Bldg 5

CLINICOPATHOLOGICAL SESSION 5:
"A growing problem"

Overall aims: To introduce you to the diagnosis and management of metabolic syndrome and its complications.

Specific learning objectives:

At the conclusion of this session, you should be able to:

1. Discuss your approach to history taking and examination of the overweight patient
2. Understand the diagnostic criteria for metabolic syndrome
3. Understand the pathophysiology of metabolic syndrome
4. Discuss your approach to investigations and monitoring of the patient with metabolic syndrome
5. Interpret liver function tests and glucose tolerance tests
6. Understand the diagnosis of impaired fasting glycaemia, impaired glucose tolerance and diabetes
7. Discuss the management of metabolic syndrome
8. Discuss the management of diabetes
9. Understand the diagnostic criteria for overweight and obesity
10. Understand what the HbA1c test is, and how it is used

Instructions

- Pre-reading
  → review of previous lectures/practicals and PBLs related to this topic
  Prepare answers for questions 1-4 in the clinical scenario prior to the tutorial
- The session will be discussed in a question and answer format
- The topic will be introduced with a clinical history
- You will be shown laminated pathology reports

Clinical History:

Robert Forster, a 56 year-old IT consultant, has come to see you, a general practitioner, for the first time for an annual check up. Robert says that he's "pretty healthy", but you notice that he appears markedly overweight and sounds slightly breathless.

1. Which areas in the history will be particularly important? (5 min)

- Any current illness?
- Past Medical History: including cardiovascular disease, hypertension, hyperlipidaemia, diabetes, impaired glucose tolerance, gout, renal disease, obstructive sleep apnoea, weight history, arthritis
- Lifestyle Issues: Exercise history/tolerance, occupation, stress levels, diet, smoking, alcohol
- Drug history: Medications past/present, illicit drugs
- Family history: especially cardiovascular disease, obesity, type II diabetes, obstructive sleep apnoea.

Robert reports that he has had "cholesterol and blood pressure problems" for a while, and has a family history of heart disease and type 2 diabetes. He also reports consuming ~3 standard drinks per day.

2. What physical examination would you perform? (5 min)

- General physical examination (including blood pressure, waist circumference, height, weight). Specific examination of:
  - Cardiovascular examination
  - Respiratory exam
  - Abdominal exam
  - Musculoskeletal exam
  - Dip Stick – Protein/Glycosuria

On examination, you find that Robert has a BMI of 30, a waist circumference of 115cm and a blood pressure of 145/94.

3a. Does Robert have Metabolic Syndrome? What are the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) 2005 diagnostic criteria for metabolic syndrome? (5 min)

Any three of the following:

- Waist circumference: >102cm (males), >88cm (females)
- Triglycerides: ≥1.7mmol/L or drug treatment for elevated triglycerides
- High Density Lipoprotein: <1mmol/L (males), <1.3mmol/L (females)
- Blood pressure: ≥135/≥85 mmHg
- Fasting glucose: ≥5.6mmol/L or drug treatment for elevated blood glucose levels

3b. What is the pathophysiology of metabolic syndrome? (5 min)

- Adipose tissue storing large quantities of lipid releases substances that reduce the response of tissues to insulin and affect glucose and fatty acid utilisation in the peripheries.
- The hormonal activities of adipose tissue results in insulin resistance.

- Insulin resistance is the main mechanism involved in metabolic syndrome, as it predisposes to type 2 diabetes and cardiovascular disease.
- Other effects of adipocyte cytokines include mediating blood vessel inflammation, effects on lipid profile, hypertension and vascular endothelial dysfunction.

4. What investigations would you order now? (8 min)

Test	Expected result	Cost (2013)
Full Blood Count	Normal	$16.95
Electrolytes, Urea, Creatinine	Normal	1 test= $9.70 5 or more= $17.70
Liver Function Tests	Elevated ALT, AST, GGT and ALKP, normal bilirubin and albumin	
Urinalysis	± protein	
Triglycerides and total cholesterol	Total cholesterol and triglycerides elevated	
High Density Lipoprotein	Low	$11.10
Glucose Tolerance Test	Impaired glucose tolerance or diabetes	$18.95
HbA1c (glycosylated haemoglobin)	High	$16.80
Chest X-Ray	Normal	$35.35(with report)
Electrocardiogram	May be normal or show ischaemic changes	$31.25 (with report)

Robert's HDL is <1mmol/L, and his triglycerides and total cholesterol are raised (total cholesterol >5.5mmol/L). His FBC, ECG and CXR are normal.

Results of Robert's liver function tests are provided as a handout: **See appendix 7 (tutor pg 120, student pg 113)**

5. Please comment on Robert's LFT results provided as a laminated handout. (4 min):

ALT moderately elevated, GGT mildly elevated, ALKP mildly elevated, bilirubin normal, albumin normal. This could indicate non-alcoholic fatty liver disease.

Robert's fasting glucose is 6.8mmol/L, so he proceeds to glucose tolerance test. His pre-test glucose is 6.7mmol/L, his one-hour glucose level is 8.3mmol/L and his two-hour glucose level is 7.9mmol/L.

6. Interpret the glucose tolerance test results, using the parameters below: (2 minutes)

Condition	**Fasting**	**2 hours**
Normal	*<5.5mmol/L*	*<7.8mmol/L*
Impaired glucose tolerance	*<5.5mmol/L*	*7.8-11.1mmol/L*
Impaired fasting glycaemia	*5.5-6.9mmol/L*	*<7.8mmol/L*
Diabetes mellitus	*≥7.0mmol/L*	*≥11.1mmol/L*

Robert has impaired fasting glycaemia and impaired glucose tolerance

7. How should Robert's metabolic syndrome be managed? (10 min)

1. Treat the underlying causes intensively

- Diet: with reduced intake of simple sugars, saturated fats, cholesterol and transfats, and increased intake of fruits, vegetables and whole grains. The aim is for 7-10% bodyweight loss over 6-12 months. Consider a referral to a dietician for more detailed advice if weight loss is inadequate.
- Pharmaceutical or surgical weight loss aids (not as a first line treatment, but they may be useful if conservative management does not produce adequate weight loss)
- Physical activity: A formal exercise program may help but high risk patients need cardiovascular evaluation first. 60-90 minutes per day of physical activity can produce modest weight reduction, but 30 minutes per day provides significant health benefits.

2. Treat cardiovascular disease risk factors

- Lipids: Consider statins or fibrates (Robert fulfils PBS criteria for lipid lowering drugs)
- Hypertension: ACE inhibitor or angiotensin 2 inhibitor to treat hypertension and prevent renal damage
- Type 2 diabetes: Treatment if present (no evidence for pharmaceutical agents to prevent diabetes if absent)
- Smoking cessation (if relevant)
- Regular monitoring: blood glucose levels, blood pressure, triglycerides, cholesterol

8. What monitoring tests are important in metabolic syndrome? (4 min)

Components of metabolic syndrome tend to co-occur, and so all components should be assessed and monitored regularly:

- Fasting blood glucose level/HbA1c
- TGs, HDL, LDL
- BP measurement, weight and waist circumference measurement
- LFT
- EUC
- Uric acid level (if patient has gout)

9. What diseases have an increased risk of development because of Robert's metabolic syndrome? (5 min)

- Cardiovascular disease
- Type 2 diabetes
- Non-alcoholic fatty liver disease (which can progress to fibrosis and cirrhosis)
- Hyperuricaemia and gout
- Obstructive sleep apnoea
- Chronic renal disease
- Female patients are susceptible to polycystic ovarian syndrome. (Robert is not, for obvious reasons)
- Malignancy. Overweight increases the risk of colorectal cancer, oesophageal cancer and kidney cancer (in females, the risk of breast and endometrial cancer is also increased)

After an initial good response, over two years Robert's fasting glucose level has deteriorated. You refer him for another glucose tolerance test, and find that he now has diabetes.

10. How will Robert's management change now? (7 min)

- Diabetic Education about diabetes and self-monitoring of blood glucose levels –Diabetic Educator/Dietician
- Hypoglycaemic agents - Metformin/Thioglitazone are Insulin enhancers. (? add sulfonylurea or sitagliptin if not controlled with metformin.)
- Regular physical examination to detect complications:
    - vision, visual acuity, visual fields, fundoscopy
    - cardiovascular system examination
    - orthostatic blood pressure
    - diabetic foot examination
    - neurological examination of the upper and lower limb
- Add HbA1c, renal function tests and microalbuminuria (protein:creatinine ratio) to regular monitoring
- Consider referral to podiatrist for assessment of/advice about footwear and foot care.

Robert's blood glucose levels respond well to medication. He takes up competitive orienteering and loses 20kg over the next 3 years. His orienteering team wins a national orienteering championship for his age division. 10 years later, his fasting blood glucose levels are excellent and he remains complication-free.

If time (or for homework tasks): Use resources/links on Wattle/ANUpath to help you answer these questions

1. What are the WHO diagnostic criteria for overweight/obesity? Does ethnicity matter?

BMI >25 and <30 for overweight.

- BMI 30.0-34.9 obesity class I
- BMI 35.0-39.9 obesity class II
- BMI ≥40.0 obesity class III
- Obesity refers to a state of increased body fat, and BMI may therefore be misleading, as individuals with the same BMI may have different proportions of body fat. Waist circumference measurement may more accurately indicate central abdominal adiposity. There are sex- and ethnic-specific values that indicate increased disease risk.

Ethnic group	Waist circumference indicating increased risk
Europe:	
- Males	>94 cm
- Females	>80cm
China and South Asia:	
- Males	>90cm
- Females	>80cm
Japanese:	
- Males	>85cm
- Females	>90cm

2. Patients with metabolic syndrome are at increased risk of developing type-two diabetes. What is the HbA1c test and what is it used for? What is the target level?

- HbA1c is a measure of the % of haemoglobin that is glycated.
- The test monitors the effectiveness of diabetic management, as the HbA1c % relates to the average BSL over the previous three months.
- The target level is <7%.

Related lectures/practicals/PBLs
Year 2:
Block 3 lecture – Epidemiology of some major endocrine disorders
Block 3 - practical: Glucose tolerance test
PBL 4.6 – "I've tried everything"
Block 4– lecture Consequences of obesity
Block 4– lecture Control of body weight
Block 4– lecture The four lifestyle factors: Nutrition and physical activity

References/Learning Resources
Appendix 1: Useful web sites
Appendix 2: Glossary of pathological terms
Appendix 6: Pathology report

Kumar, Abbas and Fausto (editors) Robbins and Cotran: Pathologic basis of disease 9th edition. Elsevier Saunders, pp 444-448 and 1105-1120

Department of Health and Ageing. PBS-eligibility criteria for lipid lowering drugs fact sheet. 6 September 2006. Accessed at http://www.health.gov.au/internet/main/publishing.nsf/content/lipid_eligibilitycriteria.htm. Accessed 22/1/10

• Eckel Robert H, "Chapter 236. The Metabolic Syndrome" (Chapter). Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J: Harrison's Principles of Internal Medicine, 17e: http://www.accessmedicine.com/content.aspx?aID=2887926.

http://www.uptodate.com/online/content/topic.do?topicKey=hep_dis/20083&selectedTitle=1%7E28&source=search_result (accessed 13/12/09)

Avenell A, Brown TJ, McGee MA, Campbell MK, Grant AM, Broom J, Jung RT, Smith WC. What are the long-term benefits of weight reducing diets in adults? A systematic review of randomized controlled trials. J Hum Nutr Diet. 2004 Aug;17(4):317-35.

• Boon NA, Colledge NR, Walker BR, Hunter JAA. Davidson's principles and practice of medicine. 20th ed. Churchill Livingstone Elsevier, 2006, Edinburgh, p829

• Charbonnel B, Karasik A, Liu J, Wu M, Meininger G; Sitagliptin Study 020 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care. 2006; 29(12): 2638-43.

• Fonseca VA. The metabolic syndrome, hyperlipidaemia, and insulin resistance. Clinical Cornerstone 2005; 7(2-3): 61-72

• Gonzales Ralph, Kutner Jean S, CURRENT Practice Guidelines in Primary Care, 2009: http://www.accessmedicine.com.virtual.anu.edu.au/guidelines.aspx

• Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. BMC Public Health 2009; 9:88. doi:10.1186/1471-2458-9-88. accessed at http://www.biomedcentral.com/1471-2458/9/88. accessed 17/1/10

• Kushner Robert F, "Chapter 75. Evaluation and Management of Obesity" (Chapter). Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J: Harrison's Principles of Internal Medicine, 17e: http://www.accessmedicine.com/content.aspx?aID=2883857

• Meigs JB. The metabolic syndrome (insulin resistance syndrome or syndrome X). UpToDate. Last updated 11/2/09. Accessed at

http://www.uptodate.com/online/content/topic.do?topicKey=diabetes/21989&selectedTitle=1%7E150&source=search_result (accessed 10/12/09)

• Powers Alvin C, "Chapter 338. Diabetes Mellitus" (Chapter). Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J: Harrison's Principles of Internal Medicine, 17e: http://www.accessmedicine.com/content.aspx?aID=2891108
• Royal College of Pathologists of Australasia Sydney. Glucose tolerance test in RCPA Manual Version 5. Surrey Hills. Last updated 12/8/09. http://www.rcpamanual.edu.au/sections/pathologytest.asp?s=33&i=680 (accessed 15/12/09)
• World Health Organization. Fact Sheet N° 311 Obesity and overweight. WHO Media Centre. 9/2006. Accessed at http://www.who.int/mediacentre/factsheets/fs311/en/index.html (accessed 17/12/09)

Please look regularly at ANUpath and Wattle Websites for extra useful resources relating to CPC topics. This includes the smartsparrow learning cases accessed via Wattle.

Appendix 6: McDonald Criteria for diagnosis of MS:

Revised McDonald et al. (2005) Diagnostic Criteria for Multiple Sclerosis

CLINICAL (ATTACKS)	OBJECTIVE LESIONS	ADDITIONAL REQUIREMENTS TO MAKE DIAGNOSIS
2 or more	2 or more	None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS
2 or more	1	Dissemination in space by MRI ***or*** 2 or more MRI lesions consistent with MS plus positive CSF ***or*** await further clinical attack implicating other site
1	2 or more	Dissemination in time by MRI ***or*** second clinical attack
1	1	Dissemination in space by MRI ***or*** 2 or more MRI lesions consistent with MS plus positive CSF **AND** dissemination in time by MRI ***or*** second clinical attack
0 (progression from onset)	1 or more	Disease progression for 1 year (retrospective or prospective) **AND** 2 out of 3 of the following:
		Positive brain MRI (9 T2 lesions ***or*** 4 or more T2 lesions with positive VEP)
		Positive spinal cord MRI (2 or more focal T2 lesions)
		Positive CSF