Diabetes type 1

History

IS IT TYPE 1 OR 2 ??

extremely important, since patients with type 1 diabetes are dependent on a continuous source of exogenous insulin and carbohydrate for survival.

Duration of diabetes:
The chronic complications of diabetes are related to the length of time the patient has had the disease.

Diabetes care: Inquire about insulin type, dose, and frequency; oral antidiabetic agents, if any; and adherence to a specific diet or program of regular exercise.

Treatment monitoring
Does the patient self-monitor blood glucose?
Note the frequency and range of values at each time of day.
Note date and value of last glycosylated hemoglobin (HbA1c) level

Hyperglycemia
Does the patient give a history of recent polyuria, polydipsia, nocturia, or weight loss?
Are frequent infections a problem?

Hypoglycemia
when, how often, and how the patient treats these episodes.
Note whether the patient has hypoglycemia unawareness (ie, lacks the adrenergic warning signs of hypoglycemia).

Microvascular complications
When was the last dilated eye exam? What were the results?
Is the patient known to have kidney disease?
What were the dates and results of the last measurements of urine protein and serum creatinine?

Macrovascular complications
Does the patient have hypertension?
What medications are taken?
Does the patient have coronary artery disease (CAD)?
Does the patient have a family history of CAD?
Does the patient have symptoms of claudication or a history of vascular bypass?
Has the patient had a cerebrovascular accident or transient ischemic attack?
What are the patient's most recent lipid levels? Is the patient taking lipid-lowering medication?
Does the patient have a history of neuropathy?
Are symptoms of peripheral neuropathy or autonomic neuropathy present (including impotence if the patient is male)?
Does the patient have a history of foot ulcers or amputations? Are any foot ulcers present?

Findings on Examination

LOOK:
Dehydrated?
Comatose?
Kussmaul Breathing ("air hunger", deep and rapid) = ketoacidosis
Obese? (type 2)
Recent weight loss
Abnormal endocrine face? Eg. cushings, acromegaly?
Pigmentation: bronze? = haemochromatosis

BEGIN WITH LOWER LIMBS: Skin:
Hairless and atrophied with loss of subcutaneous tissue
Ulcers
Infections, eg. cellulitis, boils, fungus
Pigmented scars
Fistulae with underlying abscess
Muscle wasting
Charcots joint (horribly swollen due to repeated injury)

PALPATE LEG PULSES and TEMPERATURE OF EXTREMITIES
Check capillary return
Auscultate femoral and popliteal bruits
!!! Neuro exam @ the lower limbs !!!

UPPER LIMBS:
Look at the injection sites

Blood pressure lying and standing (autonomic neuropathy)

EYES
Test visual acuity
Look for Argyll-Robertson pupil (accommodates but does not react to light)
Cataracts
FUNDOSCOPY
Look for proliferative retinopathy, dot-and-blot haemorrhages and microaneurysms
NEURO EXAM OF CN 3, 4, 6 (diabetic 3rd nerve palsy affects movement but not the pupil reflex)
EARS:
Infected?
MOUTH
Candida thrush?
NECK + SHOULDERS:
Carotids: bruit?
Scleroderma?
Acanthosis nigricans?
ABDOMEN:
hepatosplenomegaly?
Tests and Investigations: looking at the EXTENT OF COMPLICATIONS

**Pinprick Glucose Spot-Test** is fine in an emergency situation (e.g., comatose presentation)

**Blood Glucose (the Laboratory Assay)** is indicated when you have the time

**Glycosylated Hemoglobin (Hemoglobin A1C):**
- to gauge the average glucose levels of the last 120 days

**Urinalysis →** to look for signs of nephropathy, e.g.
- **DIPSTICK** is ok for proteinuria and hematuria of chronic renal failure
- **LABORATORY ANALYSIS** is necessary for the assay of microalbuminuria of early presenting diabetic nephropathy

**Electrolytes →** looking predominantly for ACIDOSIS

**Free T4 and TSH →** to rule out hypo/hyperthyroid as the reason for derangement

**Oral Glucose Tolerance Test:** rarely indicated, mainly as screening for gestational diabetes

A fasting C-peptide level = measuring a co-secreted product of the beta cells

**Measurement of islet-cell and antiinsulin autoantibodies...**

**Table 333-2: Criteria for the Diagnosis of Diabetes Mellitus**
- Symptoms of diabetes plus random blood glucose concentration $\geq 11.1$ mmol/L (200 mg/dL)$^a$
- Fasting plasma glucose $\geq 7.0$ mmol/L (126 mg/dL)$^b$
- Two-hour plasma glucose $\geq 11.1$ mmol/L (200 mg/dL) during an oral glucose tolerance test$^c$

In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

**Prognosis**
- Diabetes is the major cause of blindness in adults aged 20-74 years,
- the leading cause of nontraumatic lower-extremity amputation
- the leading cause of end-stage renal disease

**Epidemiology**
- Whites seem to be affected more often than blacks
- Males as often as females
- Incidence peak is in adolescence
- Type 1 Diabetes occurs in 10-15% of all cases of Diabetes.
- Scandinavia has the highest rate of type 1 DM
  - in Finland, incidence is 35/100,000 per year
  - Much of the increased risk of type 1 DM is believed to reflect the frequency of high-risk HLA alleles among ethnic groups in different geographic locations.

Although the prevalence of both type 1 and type 2 DM is increasing worldwide, the prevalence of type 2 DM is expected to rise more rapidly
Managing the Diabetic

This is what group 10 had decided to do; the actual PBL case is managed less aggressively by the cowardly faculty.

<table>
<thead>
<tr>
<th>GOALS</th>
<th>OPTIONS</th>
<th>QUALIFYING FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMMEDIATE: Resolve ketoacidosis and dehydration</td>
<td>Cannulate and replace fluids: Slow saline drip with 5%dextrose</td>
<td>For some reason bicarbonate IV is a last-ditch measure (Rational explanation for this is pending)</td>
</tr>
<tr>
<td></td>
<td>Give fast-acting insulin IM; Give glucose 10 minutes after (as initial insulin injection will cause the glucose to fall dramatically, thus avoid hypo attack)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Give bicarbonate intravenously ONLY if completely acidic and on the brink of coma</td>
<td></td>
</tr>
<tr>
<td>IMMEDIATE: Manage infection empirically</td>
<td>Gentamycin and amoxycillin bolus through IV cannula</td>
<td>Justification for IV antibiotic cocktail is the presence of a raging cellulitis, high temperature AND ketoacidosis. Before the blood cultures come back it would be prudent to just assume that Gram-negatives are holidaying in Mary’s bloodstream and she’s on the brink of DIC. Lesion may need debriding so those anaerobes don’t have anywhere to hide.</td>
</tr>
<tr>
<td></td>
<td>Inspect lesion and debride if necessary</td>
<td></td>
</tr>
<tr>
<td>SHORT TERM EDUCATE</td>
<td>Show how to inject insulin. Explain why its necessary. Explain what will happen if she doesn’t. Show how to self-test for glucose Book monitoring program in diabetes clinic Advise to increase fluid intake Advice to EXAMINE FEET DAILY while she still has feet Engage partner in discussion + management education: social support = better compliance</td>
<td>COMPLIANCE might decline after symptoms resolve</td>
</tr>
<tr>
<td>SHORT TERM Manage Infection</td>
<td>Wait for cultures until managing orally with the sensitivity-exploiting antibiotic (in this case flucloxacillin)</td>
<td>Oral antibiotics are sufficient now that you’re certain its not a systemic sepsis situation. Topical creams for mucosal opportunistic infections</td>
</tr>
<tr>
<td>SHORT TERM Discuss the issue of occupation</td>
<td>The RTA have to know (namely, the DLA, Drivers Licensing Authority). However the physician is not obliged to dob the patient in- UNLESS the patient is somehow cognitively unable to understand that its dangerous to drive while diabetic; OR the patient understands but is not willing to consider the doctor’s advice. IN WHICH CASE: you have to dob them in. BUT: you also HAVE TO TELL THE PATIENT THAT YOU ARE DOBBING THEM IN. AND, of course, DOCUMENT EVERYTHING lest ye be sued. More info at <a href="http://www.austroads.com.au/aftd.html">http://www.austroads.com.au/aftd.html</a></td>
<td></td>
</tr>
<tr>
<td>LONG TERM MAINTENANCE OF GLUCOSE LEVELS WITHIN NORMAL RANGE</td>
<td>Long acting insulin twice daily Regular monitoring of glucose levels FOOT + VAGINA WATCH: don’t let the ulcers get too far; don’t let the candidiasis spread into peritoneum (eeew)</td>
<td>!!COMPLIANCE!!</td>
</tr>
</tbody>
</table>

**IDEAL GLUCOSE TARGETS**

<table>
<thead>
<tr>
<th>Index</th>
<th>Normal Range</th>
<th>Goal</th>
<th>Additional Action Suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average preprandial glucose, mmol/L (mg/dL)</td>
<td>&lt;5.5 (100)</td>
<td>4.4-6.7 (80-120)</td>
<td>&lt;4.4 (80) or &gt;7.8 (140)</td>
</tr>
<tr>
<td>Average bedtime glucose, mmol/L (mg/dL)</td>
<td>&lt;6.1 (110)</td>
<td>5.5-7.8 (100-140)</td>
<td>&lt;5.5 (100) or &gt;8.8 (160)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>&lt;6</td>
<td>&lt;7</td>
<td>&gt;8</td>
</tr>
</tbody>
</table>
INSULIN and the METABOLISM

The major signal for insulin secretion is a rise in blood glucose levels above 5 mM lower than 3 - 4 mM = brain starvation. above 9-10 mM for a while = cellular damage

INSULIN is:
- Small polypeptide, weight 5000
- 2 chains, A and B joined by disulfide bonds
- Structurally homologous to insulin-like growth factors 1 and 2 (IGF-1 and -2) and also to the ovarian hormone, relaxin
- Secreted in pulses every 10 min
- A t 1/2 of 3 minutes.
- About 50% is removed by the liver

Also stimulated by gastrointestinal hormones and sympathetic nerves which stimulate insulin release via beta-adrenergic receptors (and inhibit via alpha-adrenergic receptors)

INCREASED Amino Acids @ bloodstream
INCREASED Fatty Acids (minor effect)

FACILITATED DIFFUSION of trigger into the cell where K+ channels close and Ca++ channels open, thus DEPOLARISING the Islet beta-cell

IMMEDIATELY:
Insulin is released from storage granules (if this peak is blunt and low, you may have diabetes)

SLOWLY:
Insulin is synthesised de novo by the below mechanism:

Preproinsulin mRNA is transcribed
Preproinsulin is inserted into the Endoplasmic reticulum; thus signal protein is removed, making it PROINSULIN: a 3-part peptide
CLEAVAGE by endopeptidases
C-Peptide is co-secreted with insulin
Ready INSULIN is packaged by the golgi apparatus into secretory granules and is left hanging around in the cytoplasm

THE EFFECTS: “pleiotropic” insulin is the BUILDER
- Stimulates the use and storage of carbohydrate by promoting the synthesis of macromolecular fuel stores such as glycogen and lipid.
- Insulin also has powerful anti-degradative effects and inhibits the breakdown of glycogen, lipid and protein.
- Insulin stimulates the synthesis of protein.
- Insulin can modulate the transcription and translation of many genes and can stimulate the division (mitosis) of cells

@ LIVER, FAT and MUSCLE: glucose homeostatic effects:

FAT AND MUSCLE: insulin binding to receptor causes vesicles with GLUT-4 hexose transporters to fuse with the membrane of the cell; THUS:
INCREASE IN GLUCOSE UPTAKE BY GLUT-4
When the glucose concentration falls, GLUT-4 is withdrawn back into the cytoplasm.
Insulin inhibits breakdown of fat in adipose tissue by inhibiting the intracellular lipase that hydrolyzes triglycerides to release fatty acids.
Insulin also increases triglyceride synthesis by increasing uptake and synthesis of glycerol, and upregulation of pyruvate dehydrogenase, acetyl CoA carboxylase, and fatty acid synthetase.

BRAIN AND LIVER DO NOT REQUIRE INSULIN TO SUCK UP THEIR GLUCOSE!!

@ LIVER: insulin stimulates GLYCOGEN SYNTHESIS
- Upregulates hexokinase, which traps glucose in cells by phosphorylating it. Also disables glucose-6-phosphatase
- PLUS: activates phosphofructokinase and glycogen synthase
- THUS: increased glycogen synthesis and storage
When the liver is saturated with glycogen (~5% of liver mass!), any additional glucose taken up by hepatocytes is shunted into pathways leading to synthesis of fatty acids, which are exported from the liver as lipoproteins.

@ EVERYWHERE: nuclear and protein synthesis effects
- Increased uptake of amino acids, and decreased proteolysis
- Increased permeability to magnesium, potassium and phosphate (eg. Na+/ K+ ATPase is activated, depleting K+ from the ECF)
- Inhibits the release of cAMP which phosphorylates all those glycogen-cleaving enzymes; THUS the fuel is stored

The insulin receptor is a tyrosine kinase. In other words, it functions as an enzyme that transfers phosphate groups from ATP to tyrosine residues on intracellular target proteins. Binding of insulin to the alpha subunits causes the beta subunits to phosphorylate themselves (autophosphorylation), thus activating the catalytic activity of the receptor. The activated receptor then phosphorylates a number of intracellular proteins, which in turn alters their activity, thereby generating a biological response.

1. Insulin levels decline
2. Glucose uptake decreases because GLUT-4 transporters are withdrawn from cell surfaces
3. In absence of insulin inhibition, cAMP is free to phosphorylate lytic enzymes:
   - @ LIVER: glycogen phosphorylase
     - degrades glycogen, releasing glucose into the bloodstream
     - this is good; brain needs over 4mM/L of glucose
   - @ADIPOCYTE: triacylglycerol lipase,
     - which catalyses the release of fatty acids and glycerol
     - this is OK, but brain can’t use fatty acids.
     - BUT everything else can, thus muscle fat and liver cells switch to using fatty acids so as to save the glucose for the brain
     - ALSO: fatty acid oxidation inhibits PYRUVATE DEHYDROGENASE (enzyme which converts Pyruvate into Acetyl CoA)
     - THUS: no wasteful glucose oxidation. Glucose can be recycled!
     - Instead of turning into acetyl CoA irreversibly, pyruvate is converted into lactate which is transported into the liver and turned into glucose again

4. PROLONGED EXPOSURE TO SO LITTLE INSULIN results in massive lipolysis (!)
   - Excess fatty acids are thus released into the bloodstream
   - They are converted into ketone bodies by the liver;
   - BECAUSE the brain can slowly nibble on ketone bodies but not on fatty acids

5. Plus there is !! massive PROTEOLYSIS !! which means some glucose is still available (some amino acids can be turned into glucose by the liver)

Diabetes Type 1
- CHRONIC HYPOINSULINAEMIA = GREAT HARM
- Disposal of glucose from the bloodstream is impaired: THUS after a meal...
- CONCENTRATION WILL RISE ABOVE 10mM (glucose will appear in urine at this stage)
- Later, UNCONTROLLED LIPO+PROTEOLYSIS = release of fatty acids and ketone bodies
- THUS inhibition of carbohydrate metabolism by switching off of pyruvate dehydrogenase
- So much glucose! THUS osmotic changes: glucose in blood starts draining water from the tissues!
- THEREFORE CELLULAR DEHYDRATION RESULTS:
  - Hence, UNQUENCHABLE THIRST and frequent urination (kidney expells water and glucose)
  - So much acid (ketones, lactic acid, fatty acids) in the bloodstream upsets the pH:
  - THUS: ACIDOSIS (KETOACIDOSIS)
  - And, from proteolysis/lipolysis, ENORMOUS + RAPID WEIGHT LOSS

HYPOGLYCAEMIA
The brain loves its glucose, will do anything to maintain normal levels.
Its acts of desperation in the face of falling glucose concentration are as follows:
DECREASE INSULIN SECRETION thus, less glucose taken up into fat and muscle
INCREASE
- GLUCAGON thus more glycogen breakdown
- ADRENALINE
- GROWTH HORMONE
- CORTISOL
GLUCOSE LEVELS STILL FALLING DESPITE COUNTERMEASURES? ➔ NEUROGLYCOGENIC SYMPTOMS: brain is starving!
➔ headache, altered mental status, visual disturbances, neurological deficit and seizures.

Common causes of hypoglycaemia
- increased physical activity with insufficient food,
- consumption of alcohol (which inhibits gluconeogenesis),
- delayed or missed meals,
- errors in insulin dose or inappropriate insulin regimens.
- many episodes of hypoglycaemia have no identifiable precipitating factor.

Management of hypo attacks:
- ingestion of 15 to 20 G of oral glucose (eg. 6-7 jelly beans OR 150 mls normal Coke)
- followed by some complex carbohydrate (eg. a slice of bread OR a piece of fruit),
- patient is unconscious? treat with either an intravenous injection of glucose (50%),
- or an intramuscular injection of glucagon, followed by ingestion of complex carbohydrate as soon as the patient regains consciousness.

Within normal range: insulin regulated
Below 3.8 mmol/L: hormonal response with glucagon, adrenaline etc.
Below 3 mM/L: symptoms of hypo
Below 2.7mM/L: cognitive dysfunction

Sympathetic symptoms of hypo attack: tremor, tachycardia, palpitations, sweating, weakness.

This response may become blunted after years of hypoglycemia; thus patient may be unaware of having a hypo

Near-Normoglycaemia ➔ less pathology BUT ➔ more chances of hypoglycaemia
THUS if you’re at risk of sever hypo (eg. have had them recently and en masse) its better to be slightly hyperglycemic
So, You’ve Got Ketoacidosis.  

!!! Keep that pH between 7.37 and 7.45 !!!

Normally, blood is slightly alkaline: proteins suspended in it are alkaline, plus there is the bicarbonate and phosphate. However, it also contains carbonic acid. Thus there is a balance between the main acid and the main base.

**THEREFORE:**
- Acetacacetate and beta-hydroxybutyrate are acidic molecules which release H⁺ ions;
- These H⁺ ions react with bicarbonate to form carbonic acid; 
- Thus, blood becomes even more acidic but its good CO₂ acid and can be exhaled;
- ...Which is indeed what happens: “Kussmaul’s breathing”-style hyperventilation;
- This happens because of rising acidity of the blood as sensed by the respiratory centres at the open medulla (floor of 4th Ventricle).

**MEANWHILE AT THE KIDNEY:**
- Bicarbonate ions are resorbed so as to keep some alkali in the bloodstream while the lungs puff out all that acidic CO₂.
- PLUS tubule cells create new bicarbonate.
- PLUS the same cells excrete ammonia in the urine...
- ...Which scavenges H⁺ ions and thus also de-acidifies the blood.
- PLUS you can also excrete amino acidsthis way.

**THEREFORE** slowly does the balance creep back into place between 7.37 and 7.45 pH.

---

**GENETICS OF TYPE 1 DIABETES**

Autoimmune destruction of beta cells in pancreas: CAUSE UNKNOWN.

**NO ONE SINGLE GENE RESPONSIBLE!!**

Associated genes: diabetes is more likely in Caucasians if these genes are expressed:

- HLA DR type 3 and or 4
- HLA DQ β an amino acid other than aspartate in position 57
- HLA DQA the amino acid arginine in position 52

**amino acid aspartate in position 57 on DQ β conveys protection from developing diabetes. (!)**

**If one concordant twin develops diabetes, the other twin has only a 50% chance of developing this disorder.**

Thus there are non-genetic factors which affect the expression of the genetic material.

**INHERITANCE:**
- Generations are often skipped
- Risk is higher if the father has diabetes (rather than mother)
- Families with inherited Type 1 diabetes are at NO HIGHER RISK of developing Type 2

**PREDICTING THE LIKELIHOOD:** look for
- Antibodies to islet cells,
- Antibodies to insulin
- Antibodies for glutamic acid decarboxylase.

- Can be detected in the serum of more than 90% of patients with newly diagnosed Type 1 diabetes.

**These antibodies can also be detected prior to diagnosis**

Factors associated with a higher risk of progression to Type 1 diabetes are:
- Younger age,
- Presence of multiple autoantibodies in serum,
- Finding of low first phase insulin production in a glucose challenge test
- HLA identity with the relative who has Type 1 diabetes.

In addition, anti-islet autoantibodies have been detected in the serum of patients presenting with clinical features of Type 2 diabetes, but who progress to require insulin more rapidly. These patients are thought to have “slowly progressive Type 1 diabetes” and could account for up to 10% of patients presenting with apparent Type 2 diabetes.

Despite the strong familial association of Type 1 diabetes it should be emphasised that **90% of individuals developing the disease do not have an affected first degree relative.**

Thus, if preclinical screening and prevention are to become a reality, it will be critical to develop methods by which those without a first degree relative with Type 1 diabetes, destined themselves to develop Type 1 diabetes can be identified.
GOOD CONTROL OF GLUCOSE LEVELS
= EQUALS =
FEWER MICROVASCULAR COMPLICATIONS
...but:
NO CHANGE IN MACROvascular effects
(which depend more on cholesterol and blood pressure)

DIABETIC RETINOPATHY
= one of the most common causes of new blindness.

Background retinopathy =
- weakening,
- rupture
- leakage
- occlusion of blood vessels
- manifest as
  - microaneurysms,
  - dot and blot haemorrhages,
  - hard exudates (lipid deposits)
  - cotton-wool spot ischaemic exudates, due to localised arteriolar occlusion.

In proliferative retinopathy, new fragile vessels form on the retina,
= substantial risk of rupture with haemorrhage.

Maculopathy, occurring more in Type 2 diabetes,
= swelling, exudate or haemorrhage close to the macula.

due to privacy considerations,
doctors are not generally required to inform authorities that their patients have diabetes
unless it is considered to be absolutely necessary.
They should only do so after discussing with the patients.

DIABETIC NEPHROPATHY
characterised by
- proteinuria,
- hypertension,
- oedema
- renal insufficiency.

= affects approximately 30% of people with Type 1 diabetes.
INCIDENCE IS IMPROVING
due to improved diabetic and blood pressure control.

CHRONOLOGY of PATHOGENESIS:
2-3 years from diagnosis of diabetes:
- some histological evidence of mesangial expansion and basement membrane thickening
  accumulation of these extracellular matrix materials is central to the development of nephropathy.

microalbuminuria, after many years progresses to overt proteinuria.
A patient with microalbuminuria has 10-20 fold increased risk of developing diabetic nephropathy.
Levels of 20-200ug/min, may be reversed with intensive glycaemic control, treatment of blood pressure and by ACE inhibitors,
even in normotensive patients.

Microalbuminuria in Type 2 diabetes also indicates severe vascular disease.
Those with overt proteinuria (>0.5gm/day) must have their hypertension aggressively managed.
By this stage, deterioration is inevitable and improving glycaemic control is of less benefit.
If end stage renal failure ensues, dialysis or transplantation are the options.

DIABETIC NEUROPATHY
most common = sensory neuropathy
, mainly affecting the lower limbs,
"stocking and glove distribution".
Patients may complain of pain, paraesthesia or numbness at these sites.
Paradoxically, some with chronic neuropathy have no symptoms, but physical examination reveals a loss of sensation which predisposes to foot ulceration.
It is therefore important to look for neuropathy irrespective of whether a patient complains of any symptom.

MACROVASCULAR DISEASE
= affect coronary arteries, peripheral and cerebral vessels.
They are commoner, occur at an earlier age, and are more extensive and severe in diabetes.
Diabetes = independent risk factor for cardiovascular disease !! AS BAS AS HAVING HAD A PREVIOUS ATTACK !!
Patients with microalbuminuria or proteinuria have increased risk of cardiovascular death
Controlling glucose levels does nothing. ACE inhibitors seem to help normotensive diabetics.
MUST ALSO CONTROL ChOLESTEROL !!
Diabetic foot disease : Neuropathy + microvascular disease = gangrene, ulceration, infection.
About 25% of all patients with diabetes will require insulin therapy.
This includes everyone with Type 1 diabetes
PLUS a proportion of patients with Type 2 diabetes in whom oral therapy has failed.

In patients with Type 1 diabetes, insulin is essential in preventing death from ketoacidosis.
Insulin also relieves symptoms of hyperglycaemia. In addition, an important goal of insulin therapy is to maintain a near-to-normal blood glucose concentrations to prevent development of diabetic complications. Tight metabolic control before and during pregnancy is also essential to minimise the risk of fetal abnormalities and to prevent maternal ketoacidosis during pregnancy.

An essential prerequisite for successful insulin therapy is for all patients and their immediate family to
- receive practical education about giving insulin,
- avoid metabolic complications (eg. hypoglycaemia) by keeping the blood glucose levels within the normal range (3.5 - 7 mmol/L),
- and monitoring blood glucose levels at home.

Ideally this training should be given by a specialised diabetes nurse educator.

Insulin must be given parenterally because it is degraded by proteolytic enzymes in the gastrointestinal tract.

After subcutaneous injection, the absorption and therefore the therapeutic action of insulin can vary considerably both between but also within individuals. This variability is one of the major reasons for the difficulties encountered in trying to maintain normoglycaemia in a diabetic individual. The major route of elimination of insulin is via cellular uptake, by internalisation of the insulin-receptor complex in liver and muscle.

The plasma half-life for insulin is 4 minutes.

Most insulin used nowadays is human insulin derived biosynthetically using recombinant DNA techniques.

Classification of Insulin:
The various formulations of insulin vary in their absorption profile and duration of action. Patients are usually treated with a combination of insulins, to provide their tissues with appropriate insulin availability throughout the day.

i. **Short acting insulin (synthetic soluble or regular)**
   This is a solution of insulin (clear to inspection) with an onset of action within 30 mins of subcutaneous injection and a duration of effect of 6-8 hours. This can be given intravenously or intramuscularly in emergencies.

ii. **Intermediate-acting insulin (synthetic isophane or NPH)**
   This is a complex of insulin (cloudy to inspection) bound to a fish protein known as protamine, which is non-immunogenic; the insulin is released gradually in the tissues and absorbed into the circulation.

iii. **Long-acting insulin**
    Insulin is complexed with zinc to form an insulin zinc suspension (IZS). IZSs are either amorphous with intermediate duration of action or crystalline with a more prolonged action. Intermediate and long-acting insulins have an onset of action about 1-2 hours after subcutaneous injection, a maximal effect at 4-12 hours, and a duration of action of 16-35 hours.

iv. **Very rapid and short acting insulin**
   These are analogues of human insulin with minor modifications to the amino acid sequence of the native hormone. As a result they are absorbed very rapidly and have a short acting time of 2-3 hours. Their injection must be followed immediately by a meal (ie. quite different from conventional insulins). They are best given before each meal to control the post-prandial hyperglycaemia. Their short action means they are less likely to cause hypoglycaemia.

v. **Pre-mixed insulin**
   Some insulins contain a mixture of short (or very short) acting insulin with longer acting insulin. They are very popular because they are more convenient for some patients.

vi. **Very long acting insulin**
   Two very long acting insulins have been developed (~ 24 hours in duration of action). Glargine is an insulin chemically modified so that it has an isoelectric pH which renders it insoluble after injection. It is therefore absorbed slowly. Detemir is an insulin which binds to albumin from which it is released slowly, again giving it a prolonged action. These very long acting insulins are particularly suitable to provide a basal level of insulin and complements with the injections of short acting insulin before each meal.

### Table 332-8: Nutritional Recommendations for All Persons with Diabetes

- **Protein** to provide ~10-20% of kcal/d (~10% for those with nephropathy)
- **Saturated fat** to provide <10% of kcal/d (<7% for those with elevated **LDL**)
- **Polyunsaturated fat** to provide ≤10% of kcal
- **Remaining calories** to be divided between carbohydrate and monounsaturated fat, based on medical needs and personal tolerance
- **Use of caloric sweeteners**, including sucrose, is acceptable. Sugars must be accounted for so that the insulin demand they create is matched to available insulin
- **Fiber (20-35 g/d)** and sodium (≤3000 mg/d) levels as recommended for the general healthy population
- **Cholesterol intake** ≤300 mg/d
- **The same precautions** regarding alcohol use in the general population also apply to individuals with diabetes. In addition, alcohol may increase risk for hyperglycaemia and therefore should be taken with food.
Organism: widely occurring soil fungus Candida Albicans

It is a yeast which occurs mainly as single cells (blastospores) though elongated forms (pseudohyphae) are also seen. They are about 5 micrometres in diameter and are easily recognised by direct microscopy (stained or unstained). They also grow on many common bacteriological media within 24-48 hours, but better on special fungal media (e.g. Sabouraud's medium). They are usually acquired from the environment (especially in foods) but may be transmitted sexually or to the child during birth.

Infections usually involve only mucous membranes (mainly oral cavity, vagina/vulva).

They cause an intense irritation (commonly called "thrush") leading to a raw, red mucosa, often with a white cheesy exudate, which consists of clumps of organisms. Although unpleasant, in most individuals deep tissue invasion does not occur and the infection is more an annoyance than a serious medical problem. Oral cavity infections are common in young children. Vaginitis and vulvitis are common in women of reproductive age. Some women have frequent recurrences after successful treatment. Infections in moist folded skin are also common e.g. under the prepuce, under pendulous breasts, in the groin folds (especially in babies with wet nappies).

Diagnosis

This is often clinically apparent, though identification (direct microscopy, culture) of yeasts from surface specimens is confirmatory. Culture and histology of deeper specimens may be necessary in deep-seated disease. Drug sensitivity testing is usually not performed as sensitivities are very predictable except when the patient has had significant prior exposure to antifungal drugs.

Treatment

1. Remove or modify the underlying predisposing cause, if possible.
2. Topical (usually creams, pessaries) poorly-absorbed drugs are used for mild to moderate mucosal infections (mainly the imidazole group or amphotericin).
3. Systemic drugs are given by mouth (imidazoles) or occasionally intravenously (imidazoles or amphotericin) for more serious infection.

Patients with diabetes mellitus, especially if poorly controlled, are generally more susceptible to infections, especially those caused by bacteria and fungi, than other individuals. Such infections are also associated with worse outcomes. The risk is substantially greater in the presence of ketoacidosis.

Common examples are:

Skin and soft tissue infections:
* furunculosis, cellulitis, and infected wounds (after either trauma or surgery);

Foot ulcers:
* diabetic patients often develop ulcers on the feet, in association with sensory loss from peripheral neuropathy. These may give rise to superficial cellulitis or extend into deeper structures (notably bones) where infection may occur (osteomyelitis)

Urinary tract infections:
* cystitis, pyelonephritis, complicated UTIs (associated with urinary obstruction, stones, pregnancy

Deep infections associated with surgery or other invasive medical interventions. Diabetes is associated with ischaemia from angiopathy and poor wound healing. These predispose to local infection which may give rise to systemic sepsis (septicaemia). The microorganisms causing these infections are usually similar in diabetic and nondiabetic patients.

BLOOD SUGAR TUTORIAL: Glycaemic index

Glycaemic index is the ability of a food to raise blood sugar
Western starchy foods, eg. white bread = HIGH index
Barley, legumes, pasta, wholegrain bread, pita and sourdough- not so much
LOW Gl eating = more satisfying and longer lasting energy
Chose low saturated fat.
Insulin signal transduction pathway. The insulin receptor has intrinsic tyrosine kinase activity and interacts with insulin receptor substrates (IRS and Shc) proteins. A number of “docking” proteins bind to these cellular proteins and initiate the metabolic actions of insulin [GrB-2, SOS, SHP-2, p65, p110, and phosphoinositot phosphate 3- kinase (PI 3-kinase)]. Insulin increases glucose transport through PI 3-kinase, which promotes the translocation of intracellular vesicles containing GLUT4 glucose transporter to the plasma membrane. (Adapted from Lowe, 1998; Virkamaki et al, 1999)

Temporal model for development of type 1 diabetes. Individuals with a genetic predisposition are exposed to an immunologic trigger that initiates an autoimmune process, resulting in a gradual decline in beta cell mass. The downward slope of the beta cell mass varies among individuals. This progressive impairment in insulin release results in diabetes when ~80% of the beta cell mass is destroyed. A “honeymoon” phase may be seen in the first 1 or 2 years after the onset of diabetes and is associated with reduced insulin requirements. (Adapted from Medical Management of Type 1 Diabetes, 3d ed, JS Skyler (ed). Alexandria, VA, American Diabetes Association, 1998)

Pancreatitis and Pancreatic Cancer At-A-Glance:

**PANCREATITIS:**

**Acute vs. Chronic**

Acute is worse!! → Hemorrhage, necrosis, infarction
Extremely scary, histologically: great big holes in parenchyma
(!! AUTODIGESTION !! Fat necrosis = because the lysis of pancreatic acinar cells releases LIPASES which rampage though)
Leucocytes infiltrate + inflame, thusmore destruction and necrosis
A MAJOR ARTERY MAY BECOME DIGESTED → HEMORRHAGE

**PANCREATIC CANCER:** “Why am I yellow, Doctor?”

→ asymptomatic at early stage
→ LATER = VERY PAINFUL
→ may result in jaundice
  weight loss
  malaise

KEY TO SURVIVAL is to STOP EATING
PATHOGENESIS OF TYPE ONE DIABETES

**Genetic predisposition**
- HLA-DR3, and/or DR4
- Caucasian race
- The other twin has a 50% chance the type of diabetes that is inherited is which runs in the family

**@ Birth the pancreas is normal**

**Loss of self-tolerance**

**CROSS-REACTIVITY**
- UNKNOWN viral antigen
- Coxsackie virus has been implicated

**An Aside: The Islets are concentrated in the tail of pancreas**

**Autoimmune reaction**

**Humoral:**
- Antibodies (IgG) vs.
  - Glutamic acid Decarboxylase (makes GABA)
  - Insulin
  - Phagin (insulin vesicle protein)
- None are specific to beta islet cells

**1st Cellular:**
- CD8 T-Lymphocytes are finding infiltrating the parenchyma of the pancreas during the first few months of diabetes (while there are still beta cells left)
- INDUCE OTHER RESPONSES

**Non-Specific:**
- Macrophages invade
  - Via T-cell mediated chemotaxis
  - Macrophages are responsible for destroying much of the pancreatic islets, and they in turn invite fibroblasts (with Fibroblast Growth Factor) which then fibrose everything with collagen.

**End result: Atrophic Changes**

**Honeymoon Period** → until at least 80% of beta cells are destroyed there are NO SYMPTOMS except impaired performance on glucose tolerance tests

**NO UPTAKE OF GLUCOSE BY MUSCLE AND FAT**
Hence, HYPERGLYCAEMIA

**No insulin @ hypothalamic safety centres means no glucose uptake and thus no signal to stop being hungry**

**Renal Threshold:** 15 mmol/L of glucose:
- Once this is reached, NO MORE GLUCOSE IS RESORBED AT THE DISTAL TUBULE:
- Thus, glucose is excreted in the urine, and it DRAGS WATER OUT OF THE CAPILLARIES WITH IT!

**Water is lost** and thus the blood volume fails

**Hypersomolarity:** increased glucose concentration and decreased water to dissolve all those electrolytes leads to the sucking of water out of cells:
- Eventually → INTRACELLULAR DEHYDRATION

**High Intracellular Glucose = some gets converted to sorbitol by the enzyme aldose reductase**

**Proteolysis** takes place because the tissues are convinced that there is not enough glucose;
- THEREFORE important muscle proteins are degraded, and eventually leads to weakness of respiratory muscles; in combination with increased ketoadicotic resp. drive, this leads to...

**Immune Effects:**
- Reduced adhesion, chemotaxis, phagocytosis, and T-cell maturation:
  - PLUS reduced healing due to dysfunctional supply of nutrients
  - PLUS increased glucose and ketone concentration makes the blood an excellent MEDIUM FOR CULTURING BACTERIA

**Microvascular effects:**
- Glycation of amino acid ends of proteins in blood vessel lumen → Hyaline Sclerosis (thickening of basement membranes)
  - PLUS: increased synthesis of diacylglycerol from excess glucose activates Protein Kinase C
  - And PKC activates transcription of Vasc. Endothel. Growth factor, Transforming growth factor Alpha, and others → THUS:
  - Increase in THICKNESS and THROMBOGENICITY OF VASCULAR ENDOTHELIUM → OBSTRUCTION

**MACROVASCULAR DISEASE**
- due to increased thrombogenicity and irregularity of endothelial surface, combined with diabetic hyperlipidaemia, microvascular changes result in macrovascular Atheroma

**@ renal tubules:** the capillaries undergo the same changes; therefore filtration is poor and protein escapes into the urine

**Lipolysis Continues uninhibited:** insulin is not there to oppose the actions of glucagon

**Free Fatty Acids At Liver**
- Are broken down by the mitochondria into KETONE BODIES such as:
  - Acetoacetate
  - Beta-Hydroxybutyrate
  - Acetone ('Smelly!')

**There is no insulin to switch the metabolism of fatty acids back to triglyceride synthesis, thus ketone production persists until KETOACIDOSIS OCCURS**

**Detachable signs and symptoms**

- **Increased Appetite**
- **Sweet Urine**
- **Hyperlipidaemia**
- **Characteristic Halitosis**
- **Polydipsia**
- **Confusion and Coma**
- **Reversible Lens Opacity**
- **Kussmaul Breathing**

**Death from Respiratory Arrest**

**Ketones dissociate, producing**

- H⁺ ions; thus **the pH drops**

- H⁺ ions then bind to Bicarbonate
  - Thus producing Carbonic Acid (CO₂)...
  - And depleting bicarbonate, THEN **MORE ACIDIC!**
  - **THIS CAN BE EXHALED TO DECREASE THE ACIDITY OF THE BLOOD...** WHICH IS INDEED WHAT HAPPENS.

**Heart Disease and Peripherals Vascular Disease**

**First, Microalbuminuria; then overt proteinuria**

**Heart Disease and Peripheral Vascular Disease**

**Reduced excretion of bicarbonate**
- Increased excretion of amino acids
- Increased excretion of H⁺ scavenging ammonia
- Increased neo genesis of bicarbonate by tubule cells
- Thus pH SLOWLY CLIMBS BACK TO NORMAL

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SPECIAL CASES OF INSULIN ACTION

GLUCOSE

- GLUCOSE uptake
  - Golgi vesicles (containing glucose transporters GLUT-4)
  - fuse with cell membrane, GLUTs brought to surface
  - facilitated diffusion
  - GLUCOSE enters cell by GLUT-2 and metabolised

- Glucose phosphorylation by GLUCOSE KINASE
- blocks K+ channels
- Ca2+ channels open
- granules move to cell surface

- PULSATILE EXOCYTOSIS
  - daily adult secretion = 5mg
  - phase 1 = rapid, stores
  - phase 2 = slower, synth

- INSULIN SECRETION!!!

- SYNTHESIS
  - PREPROINSULIN (rough endo retic)
  - PROINSULIN 2 chains joined by C-peptide
  - cleaved in secretory granules to form INSULIN and C-PEPTIDE

- GI HORMONE POTENTIATORS
  - GLUCAGON
  - GLUCAGON-LIKE PEPTIDE I
  - GASTRIC INHIBITORY PEPTIDE

- NEURAL EFFECTORS
  - SYMPTOMS?
  - inhibits secretion
  - PARASYMPATHETIC?

- ACTION @ CELL
  - INSULIN affects all tissue cells
    - Insulin receptor: 2 subunits – αβ
    - Receptor = a TYROSINE KINASE enzyme.
    - ie. Transfers phosphates from ATP

- BLOOD GLUCOSE = 5Mm
  - MAJOR STIMULUS

- AMINO ACIDS

- BLOOD GLUCOSE

- FOOD INTAKE

- PORTAL CIRCULATION

- SYRINGE FIGURE

- GI HORMONE POTENTIATORS
  - req’d by β to deal with glucose:
    - glucagon
    - glucagon-like peptide I
    - gastric inhibitory peptide

- NEURAL EFFECTORS
  - SYMPTOMS?
  - inhibits secretion
  - PARASYMPATHETIC?

- ACTION @ CELL
  - INSULIN-binding@ α subunit activates TYROSINE KINASE @ β subunit
  - β subunits PHOSPHORYLATE themselves
  - activated receptor phosphorylates intracellular proteins especially:
    - INSULIN RECEPTOR SUBSTRATE: IRS-1,2,... interact with & activate downstream elements

- INSULIN: RELEASE & ACTIONS

- SEQUESTERS

- STORES

- PREVENTS BREAKDOWN

- GLUCOSE
  - GLUCOSE uptake
  - Metabolised
  - GLUCOSE enters cell by GLUT-2

- LIPID uptake
  - via LDL receptors on cell surface

- PROTEIN uptake

- LIVER
  - PREVENTS BREAKDOWN
  - ADEQUATE blood glucose levels:
    - LOW < 3-4mM brain suffers
    - HIGH > 9-10mM cellular damage
  - LIVER
  - EXERCISE?

- @ KIDNEY: excretes XS glucose
  - deals indirectly with insulin via lx on [glucose]
  - NORMALLY, XS glucose filtered out of blood, then reabsorbed
  - BUT?? blood glucose, max capacity reached
  - ?? must be excreted in urine
  - indicates HYPERGLYCAEMIA
  - Glucose holds water to it – when filtered for excretion
  - ? water follows? ? vol sweet urine
  - !!POLYURIA!! !!POLYDIPSIA!!

- @ LIVER: REDUCE GLUCOSE OUTPUT
  - ADEQUATE blood glucose levels:
  - LOW < 3-4mM brain suffers
  - HIGH > 9-10mM cellular damage

- GLUCONEOGENESIS
  - Glucose
  - Blood

- @ MUSCLES: EXERCISE
  - independent glucose uptake (GLUTs recruited by exercise)

- INTESTINE
  - independent glucose transport

- @ BRAIN: maintains fuel supply
  - independent glucose transport
  - except SATIETY CENTRE: hypothalamus
  - INSULIN maintains ADEQUATE blood glucose levels:
    - LOW < 3-4mM brain suffers
    - HIGH > 9-10mM cellular damage

- o-subunit
  - (hormone binding domains)

- β-subunit
  - (ATP binding & tyrosine kinase domains)
**LEPTIN**

- **!!! THIN !!!**
- protein product of the 
  obese (ob) gene, on 
  chromosome 7.
- SYNTHESIZED in the 
  ADIPOCYTE. Functions as a SATIETY FACTOR.
- with specific transport protein to cross blood brain 
  barrier.
- Fat cell release stimulated by:
  - INSULIN, G-C’s, ↑ NUTRITION
  - leptin secretion rate and plasma content 
  determined by size of adipose tiss
  - role in long-term weight control 
  if high [leptin] → thin, ↑ metab, early 
  puberty
- but/ obese tend to have high leptin, suggesting 
  resistance to its actions, not deficiency

**OBESITIES, (RARE)**
- early onset hyperphagia
- HUMAN LEPTIN DEFICIENCY
  - spontaneous mutn, consang 
  family
- - POMC abn: no MSH prodn
  - MCR-4 receptor defect
  - 5% of early onset obese ppl 
  heterozygous for this
- - (mice) Agouti & Agouti-
  related peptide (AGRP)
  - dysregulation. These antagonize 
  MC4 receptor function

- **VAGAL NERVE**
  - Afferents
  - Gut-brain conversation 
    re: carbo’s & proteins in gut
  - PSYCH FACTORS
  - HORMONES
    - Insulin
    - Cholecystokinin
    - Glucagon
    - Adr
  - Brain
  - Body Temp
  - Hot
  - STOP!!

- **FEEDING BEHAVIOIR (-'ve feedback sys)**
  - TO BRAIN
    - (1) neural signals from digestive tract
    - (2) bloodborne signals relating to E stores
    - (3) hormones
    - (4) body temp
    - (5) psych factors

**APPETITE SUPPRESSANTS**
- Serotonin (hypothal)
- α-MSH
- CART: cocaine-amphetamine-related transcript (hypothal)
- CCK: cholecystokinin (released by intestine during digestion)
- CRH: corticotrophin-releasing hormone
- glucagon
- bombesin/gastrin-releasing peptide
- neurotensin

**APPETITE STIMULANTS**
- Neuropeptide Y (NPY): synth & fns in hypothal → CARBO CRAVING
- Melanin-concentrating hormone
- Agouti & Agouti-related peptide: endogenous antags to MC4 receptors
- Ghrelin (gut)
- Orexin (hypothal: responds to Δs in NPY and POMC neurons)
- NADr
- Opioids
- Galanin → FAT CRAVING
  - Nitric oxide

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Figure 1. Response of the hypothalamus to increase and reduction in leptin action. Increased leptin action (left) decreases appetite and 
promotes weight loss. Reduced leptin action (right) increases appetite and promotes weight gains. AgRP, agouti-related peptide; α-MSH, 
α-melanocyte-stimulating hormone; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus.
SCHEMA OF ANASOMOSIS IN THE PANCREATIC BLOOD SUPPLY

Celiac Trunk
- common hepatic artery
  - gastroduodenal artery
    - anterior superior pancreaticoduodenal a.
    - posterior superior pancreaticoduodenal a.
    - anterior arcade on head of pancreas
    - posterior arcade on head of pancreas
  - pancreas and duodenum
    - anterior inferior pancreaticoduodenal a.
    - posterior inferior pancreaticoduodenal a.
    - inferior pancreaticoduodenal artery
  - SMA

AXIAL & LONGITUDINAL SECTIONS AT L1 VERTEBRAL LEVEL

Longitudinal section viewed from right
- Splenic artery
- Superior mesenteric artery
- Inferior mesenteric artery
- Pancreaticoduodenal arcade
- Superior mesenteric vein/artery
- Right renal artery
- Inferior mesenteric artery

Axial (cross) section looking up
- Junction of portal & superior mesenteric veins
- Uncinate process of pancreas
- Transverse mesocolon
- Inferior mesenteric vein
- Splenic vein
- Left renal artery
- Portal vein
- Left renal artery

PANCREAS - RELATIONS
- Anterior: lesser sac, pylorus, 1st part of duodenum, superior mesenteric artery & vein, transverse mesocolon, stomach
- Superior: splenic artery
- Lateral on right: 2nd part of duodenum, ampulla of Vater
- Lateral on left: hilum of spleen
- Posterior: left crus of diaphragm, psoas, right renal vein, inferior vena cava, bile duct, spleen, left renal vessels, left kidney, left suprarenal gland, celiac plexus, inferior mesenteric vein, splenic vein, portal vein, superior mesenteric artery & vein, aorta

Pancreatico-duodenal vessels. Watershed between foregut & hind gut
- Superior mesenteric artery & vein
- Uncinate process
- Inferior mesenteric vein
- Portal vein
- Superior mesenteric artery/vein
- Transverse mesocolon
- Uncinate process
The pancreas is for the most part retroperitoneal but becomes suspended in a mesentery (the lienorenal ligament) as the tail reaches the hilum of the spleen. The uncinate process, head and neck of the pancreas lie within the curvature of the duodenum. The pancreatic ducts drain into the duodenum. The main pancreatic duct drains the tail, body, uncinate process and part of the head. In the head the main pancreatic duct joins the bile duct to form the ampulla of Vater to drain into the second part of the duodenum. The sphincter of Oddi controls flow into the duodenum through the major duodenal papilla. The accessory pancreatic duct drains part of the head, either joining the main pancreatic duct or entering the duodenum separately as the minor duodenal papilla. The portal vein is formed behind the neck of the pancreas. The superior mesenteric artery and vein lie anterior to the uncinate process. The splenic artery supplies the body and tail of the pancreas. The neck and head of the pancreas are supplied by the anterior and posterior superior pancreaticoduodenal arteries which branch from the gastroduodenal artery. The uncinate process and part of the head are supplied by the anterior and posterior inferior pancreaticoduodenal arteries which arise from the superior mesenteric artery. The pancreatic veins drain into the portal vein.
ATTACHMENTS OF MESENTERIES WITH BOWEL EXCISED

The purpose of this diagram is to illustrate the width of the 'bare area' of peritoneum that would be left on the posterior abdominal wall if the bowel was excised. If the pink area is narrow then the bowel was on a mesentery. If it is wide then the bowel was retroperitoneal. Note that the majority of the duodenum has been left undisturbed.

Right subphrenic space
- Mesentery of stomach
- Right mesocolic cut
- Right paracolic gutter
- Right paracolic compartment
- Caecal mesentery
- Intersigmoid fossa alongside sigmoid mesocolon (half way along pelvic brim to S3 mid-line)

Left subphrenic space
- Left mesocolic cut
- Left paracolic gutter
- Left paracolic compartment
- Small bowel mesentery
- IVC

Note: lesser sac is left subphrenic space
Note: Small bowel mesentery runs from the left L2 transverse process to the right sacro-iliac joint (S2). It is 6 inches (15cm) long and crosses left psoas, aorta, IVC, right psoas, right ureter, right common iliac bifurcation & into right iliac fossa.

PERITONEAL CAVITIES AND LESSER SAC

Subphrenic space
- Midline sagittal view of abdomen
- Lesser omentum
- Gastrocolic omentum
- Transverse mesocolon
- Duodenum (retroperitoneal)
- Small bowel mesentery
- Greater sac

Opening of lesser sac (foramen of Winslow)
- Meso-oesophagus & left triangular ligament
- Retropertioneum
- Gastronrenal ligament
- Caudate lobe
- Portal vein
- IVC

Foramen (above) viewed from in front and foramen (below) viewed the right side.