blood is the source for most of these whole blood glucose
- ✓ Glucose is estimated in whole blood, serum, CSF, pleural fluid or urine
- ✓ Glucose is metabolized at room temperature at a rate of 7gm/dl/h (0.4Mmol/l/h) or 2mg/dl/h at 4°C
- ✓ Rate of glucose breakdown is high in bacterial contaminated samples or in leucocytosis.
- ✓ Serum specimen for glucose analysis is separated from cell within 30 min.
- ✓ Sodium fluoride is used to inhibit glycolysis if the sample is to be stored for more than 30min
- ✓ Glucose is stable in serum or plasma for 48 hrs.

Errors contributing to inaccurate reading in a glucometer

- Application of insufficient volume of blood
- Milking finger to acquire sufficient blood
- Use of outdated glucose strips
- Use of malfunctioning meter
- Use of dirty meter
- Touching reaction area
- Environmental factors such as humidity, heat and altitude
- Hypotension
- Measurement outside hematocrit and temperature range
- Hypertriglyceridemia.
- High level of uric acid, bilirubin, lipids, low O_2 level & drugs such as salicylates, acetaminophen

NB: Interstitial glucose measurement devices measures glucose levels in interstitial fluid of dermis or subcutaneaous fat tissue

Diabetes mellitus

- ✓ This is a condition characterized by disturbances in carbohydrate, lipid and protein metabolism
- ✓ It is also a condition when blood glucose level is elevated because of insufficient insulin secretion or abnormal insulin action.
- ✓ It is a chronic metabolic disorder characterized by glycosuria and hyperglycaemia.
- ✓ When the body is deprived off glucose, as in starvation or diabetes mellitus, the body obtains its energy by breaking down fat or fatty acids.
- ✓ This increase in breakdown of fat leads to production of ketone bodies.

Types of diabetes Mellitus

- ✓ There are two types of the conditions known as primary diabetes

- Type 1 (Juvenile –onset/ Growth onset)
  - ✓ Characterized by absolute insulin deficiency and beta cell destruction
  - ✓ Destruction can be either; autoimmune destruction, genetic susceptibility, viral infection, toxic exposure
- Type II (Adult type/ maturity-onset
  - ✓ Characterized by insulin resistance and insulin secretory deficit
    Risk factors include overweight (BMI >25kg/M^2), sedentary lifestyle, family history, hypertension
    advanced age >45yrs, ethnicity (African, American, Latinos), pregnancy (gestational diabetes), high cholesterol levels of >35mg/dl)

✓ Course of diabetes mellitus runs in four stages

1) Pre-diabetes: - period from birth until first evidence of diabetes emerges
2) Suspected Diabetes:- patients with abnormal GGT and shows symptoms of diabetes
3) Chemical or Latent diabetes:- A patient shows no diabetes signs/symptoms but displays abnormal GGT
4) Overt diabetes: - patients shows symptoms of polyuria, polydipsia, & wt loss which are linked to fasting hyperglycaemia and glycosuria.

Modern classification of diabetes Mellitus

1. Idiopathic Diabetes Mellitus

a) IDDM type I - Also known as insulin dependent diabetes mellitus (IDDM)
   - ✓ Individual in this category produce very little insulin
   - ✓ Satisfactory control of blood sugar is obtained with insulin treatment
   - ✓ About 10% of diabetes mellitus cases belong to this category

b) NIDDM – Non- Insulin dependent diabetes mellitus
   - ✓ Most common form of diabetes mellitus forming about 80 -90% of the cases
   - ✓ Most patients with this form are relatively deficient in insulin and have mild hyperglycemia
   - ✓ Obesity is commonly associated with NIDDM although some patients may be non-obese
   - ✓ A small percentage of NIDDM patients may require insulin injection or oral hypoglycaemia agents to control hyperglycaemia

2. Gestational diabetes Mellitus

- ✓ Glucose intolerance is discovered for the first time during pregnancy
- ✓ Such a woman is at high risk for foetal morbidity and should be promptly treated

3. Impaired glucose tolerance

- ✓ Persons with IGT are boarderline cases with slightly raised glucose levels without overt hyperglycaemia
- ✓ Such cases may latter develop diabetes mellitus or revert back normal
- ✓ Such patients are at higher risk of development of cardiovascular disease.

4. Previous abnormality of glucose tolerance (Pre. AGT)

- ✓ Patients here have history of diabetes but have reverted back to normal levels

5. Potential abnormality of glucose tolerance (Pot. AGT)

- ✓ Patients here are at more than average risk of developing diabetes.

6. Glucose intolerance associated with other disorders.

- ✓ This is hyperglycaemia due to underlying disorder such as chronic pancreatitis, cushings disease etc.

Clinical Symptoms of Diabetes Mellitus

- Obesity in elderly
- Loss of weight in middle aged patients
- Frequency of micturition (needing to urinate more often than usual)
- Increased thirst leading to increased fluid intake (polydipsia)
- Increased hunger leading increased food intake (polyphagia)
- Lowered resistance to infection leading to slow wound healing
- Regular thrush or genital itching(groin area) / irritation of the skin (pruritus)
- Blurred vision
- Weak and tired for no reason (Fatigue)
- Nausea and dry mouth

Laboratory diagnosis of diabetes mellitus

Urine glucose:

- Volume is large(polyuria)
- Specific gravity is higher than 1.030
- Glucose is presence (glycosuria)
- Ketone bodies are detectable (ketonuria)
- True glucose must exceed 10Mmol/L (180mg/dl) in blood before glucose can pass into the urine (this is known as **Renal threshold**)

Blood glucose:

- Fasting and Random blood sugar (FBS & RBS) are increased (hyperglycaemia)
- Fasting blood sugar level in excess of 6.6Mmol/L (120mg/dl) is suggestive of diabetes mellitus
- Fasting blood sugar values of between 6.0-6.6 Mmol/L are doubtful and should be confirmed by performing GGT)

Values diagnostic of Diabetes Mellitus

Specimen	FBS	RBS
Plasma: Venous Capillary	≥ 7.8 Mmol/L (140mg/dl) ≥ 7.8 Mmol/L (140mg/dl)	≥ 11.1Mmol/L (200mg/dl) ≥ 12.2Mmol/L (220mg/dl)
Whole blood: Venous Capillary	≥ 6.7 Mmol/L (120mg/dl) ≥ 6.7 Mmol/L (120mg/dl)	≥ 10.0 Mmol/L (180mg/dl) ≥ 11.1 Mmol/L (200mg/dl)

Two hour Post-Prandial blood glucose

- Two hours after the patient has broken fast by being fed on adequate carbohydrate meal,
  A single blood sample is collected and analysed
- Glucose level in excess of 10Mmol/L (180mg/dl) is highly suggestive of diabetes mellitus
- This should be confirmed by GGT
- Single two hour pp glucose level has limitation due to:
  - Delayed peak level due to slow absorption
  - Early hyperglycaemia due to rapid absorption
  - Quick fall in concentration of blood glucose level due to release of insulin
  - Wrong specimen collection timing

Glucose tolerance Test

- Also refered to as Oral Glucose Tolerance Test (OGTT)
- GTT is the measure of the ability of the body to tolerate standard/measured dose of glucose
- A glucose tolerance test is a medical test in which glucose is given and blood samples taken afterward to determine how quickly it is cleared from the blood.
- The test is usually used to test for diabetes, insulin resistance, and sometimes reactive hypoglycemia and acromegaly, or rarer disorders of carbohydrate metabolism.
- In the most commonly performed version of the test, an *oral glucose tolerance test* (OGTT), a standard dose of glucose is ingested by mouth and blood levels are checked two hours later.
- Many variations of the GTT have been devised over the years for various purposes, with different standard doses of glucose, different routes of administration, different intervals and durations of sampling, and various substances measured in addition to blood glucose.
- OGTT test is performed in-order to screen:

a) Patients having glycosuria with no apparent symptoms of diabetes with normal FBS and PP blood glucose level
b) Patients showing symptoms of diabetes with no glycosuria and a normal fasting level of blood glucose
c) Person with family history of diabetes but with no overt diabetes
d) Patients having glycosuria in conjunction with pregnancy, thyroxicosis, liver disease or infection
e) Patient showing evidence of neuropathies or retinopathies of un confirmed origin

Standard OGTT

Since the 1970s, the World Health Organization and other organizations interested in diabetes agreed on a standard dose and duration.

Patient Preparation

- ✓ The patient is instructed not to restrict carbohydrate intake in the days or weeks before the test.
- ✓ Place the patient on a diet containing not less than 150gm of carbohydrates for about three days before the test.

- ✓ The patient should not eat anything after supper and no breakfast is given on the day of the test.
- ✓ No drink except ordinary water should be given
- ✓ For children, should be restricted as follows:
  - Infant less than 4months – 4hrs fast
  - Infant between 4-6months – 6hrs fast
  - Children aged 6-24months – 8hrs fast
- ✓ The test should not be done during an illness, and preferably in the morning.
- ✓ A full adult dose should not be given to a person weighing less than 43 kg (94 lb), or exaggerated glucoses may produce a false positive result.
- ✓ Usually the OGTT is performed in the morning as glucose tolerance can exhibit a diurnal rhythm with a significant decrease in the afternoon.
- ✓ The patient is instructed to fast (water is allowed) for 8–12 hours prior to the tests.

Procedure

1. A zero time (baseline) blood sample is drawn.
2. The patient is then given a measured dose (below) of glucose solution to drink within a 5 minute time frame.
3. Blood is drawn at intervals for measurement of glucose (blood sugar), and sometimes insulin levels.
4. The intervals and number of samples vary according to the purpose of the test.
5. For simple diabetes screening, the most important sample is the 2 hour sample and the 0 and 2 hour samples may be the only ones collected.
6. A laboratory may continue to collect blood for up to 6 hours depending on the protocol requested by the physician.

Dose of glucose and variations

- In the US, dosing is by weight, and since the late 1970s has been 1.75 grams of glucose per kilogram of body weight, to a maximum dose of 75g. Prior to 1975 a dose of 100g was often used.
- The WHO recommendation is for a 75g oral dose in all adults: the dose is adjusted for weight only in children.[2] The dose should be drunk within 5 minutes.
- A variant is often used in pregnancy to screen for gestational diabetes, with a screening test of 50 grams over one hour. If elevated, this is followed with a test of 100 grams over three hours.
- In UK General Practice, the standard glucose load is provided by 394ml of the sports drink Lucozade (original flavour only), which the patient is asked to supply.

Substances measured and variations

NB: If renal glycosuria (sugar excreted in the urine despite normal levels in the blood) is suspected, urine samples may also be collected for testing along with the fasting and 2 hour blood tests.

Interpretation of OGTT results

- Fasting plasma glucose (measured before the OGTT begins) should be below 6.1 mmol/L (110 mg/dL).
- Fasting levels between 6.1 and 7.0 mmol/L (110 and 125 mg/dL) are borderline ("impaired fasting glycaemia"), and fasting levels repeatedly at or above 7.0 mmol/L (126 mg/dL) are diagnostic of diabetes.
- A 2 hour OGTT glucose level below 7.8 mmol/L (140 mg/dL) is normal, whereas higher glucose levels indicate hyperglycemia.
- Blood plasma glucose between 7.8 mmol/L (140 mg/dL) and 11.1 mmol/L (200 mg/dL) indicate "impaired glucose tolerance", and levels above 11.1 mmol/L (200 mg/dL) at 2 hours confirms a diagnosis of diabetes.

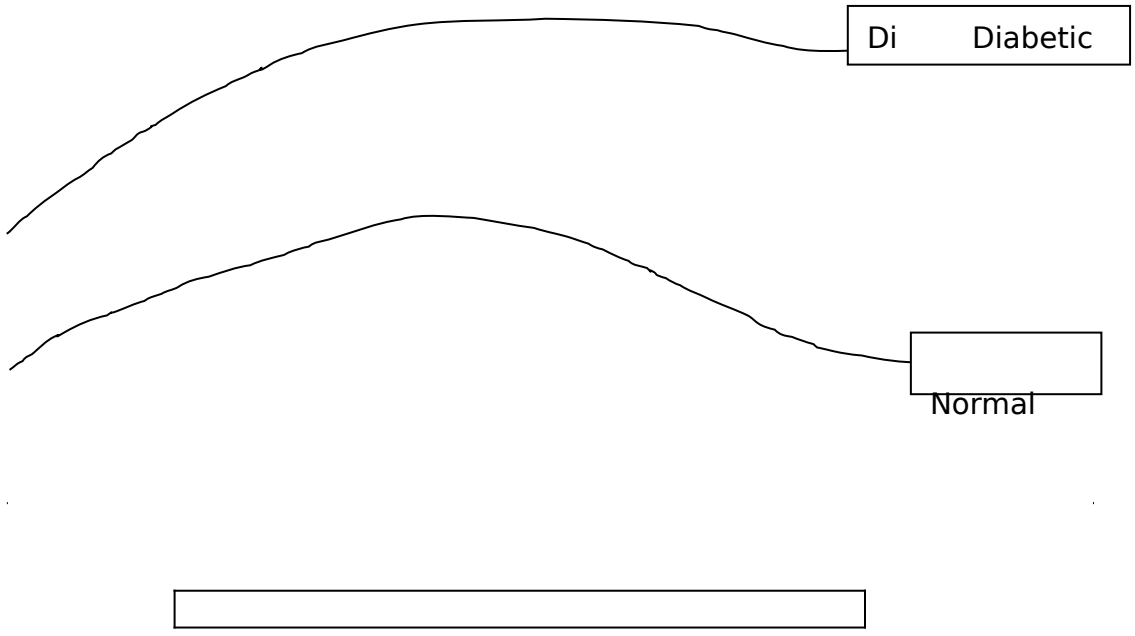
Sample Method

- It is important to stress that the diagnosis criteria stated above by the World Health Organisation (WHO) is for venous samples only i.e. a blood sample taken from a vein in the arm.
- An increasingly popular method for measuring blood glucose is from a capillary or finger-prick sample.
- This is less invasive, more convenient for the patient and requires minimal training to conduct.
- Whilst fasting blood glucose have been shown to be similar in both capillary and venous samples, postprandial blood glucose levels (those measured after a meal) can vary.
- Therefore the diagnosis criteria issued by the WHO should only be used for venous blood samples.
- Given the increasing popularity of capillary testing the WHO has recommended that a conversion factor between the two sample types be calculated.
- To date no conversion factor has been issued by the WHO despite some medical professionals adopting their own.

Variations

A standard 2 hour OGTT is sufficient to diagnose or exclude all forms of diabetes mellitus at all but the earliest stages of development. Longer tests have been used for a variety of other purposes, such as detecting reactive hypoglycemia or defining subsets of hypothalamic obesity. Insulin levels are sometimes measured to detect insulin resistance or deficiency.

The OGTT is of limited value in the diagnosis of reactive hypoglycemia, since (1) normal levels do not preclude the diagnosis, (2) abnormal levels do not prove that the patient's other symptoms are related to a demonstrated atypical OGTT, and (3) many people without symptoms of reactive hypoglycemia may have the late low Glucose.



Factors affecting GGT

Glycated hemoglobin

Glycated hemoglobin or **glycosylated hemoglobin** (*hemoglobin A1c, HbA_{1c}, A1C*, or Hb_{1c}; sometimes also **HbA1c**) is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. It is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose. Normal levels of glucose produce

a normal amount of glycated hemoglobin. As the average amount of plasma glucose increases, the fraction of glycated hemoglobin increases in a predictable way. This serves as a marker for average blood glucose levels over the previous months prior to the measurement.

In diabetes mellitus, higher amounts of glycated hemoglobin, indicating poorer control of blood glucose levels, have been associated with cardiovascular disease, nephropathy, and retinopathy. Monitoring HbA_{1c} in type 1 diabetic patients may improve outcomes.

Principle

Glycation of proteins is a frequent occurrence, but in the case of hemoglobin, a nonenzymatic reaction occurs between glucose and the N-end of the beta chain. This forms a Schiff base which is itself converted to 1-deoxyfructose. This rearrangement is known as Amadori rearrangement. When blood glucose levels are high, glucose molecules attach to the hemoglobin in RBCs. The longer hyperglycemia occurs in blood, the more glucose binds to red blood cell and the higher the glycosylated hemoglobin.
Glucose levels are intermittently raised in portal vessels carrying absorbed glucose to the liver for regulation. Passing red cells will have increased glycation after sugary drink or porridge (citation?).
Once a hemoglobin molecule is glycated, it remains that way. A buildup of glycated hemoglobin within the red cell, therefore, reflects the average level of glucose to which the cell has been exposed during its life-cycle. Measuring glycated hemoglobin assesses the effectiveness of therapy by monitoring long-term serum glucose regulation. The HbA_{1c} level is proportional to average blood glucose concentration over the previous four weeks to three months. Some researchers state that the major proportion of its value is weighted toward the most recent 2 to 4 weeks

Measuring HbA1c

There are a number of techniques used to measure A1C.
Laboratories use:

- High-performance liquid chromatography (HPLC): The HbA1c result is calculated as a ratio to total hemoglobin by using a chromatogram.
- Immunoassay
- Enzymatic
- Capillary Electrophoresis

Point of care (e.g., doctor's office) devices use:

- Immunoassay
- Boronate affinity chromatography

In the United States, A1C testing laboratories are certified by the National Glycohemoglobin Standardization Program (NGSP) to standardise them against the results of the 1993 Diabetes Control and Complications Trial (DCCT). There is an additional percentage scale, Mono S, that is in use by Japan and Sweden.

Interpretation of the results

Laboratory results may differ depending on the analytical technique, the age of the subject, and biological variation among individuals. Two individuals with the same average blood sugar can have A1C values that differ by as much as 3 percentage points. Results can be unreliable in many circumstances, such as after blood loss, for example, after surgery, blood transfusions, anemia, or high erythrocyte turnover; in the presence of chronic renal or liver disease; after administration of high-dose vitamin C; or erythropoetin treatment.[14] In general, the reference range (that found in healthy persons), is about 20–40 mmol/mol (4%–5.9%).[15]

Higher levels of HbA_{1c} are found in people with persistently elevated blood sugar, as in diabetes mellitus. While diabetic patient treatment goals vary, many include a target range of HbA_{1c} values. A diabetic person with good glucose control has a HbA_{1c} level that is close to or within the reference range. The International Diabetes Federation and American College of Endocrinology recommend HbA_{1c} values below 48 mmol/mol (6.5%), while American Diabetes Association recommends that the HbA_{1c} be below 53 mmol/mol (7.0%) for most patients.[16] Recent results from large trials suggest that a target below 53 mmol/mol (7%) may be excessive: Below 53 mmol/mol (7%) the health benefits of reduced A1C become smaller, and the intensive glycemic control required to reach this level leads to an increased rate of dangerous hypoglycemic episodes

C-PEPTIDE LEVELS TEST

A C-peptide test measures the level of this peptide in the blood. It is generally found in amounts equal to insulin. C-peptide is found in amounts equal to insulin because insulin and C-peptide are linked when first made by the pancreas. Insulin helps the body use and control the amount of sugar (glucose) in the blood. Insulin allows glucose to enter body cells where it is used for energy. The level of C-peptide in the blood can show how much insulin is being made by the pancreas. C-peptide does not affect the blood sugar level in the body. See a picture of the pancreas.

A C-peptide test can be done when diabetes has just been found and it is not clear whether type 1 diabetes or type 2 diabetes is present. A person whose pancreas does not make any insulin (type 1 diabetes) has a low level of insulin and C-peptide. A person with type 2 diabetes has a normal or high level of C-peptide.

A C-peptide test can also help find the cause of low blood sugar (hypoglycemia), such as excessive use of medicine to treat diabetes or a noncancerous growth (tumor) in the pancreas (insulinoma). Because man-made (synthetic) insulin does not have C-peptide, a person with a low blood sugar level from taking too much insulin will have a low C-peptide level. An insulinoma causes the pancreas to release too much insulin, which causes blood sugar levels to drop (hypoglycemia). A person with an insulinoma will have a high level of C-peptide in the blood.

ANTI-DIABETIC DRUGS

INSULIN

• Insulin is the mainstay of treatment in type 1 diabetes but is also used in type 2 when oral hypoglycaemics become ineffective.

• The initial source of insulin for clinical use in humans was from cows, pigs or fish pancreases. Insulin from these sources is effective in humans as they are nearly identical to human insulin (two amino acid difference for bovine insulin, one amino acid difference for porcine). Insulin is obviously a protein which has been very strongly conserved across evolutionary time.

• Human insulin is now manufactured for widespread clinical use using genetic engineering techniques, which significantly reduces impurity reaction problems.

ORAL AGENTS

Sulphonylureas

• These drugs were discovered by chance when it was noted that a sulphonamide derivative used for treating typhoid, caused marked hypoglycaemia.

• Sulphonylureas increases insulin secretion by closing the ATP-sensitive K channel on the β-cell membrane resulting in its depolarization and release of insulin. Examples include glibenclamide and chlorpropamide (not safe in renal impairment - can cause prolonged hypoglycaemia in patients with renal impairment).

• Meglitinides are related to sulfonylureas. The amplification of insulin release is shorter and more intense, and they are taken with meals to boost the insulin response after each meal.

Biguanides

• Improves insulin sensitivity by increasing glucose utilisation by skeletal muscle and also decreases hepatic gluconeogenesis. Exactly how biguanides go about in causing these effects are not well understood but a study in 2001(Zhou G et al) has indicated that they probably work by increasing cellular AMP-kinase levels. Metformin is the most widely known and used drug in this class and is frequently prescribed to overweight patients as it also promotes weight loss.

α-Glucosidase Inhibitors

• Inhibit the enzymes that catalyse the metabolism of carbohydrates in the intestines resulting in poor absorption of carbohydrates and a reduction postprandial glucose rise. Good for overweight patients.

• Undigested starch may reach the colon where it is fermented, resulting in abdominal discomfort and flatulance. This drug is used less commonly nowadays.

Thiazolidinediones

• A chance observation has also lead to the discovery of these drugs. A clofibrate analogue, ciglitazone was unexpectedly found to lower blood glucose.

• They increase insulin sensitivity by binding to a nuclear receptor called PPAR-γ (peroxisome proliferator – activated receptor-γ).

• PPAR-(forms part of a nuclear receptor family that regulates the expression of several genes and encodes proteins that regulate adipocyte differentiation as well as lipid and glucose metabolism in adipose and skeletal muscle. Examples are drugs like rosiglitazone and pioglitazone.

New developments

• The search for an oral form of insulin continues, since it would have enormous financial implications for the pharmaceutical company who can develop such a drug.

• Other experimental drugs with novel mechanism of action include drugs that increase glukokinase sensitivity and fructose 1.6-biphosphatase inhibitors.