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Contents

Disclaimer

The Cover Shot

Woman Without

This female bust belongs to a series of ceramic sculptures called 'Women Without' made in 2000, in Malaysia.

It was built up from red earthenware clay and after kiln fired to 1000 degree Celsius, sawdust fired with oxides, which gives the warm tones from red to black.

The bust is around 24 cm high x 20 cm wide x 20cm deep.

As a reflection on the female subject position it was inspired by the different cultures I have lived in, and stresses a great sense of fragility as part of the essence of femininity, reminding her as a symbol of fertility, without defence.

Ms. Simone BOON

Photography, Ceramics & Sculpture and Multimedia

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International Recognition of the CUHK-PWH Diabetes and Endocrine Centre

Dr. Norman N CHAN
MD, FRCP

Editor

Dr. Norman N CHAN

Congratulations to the Chinese University of Hong Kong – Prince of Wales Hospital (CUHK-PWH) Diabetes and Endocrine Centre which has been selected to be one of the 8 International Diabetes Federation Centre of Education (IDFCE)! This is a wonderful achievement by its founding team members and the following is a brief outline of its history and milestones. (www.idf.org/centres-education-and-recognition-programme)

The CUHK-PWH Diabetes and Endocrine Centre was established in 1985 by Professor Clive Cockram. It seeks to improve patient care through education, innovation and teamwork. It has a strong international and holistic perspective, and has trained more than 20 endocrinologists. It is currently headed by Dr Francis Chow, with 5 senior staff members including Professor Juliana Chan, Professor Ronald Ma, Professor Alice Kong, Dr Wing Yee So, Ms Rebecca Wong and a closely knit team of doctors and nurses together providing a comprehensive endocrine and diabetes service at the University's teaching hospital. The Centre has made exceptional contributions to public services, with more than 25,000 outpatient contacts annually. The unit has a strong track record in research, which is frequently integrated with clinical services to ensure relevance to patient care. In collaboration with other researchers, the unit has published more

than 300 original and review articles on diabetes, obesity and endocrine diseases in international peer reviewed journals including book chapters, and have collectively contributed several hundred abstracts and invited presentations at local, regional and international meetings.

Highlight of some milestones:

- 1985 – Opening of the diabetes and endocrine day centre. Appointment of the first full-time diabetes nurse in Hong Kong
- 1995 - Hong Kong Diabetes Registry was set up, which includes regular comprehensive assessment and risk stratification for patients with diabetes through a multidisciplinary approach
- 1995 - Professor Clive Cockram chaired the IDF-Western Pacific Regional (WPR) Council between 1995 and 2000 and has held other important regional roles.
- 1996 - The Diabetic and Endocrine Centre received the Outstanding Team Award from the Hospital Authority for its implementation of shared care programme
- 2002 – The Unit was successful in translating this holistic and multidisciplinary model to the community to establish a university affiliated Diabetes Centre through a technology transfer project
- 2005 - Professor Juliana Chan was appointed by the WHO Office of the WPR to prepare the Plan of Action (2006-2010) for the Western Pacific Declaration on Diabetes (WPDD) and now serves on the Executive Committee of the IDF-WPR Council.
- 2007 - The unit established the Yao Chung Kit Diabetes Assessment Centre with support from a generous donation to provide comprehensive assessment services to the community to help people with diabetes and their health care team to make informed decisions.
- 2009 – Ms Rebecca Wong was appointed one of the first two Diabetes Nurse Consultants in the Hospital Authority
- 2011 – The Centre was selected as one of the 8 International Diabetes Federation Centre of Education (IDFCE) in December 2011. IDFCE is a prestige institution selected by IDF to form part of an international voluntary network to initiate, facilitate, conduct, coordinate and evaluate high-quality education for health professionals in diabetes and other related chronic diseases.

With this achievement, the CUHK-PWH Diabetes and Endocrine Centre has greatly advanced our research & development in this area and hopefully will translate to improved patient care in our community.

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Management of Diabetic Nephropathy

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Dr. Fu-keung LI

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 29 February 2012.

Case history

Madam X was a 70 year old lady with a 20 years' history of diabetes mellitus (DM), managed by her family physician. She received oral hypoglycaemic agents but the glycaemic control was only fair. She also took 3 anti-hypotensive drugs, which included an angiotensin receptor blocker. Madam X was noted to have progressive fluid retention and ankle oedema in the last year. She had a history of coronary artery disease with stenting done 5 years ago. The serum creatinine in early 2010 was 150 umol/L. The 24 hours urinary protein was documented to be 5 gm. A renal biopsy was done, which showed diabetic renal disease with nodular glomerulosclerosis. (Figure 1)

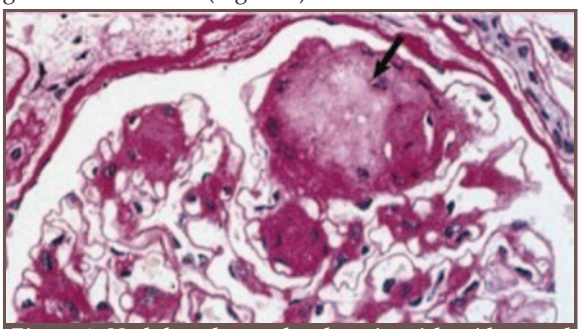

Figure 1. Nodular glomerulosclerosis with widespread mesangial expansion. There is a typical Kimmelstiel-Wilson nodule at the top of the glomerulus.

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease in Hong Kong and worldwide. 30-40% of patients with type 1 or type 2 DM will develop diabetic nephropathy. DN progresses through several stages based on the values of urine albumin excretion: normoalbuminuria, microalbuminuria, macroalbuminuria or overt diabetic nephropathy. (Figure 2) The degree of proteinuria has important prognostic significance for both the renal and cardiovascular mortality and morbidity. (Figure 3)

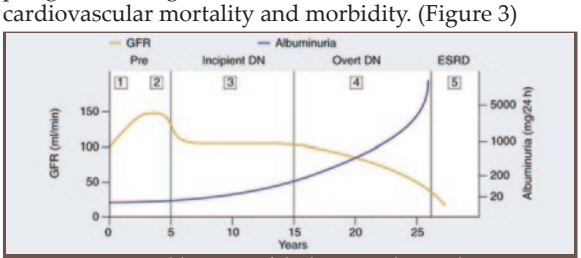

Figure 2. Natural history of diabetic nephropathy

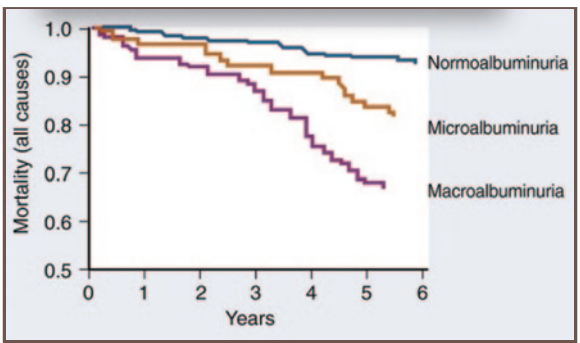

Figure 3. Impact of microalbuminuria and macroalbuminuria on mortality

Treatment of diabetic patients with micro- or macro-albuminuria

For patient with microalbuminuria or overt DN, the treatment target is to reduce the progression of nephropathy and to minimise the risk for cardiovascular events. The strategy would entail a multi-factorial approach, involving aggressive management of hypertension with an emphasis on blockade of the renin-angiotension system (RAS), tightened glycaemic control, management of dyslipidaemia, dietary modification, exercise and cessation of smoking.

Anti-hypertensive treatment

In type 1 or type 2 diabetic patients with nephropathy, hypertension is almost universal and is associated with volume expansion and salt sensitivity. Uncontrolled hypertension is associated with rapid progression of DN and increased risk of fatal and nonfatal cardiovascular events. Some have suggested that the overall effect of lowering blood pressure may be more important than the type of anti-hypertensive agent used[1]. The current recommended blood pressure target for all diabetics is below 130/80 mmHg, but even lower systolic pressure may be more beneficial in diabetic patients with established nephropathy. In a secondary analysis of the Irbesartan Diabetic Nephropathy Trial (IDNT), progressive lowering of systolic blood pressure to 120 mmHg was associated with improved renal and patient survival[2]. However, mortality increased with systolic blood pressure below 120 mmHg, although a cause and effect relationship cannot be inferred from the data. Diastolic pressure is also important but low

diastolic pressures sometimes are poorly tolerated. The incidence of myocardial infarction and mortality increases at values below 70 mmHg, at least in patients with coronary heart disease.

In diabetic patients with established DN, RAS blockade with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) confers renoprotection that is independent of blood pressure reduction. Intraglomerular haemodynamic and nonhaemodynamic renal effects of angiotensin II, some of which that are mediated by the fibrotic agent transforming growth factor β, best explain the observed renoprotection.

In type 2 diabetics, there are more data available on the renoprotective effect of ARBs compared with ACE inhibitors. In the stage of macroalbuminuria with impaired renal function, large randomised controlled trials (IDNT and RENAAL) have demonstrated that ARBs are effective in lowering proteinuria and decreased the relative risk of reaching the composite end-point of death, dialysis and doubling of serum creatinine[3,4]. Combination of RAS antagonists (including aldosterone antagonist or direct renin inhibitor) have shown to be effective in reducing proteinuria[5,6]. However, all combinations, so far, have not been reported to reduce the primary end-point of death or progression to dialysis.

Glycaemic control

The most appropriate target for glycated haemoglobin for patients with DN is 7%, especially for high-risk patients with established cardiovascular disease. Lower individualised targets may be appropriate when the focus is the treatment of microvascular disease such as nephropathy, but the potential renal benefits need to be balanced with the increased rates of adverse events such as hypoglycaemia, especially in patients with declining GFR due to decreased clearance of insulin or oral hypoglycaemic agents.

Dyslipidaemia

Most patients with DN have dyslipidaemia, characterised by low levels of high-density lipoprotein (HDL) cholesterol, high triglyceride (TG) levels, and a shift from larger towards smaller LDL cholesterol. Dyslipidaemia in diabetic patients may contribute to the development of glomerulo-sclerosis and progressive renal disease. Recently, the Study of Heart and Renal Protection (SHARP) suggested that statins with ezetimibe may be beneficial even in dialysis patients (diabetic and nondiabetic)[7].

Novel drug treatments

Peroxisome proliferator-activated receptors (PPAR) are ligand-activated transcription factors involved in regulating adipogenesis, insulin sensitivity, inflammation and blood pressure. Thiazolidinediones (e.g. pioglitazone, rosiglitazone) are PPARγ agonists with insulin-sensitising actions. Pioglitazone in combination with the ARB losartan seems to offer greater renoprotection than losartan alone in short-term studies. However, it is premature to suggest routine therapy with a thiazolidinedione in DN. Protein kinase C inhibitor, ruboxistaurin, an orally active selective inhibitor of the β-isoform of PKC, reduces the actions of vascular endothelial growth factor (VEGF) and attenuates the progression of diabetic nephropathy. A randomised study showed that patients with DN treated with 32 mg of ruboxistaurin daily had a 24% greater reduction in albuminuria than those given a placebo, and they had a stable estimated glomerular filtration rate as well[8]. Further evidence supporting its efficacy in treating microvascular complications is awaited. In a recent study, selective vitamin D receptor activator, paricalcitol, has been shown to ameliorate albuminuria in patients with type 2 diabetes[9]. Addition of 2 μg/day paricalcitol to RAS inhibition can safely lowers residual albuminuria in patients with diabetic nephropathy. Future studies on the hard renal outcomes will be useful to prove its renal and cardiovascular protective effects.

Non-pharmacologic intervention

Dietary protein restriction may alleviate uraemic symptoms in patients at or approaching ESRD. However, it is of uncertain benefit in the treatment of DN. Small trials have shown low-protein diet (0.8 g/kg per day) significantly reduce proteinuria (with an increase in plasma albumin) in type 2 diabetic patients with macroalbuminuria. A meta-analysis, however, showed that although low-protein diet improved proteinuria, it is also associated with lower serum albumin concentration and was not associated with a significant improvement of renal function in patients with either type 1 or type 2 DN. Advice from a dietitian is suggested to avoid protein malnutrition. Furthermore, all patients with DN should be given counselling on salt, potassium and phosphate restriction.

Lifestyle modifications such as smoking cessation and weight reduction can provide additive renal benefits, and lower the risk of cardiovascular events in patients with established DN[10].

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Management of Diabetic Nephropathy" by Dr. Fu-keung LI and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 29 February 2012. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. **The degree of proteinuria in diabetic patients has important prognostic significance for both renal and cardiovascular morbidity and mortality.**
2. **Blood pressure target for diabetic patients is 130 /80 mmHg.**
3. **Combination of renin-angiotensin system (RAS) antagonists has been reported to reduce the primary end-points of death or progression to dialysis.**
4. **The most appropriate target for glycated haemoglobin for patients with diabetic nephropathy is 8%.**
5. **In a recent study, statins and ezetimibe given together, may be beneficial to patients even when they are already on dialysis.**
6. **Low protein diet may reduce proteinuria in patients with diabetic nephropathy.**
7. **There are more data available on the renoprotective effects of ACE inhibitors than angiotensin receptor blockers.**
8. **Most patients with diabetic nephropathy have dyslipidaemia.**
9. **Diabetic nephropathy is the leading cause of end-stage renal failure in Hong Kong.**
10. **Selective vitamin D activator, paricalcitol, has been shown to improve the renal function in patients with diabetic nephropathy.**

ANSWER SHEET FOR FEBRUARY 2012

Please return the completed answer sheet to the Federation Secretariat on or before 29 February 2012 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Management of Diabetic Nephropathy

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Specialist in Nephrology

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Answers to January 2012 Issue

EBUS-TBNA in patients with lung cancer or mediastinal lymphadenopathy

1. T **2.** F **3.** T **4.** F **5.** F **6.** F **7.** T **8.** F **9.** F **10.** F

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Insulin therapy: A practical approach

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Ms. Lynn WW TSANG Dr. Norman N CHAN

Introduction

Type 2 diabetes is a common condition affecting ~10-12% of the adult population in Hong Kong. Good glycaemic control significantly reduces the risks of vascular complications resulting in reduced morbidity and mortality. While life-style modification is the cornerstone of management, oral medication is often required in the majority of patients. It is clear from the United Kingdom Prospective Diabetes Study (UKPDS) that there is beta-cell decline with time in people with type 2 diabetes[1]. Hence a significant proportion of sufferers will ultimately require insulin therapy. Unfortunately, insulin therapy is largely under-utilised resulting in many patients with type 2 diabetes with poor glycaemic control. The reasons for the under-utilisation of insulin are multi-factorial. These include needle phobia, misconception of insulin therapy, lack of paramedical support for the treating physicians in patient education and close follow up for dose titration.

Indications of Insulin Use

Insulin is the sole treatment therapy for type 1 diabetes and is mandatory for individuals with diabetic ketoacidosis. It is also used for type 2 diabetes when hyperglycaemia failed to be controlled by oral hypoglycaemic drugs, in hyperglycaemic hyperosmolar non-ketotic coma and gestational diabetes mellitus. Insulin is often required in the peri-operative period or during acute intercurrent illnesses.

Glycaemic goals

There is much debate on the target of HbA1c following the publication of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study which showed that intensive treatment may lead to increased mortality[2]. It is generally agreed that the HbA1c should be 6.5-7.0% by various guidelines though some have argued that it is not adequately based on clinical evidence[3]. However, in the reality of daily clinical practice, the glycaemic goal should be tailored to individuals. For instance, less-stringent A1C goals (such as <8%) may be appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education (DSME), appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin[4].

Classifications of Insulin

When insulin was discovered in 1921, only short-acting soluble insulin can be made from the pancreases of cows and pigs. Then, it was discovered in 1936 that the absorption of insulin could be delayed with the addition of proteins such as Protamine together with zinc. Over the years, insulin has been purified. Human insulin, produced by means of gene technology, was introduced in 1980.
Different types of insulin are classified by how fast they start to work and how long their effects last. The division is generally based on three factors: (1) time of onset, (2) peak action, and (3) duration of action.

The following provides approximate values for insulin effectiveness[5]. Results may vary based on the individual's diet, exercise programme, and the absorption at the injection site.

Insulin Effectiveness by Type

Type	Onset	Peaks	Duration
Rapid Acting			
Humalog (Lispro)	<15 min.	30-90 min.	<5 hrs.
Novorapid (Aspart)	10-20 min.	1-3 hrs.	3-5 hrs.
Apidra (Glulisine)	10-15 min.	.5-1.5 hrs.	<3 hrs.
Regular (R)			
Humulin R	30-60 min.	2-3 hrs.	4-6 hrs.
Novolin R	30 min.	2.5-5 hrs.	8 hrs.
NPH			
Humulin N	2-4 hrs.	4-10 hrs.	14-18 hrs.
Novolin N*	90 min.	4-12 hrs.	up to 24 hrs.
Pre-Mixed			
Humalog 75/25	15 min.	1-6.5 hrs.	18-26 hrs.
Humulin 70/30	15-30 min.	2-12 hrs.	18-24 hrs.
Novolin 70/30	30 min.	2-12 hrs.	up to 24 hrs.
Humulin 50/50	15-30 min.	2-12 hrs.	18-24 hrs.
Novo Mix 30	10-20 min.	1-4 hrs.	up to 24 hrs.
Peakless Basal			
Lantus (Glargine)	1-4 hrs.	minimal	24 hrs.
Levemir (Detemir)	1-4 hrs.	minimal	up to 24 hrs.

Rapid onset fast-acting insulin is best used at mealtime to control postprandial spikes in plasma glucose. Given the fast-acting nature, food should be consumed immediately after injection. Clear in appearance.

Regular insulin (short-acting insulin) lowers blood glucose levels within 30 minutes. Patients need to take their injections half an hour before eating. Clear in appearance.

Intermediate-acting insulin has either protamine or zinc added to it to delay their action. This insulin starts to show its effect about 90 minutes after injection, peaks at 4 to 12 hours and lasts for 16 to 24 hours.

Mixed insulin is a combination of using either a rapid onset fast-acting or short-acting insulin together with an intermediate-acting insulin. The advantage of this is that two types of insulin can be given in one injection. Mixed insulin is cloudy in appearance and the vial containing the insulin needs to be rolled so that the insulin is mixed evenly before injection.

Long-acting insulin contains added substances (buffers) that make them work over a long time and is clear in appearance. Two of its examples are:

1. Lantus (Glargine), a long-acting peakless analogue insulin that works continuously once released into the blood stream at a constant rate within the full 24 hours

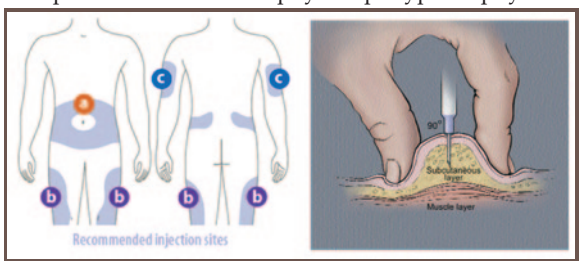
2. Levemir (Detemir), a long-acting analogue insulin that has a relatively flat action and can last up to 24 hours. The exact duration is very much dose dependent. Higher dosage of Levemir generally has longer duration of action. It may be given once or twice per day.

Insulin Injection Sites and Techniques

The best sites (shown in the left diagram below) for routine insulin administration are the areas of the body with fat under the skin. These include (a) the abdomen, (but avoid injecting within the two-inch circle around the navel); (b) the top and outer thighs, (but avoid injecting too closely to the bony area above the knees) and (c) back of the arms.

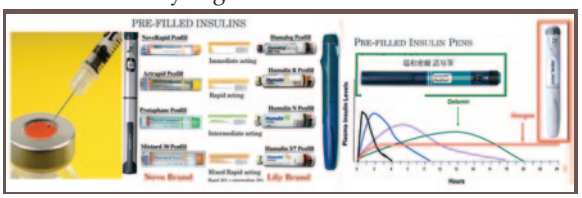
As shown in the following diagram on the right, injections should be subcutaneous and not intra-muscular. The syringe should be held perpendicular to the site. A fold of skin should be lifted up and the needle then inserted straight in (like a dart) at right angle. Do not rub or massage over the injection site after administration.

Factors that affect insulin absorption include the type of insulin, dose, and depth of injection, injection technique, location of injection, exercise, temperature, and local blood flow[5]. On occasions, different insulin types can be drawn into the same syringe for injection. Mixing insulin may affect the rates of insulin absorption and should not be mixed more than an hour before use. Insulin glargine should never be mixed with any other insulin. For patients who require relatively intensive insulin regimens (three to four shots daily), daytime insulin should be injected into the abdomen for more reliable absorption. Physical activities (e.g. running) could cause the insulin to be absorbed more quickly and lower the blood glucose too fast causing hypoglycaemia. Individuals should rotate the site of injection to avoid skin problems such as atrophy or lipohypertrophy.



Different Ways to Deliver Insulin

Syringes vs prefilled pens: Instead of having to drag a bottle and syringe around, patients can just plop a pen device into their pocket or their purse. Prefilled syringes known as Insulin Pens present an increased safety, dose accuracy and convenience for patients when compared with the multi-use vials when an error dosage is often drawn into the syringe.



Insulin by the pump: this is a continuous subcutaneous insulin infusion that replaces multiple daily injections and provides maximal flexibility in the timing of meals, which substantially reduces variability in glucose levels. Its disadvantages include high cost, mechanical failures, knowledge with handling the machine and the inconvenience of wearing an external device.

Calculating Missed Dosages

Missed Insulin Dose: Twice-a-day, intermediate or long-acting insulin
If the patient missed the twice-a-day, intermediate or long-acting insulin dose, and it is within 4 hours, take the full dose. If it is more than 4 hours, skip that dose entirely and cover any high glucose levels with rapid-acting insulin.

Missed Insulin Dose: Mealtime dose of rapid-acting insulin
If the patient missed a mealtime dose of rapid-acting insulin and realised it within the hour, advise him to take the normal dose. If it is within 2 hours, take 75 percent of the normal dose, and if it is within 3 hours, take half of the normal dose.

Storage:

Unopened vials of insulin should be stored in the refrigerator at 2-8 ° C until it expires. Never freeze insulin because this destroys the insulin crystals. Insulin in use can be stored at room temperature under 25° C away from direct sunlight for about four weeks since injecting cold insulin can hurt,.

Potential complications of insulin therapy

Hypoglycaemia is the most common complication of insulin treatment. Mild symptoms of hypoglyacemia include headache, diaphoresis, palpitations, light-headedness, blurred vision, agitation, and confusion. More severe symptoms of hypoglycaemia include seizures and loss of consciousness. In older patients, hypoglycaemia may cause stroke-like symptoms

of aphasia or hemiparesis and is more likely to precipitate stroke, MI, and sudden death. Patients with type 1 diabetes of long duration may be unaware of hypoglycaemic episodes because they no longer experience autonomic symptoms (hypoglycaemia unawareness).

Weight gain is a potential problem with improved glycaemic control with insulin. This is partly due to reduced water loss (which occurs when glycaemic control is poor) and increased size of adipocytes (fat cells) by insulin. This could aggravate the degree of obesity which is already a problem in people with type 2 diabetes. Hence the insulin-sensitiser, metformin, is often used to reduce the amount of insulin required to achieve good glycaemic control in over-weight type 2 diabetic patients.

Lipohypertrophy is a potential complication that occurs in longstanding insulin use without changing sites. This could lead to erratic glucose control as the absorption of insulin is not uniform in such areas. Regular inspection of injection sites should be a routine practice in managing insulin-treated diabetic patients.

Summary

In summary, insulin therapy plays a key role in the management in diabetes control, especially in later stages of the disease. Patient education and proper training with self-glucose monitoring are the key in successful management of these patients to prevent vascular complications.

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Multifunction Room I *(Max 15 persons)*	150.00	105.00	225.00	250.00	175.00	375.00
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Non-Peak Hour: 9.30 am - 5.30 pm Peak Hour: 5.30pm - 10.30pm						
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17 April 2012 (Tue)	7:00p.m. – 8:00p.m.	Seminar Room 1, 2/F, Clinical Sciences Building, Prince of Wales Hospital

Update on Pneumococcal Vaccination

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Introduction

Pneumococcal diseases continue to cause great morbidity and mortality globally. The diseases are caused by the bacteria Streptococcus pneumoniae. The polysaccharide capsule of this Gram-positive diplococci defines its serotypes, virulence factors and it acts as the vaccine targets. Although there are >90 serotypes which vary in distribution and pathogenicity throughout the world, less than 30 serotypes account for 90% of the isolates which cause invasive pneumococcal diseases[1]. Vaccination is the only available strategy to prevent this potentially fatal disease[2].

There are two types of pneumococcal vaccine available. The 23-valent pneumococcal polysaccharide vaccine (PPV23) has been used in both adults and children > 2 years of age since 1983[3]. The second type, which is the pneumococcal-conjugated vaccines are available in three different valents. The heptavalent PCV (PCV7) was first licensed in the USA in 2000[3] and contains 7 *S. pneumoniae* serotypes (4, 6B, 9V, 14, 18C, 19F and 23F), each conjugated to genetically detoxified diphtheria toxin CRM 197. A 10-valent PCV using recombinant non-typeable *Haemophilus influenzae* Protein D as the conjugate was first licensed in Canada, Europe and Australia in 2009 this vaccine includes serotypes 1, 5 and 7F in addition to those included in PCV. In 2009, the 13-valent PCV was first licensed, which includes serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. Indications for using conjugated vaccines in adults are currently under review by public health officials in different parts of the world.

Burden of pneumococcal diseases

Lower respiratory tract infection is currently ranked first by disability adjusted life years, ahead of diarrhoeal and ischaemic heart diseases and ranked third as the leading cause of death for all ages. Each year, approximately 1.6 million people throughout the world die from pneumococcal diseases[4]. In Hong Kong, pneumococcal disease causes 69.2 and 54/ 100,000 populations in male and female respectively. *S. pneumoniae* is the most common identified organism causing community acquired pneumonia. *S. pneumoniae* causes a broad spectrum of diseases: severe and life-threatening invasive pneumococcal disease (IPD) (bacteremia, meningitis and bacteremic pneumonia), non-invasive pneumonia, as well as otitis media and other infections of the respiratory tract[5].

The incidence of IPD in Hong Kong is bimodal with peak at the extreme of ages, in infants < 2 years of age and another peak in elderly adults (≥65 years of age)[6]. Other developed countries share a similar trend as in Hong Kong. The incidence of IPD is expected to rise secondary to the increase in the elderly populations. The at risk groups for pneumococcal infection include those of extreme of ages, immunocompetent persons with underlying medical conditions (chronic cardiovascular, pulmonary, liver and neurological diseases and diabetes mellitus), and persons with defects of immune defences or decreased immune responses (functional or anatomic asplenia, immunosuppressive conditions, post organ or bone marrow transplantation, on therapy with alkylating agents, antimetabolites or systemic corticosteroids). Other at risk factors include male sex, alcohol abuse, cigarette smoking, asthma, cerebral spinal fluid leakage, cochlear implant, recent influenza infection, institutionalisation and in certain ethnic groups (indigenous populations of Alaska, American Indians, Australian aborigines and Bedouins of Israel).

As evidenced from past influenza pandemic including the Spanish Flu 1908 and the more recent H1N1 2009, pneumococcal secondary infection played a major role in causing mortality. Review of autopsy specimens from the 1918 pneumonia death revealed evidence of severe bacterial bronchopneumonia with infiltration of neutrophils, intra-alveolar oedema with haemorrhage and subsequent repair[7]. Another study showed a high proportion of antemortem blood or lung cultures from patients succumbed during the 1918 pandemic were positive for S. pneumoniae[8]. Similar results were found in both children and adults who died during the recent H1N1 2009 pandemic in both USA[9] and South America[10, 11].

Antibiotic resistance of pneumococcal serotypes

Over the past 30 years, antimicrobial resistance among *S. pneumoniae* has increased rapidly. In Europe and USA, 15-30% of the isolates now exhibit multidrug resistance to ≥ three classes of antibiotics[12]. In Hong Kong, the penicillin resistance rates remains low (1%) after the Clinical and Laboratory Standards Institute (CLSI) redefined the penicillin susceptibility breakpoints for *S. pneumoniae* in non-meningitis cases[13]. The penicillin resistance rate increases to around 20% in meningitis cases. However, erythromycin resistance rate in Hong Kong has increased above 70% in three separate surveillance studies conducted between 1998 and

2001[14,15]. Levofloxacin resistance remains around 5.1% in 2007[16]. Globally, six serotypes (types 6A, 6B, 9V, 14, 19F and 23F) account for 80% of penicillin or macrolide resistant *S. pneumoniae* invasive isolates[12]. Antibiotic resistance resulted in treatment failure, prolonged hospitalisation, increased mortality and further justified the use of pneumococcal vaccination.

Pneumococcal vaccination of adults with PPV23

Efficacy of PPV23

The PPV23 contains 25μg of each of the twenty-three pneumococcal capsular polysaccharide antigens (types 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F). In the USA, the PPV23 covers >60% of serotypes that cause IPD[17], with a higher coverage rate of >80% in Europe[18]. Over the past decades, many clinical trials on adults have been performed on the PPV23 and its efficacy (defined as the reduction in the incidence of a disease among people who have received a vaccine compared to the incidence in unvaccinated people) remained controversial. Recent systematic review conducted by the Cochrane Collaboration determined that PPV23 vaccination was effective in preventing IPD in adults[19]. In ten prospective clinical trials that included 35,483 patients, the pooled estimate of vaccine efficacy was 74% (odds ratio [OR]: 0.26; 95% CI: 0.15-0.46). One of the more recent studies conducted in 1006 nursing home residents in Japan demonstrated that PPV23 vaccination reduced pneumococcal pneumonia by 64% and all-cause pneumonia by 45%[20]. Two other earlier studies demonstrated that PPV23 reduced hospitalisation for all-cause pneumonia by 25% and hospital deaths due to pneumonia by 59%. Nevertheless, another study from Australia showed no protective benefit in PPV23[21]. These conflicting results could be explained by the small sample sizes in some of the trials to demonstrate statistically significant differences[22]. Besides, the poor vaccine uptake in adults will result in low impact of the PPV23 on IPD[23]. Other studies however, have shown that PPV23 vaccine efficacy is poor in immunocompromised subjects especially among HIV-infected adults[24].

Immune response to PPV23 in elderly adults

In general, vaccination of the PPV23 among the elderly demonstrated a satisfactory antibody response maintaining an average of 2 fold higher than baseline for 5 or more years after vaccination[25]. Since polysaccharide vaccines contain only T-cell-independent antigens, revaccination with PPV23 cannot induce an anamnestic booster response[26]. Nevertheless, significant antibody responses to most pneumococcal serotypes have been observed in elderly persons who have received a second dose of PPV23. Currently, there is free coverage of PPV23 vaccination for all the at risk groups by the Hong Kong Government. This includes persons aged 65 years of above, with or without additional at risk conditions, persons aged between 2 to 65 years with history of invasive pneumococcal disease, immunocompromised states secondary to asplenia, HIV infection, immunodeficiency related to malignancy, transplantation or immunosuppressive medications and patients with cochlear implants[27].

The role of dual PPV23 and influenza vaccinations

Dual vaccination of PPV23 and influenza (TIV) is recommended by the WHO for elderly persons and chronically ill patients, and its cost effectiveness has been well demonstrated[28]. Besides, a recent study from Hong Kong demonstrated the effectiveness and clinical impact of dual vaccination in elderly patients[29]. Dual vaccination resulted in fewer coronary (HR, 0.59; 95% CI, 0.44–0.79; P<0.001) and intensive care admissions (HR, 0.45; 95% CI, 0.22–0.94; P=0.03), compared with unvaccinated subjects. Dual vaccination with PPV23 and TIV was shown to be effective in reducing development of complications from respiratory, cardiovascular, and cerebrovascular diseases in elderly patients with chronic illnesses. Therefore, dual vaccination should be encouraged in elderly and chronically ill patients, to reduce hospitalisation and death.

Pneumococcal vaccination of children with PCV7

Introduction of PCV7 vaccination for children in the developed countries over the last decade resulted in a dramatic reduction in the incidence of IPD caused by PCV7 serotypes. This reduction occurred not only in vaccinated children but also among unvaccinated children and adults. This indirect protective effect of PCV7 vaccination is known as herd protection[30,31], resulted from reduced nasopharyngeal carriage of PCV7 serotypes in children and a corresponding reduction in the transmission of these serotypes to unvaccinated adults. Compared to the PPV23, the PCV7 has better efficacy in immunocompromised subjects[32]. Nevertheless, this reduction of incidence of PCV7 serotypes is accompanied by a rise in the incidence of IPD caused by non-PCV7 serotypes, a phenomenon known as serotype replacement[31]. This may be explained by the lack of immunity against the non-vaccine serotypes, the unmasking of previous minority strains and also serotype switching of the bacteria[31,33]. In Hong Kong and many of the western countries, the most common replacement serotype is 19A, which is emerging to be one of most important causes of IPD and multiple antibiotics resistant strain[13,34]. Other important non-PCV7 serotypes include 1, 3, 5, 6A and 7F[34]. These serotypes are covered by the new PCV13, which has replaced the PCV7 as part of the childhood immunisation programme provided by the Department of Health in Hong Kong for those < 2 years old[27].

Conclusions

Studies undertaken worldwide have shown that PPV23 vaccination in the elderly is cost-effective. Recommendations for PPV23 vaccination have been issued in countries throughout the world. Despite these recommendations, the uptake of PPV23 has varied greatly and remains poor. Moreover, uncertainty about the value of pneumococcal polysaccharide has increased in recent years because the use of PCV in children has reduced the incidence of IPD in older adults due to herd protection. This raised questions whether PPV23 should continue to have a role in public health vaccination programme. Effective protection against pneumococcal disease requires monitoring the changing epidemiology

of pneumococcal serotypes causing IPD and improving vaccine coverage. For elderly adults, it will be critically important for pneumococcal vaccination recommendations to be based on comparative evaluation of the PPV23 and the PCV13 with regard to their long-term immunogenicity and effectiveness. Health care providers, public health officials, and policy makers should recognise the serious health impact of pneumococcal disease in adults, closely monitor the epidemiology of pneumococcal serotypes following the implementation of PCV programmes for children and ensure increased pneumococcal vaccination coverage.

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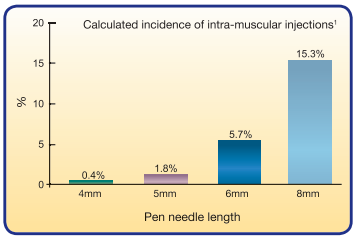

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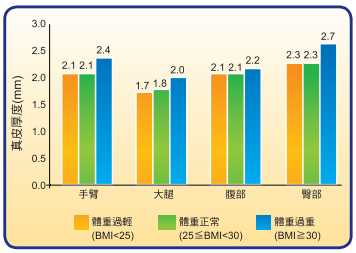

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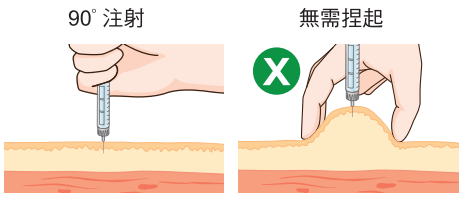

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Novel Oral Anticoagulants for Stroke Prevention in Non-valvular Atrial Fibrillation

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Risk of stroke in atrial fibrillation

Non-valvular atrial fibrillation(AF) is the most common clinically significant cardiac arrhythmia. It is a potent independent risk factor for ischaemic stroke, associated with a 4-fold to 5-fold increase in stroke risk across all age groups[1]. Furthermore, strokes associated with AF are more severe than non–AF-associated strokes[2]. Assessing each patient's risk of stroke is essential when determining which antithrombotic strategy should be used. The most commonly used scoring system to help clinicians to estimate the AF stroke risk is the CHADS2 score[3]. One point each is assigned for the presence of **C**ongestive Heart Failure, **H**ypertension, **A**ge≥75, and **D**iabetes and 2 points for history of prior Stroke or transient ischaemic attack. Patients classified as high risk for thromboembolism (CHADS2 score > 2) should receive oral anticoagulation (OAC) while those with intermediate risk (CHADS2 score of 1) can receive either anti-platelet or OAC. Patients with a CHADS2 score of 0 can receive anti-platelet only[4]. A new scheme (CHA2DS2-VASc) has been introduced recently which may better stratify the risk and better identify those patients who may benefit from OAC[5]. In this scheme, 2 points will be assigned for **A**ge ≥75 and additional one point for **A**ge 65- 74, female **S**ex, or co-existing **V**ascular disease. OAC is still recommended for those with CHA2DS2-VASc score > 2. OAC is preferred to aspirin for those with score of 1 while no antithrombotic therapy is recommended for CHA2DS2-VASc score of 0.

Reasons for underutilisation of warfarin

For more than 50 years, warfarin (a vitamin K antagonist) was the only available oral anticoagulant. Warfarin prevents more than 60% of strokes in patients with atrial fibrillation and has been the recommended treatment for those with this rhythm abnormality and one additional risk factor[6]. However, the use of warfarin is associated with > 10-fold inter-individual variation in dose to achieve therapeutic anticoagulation; genetic polymorphisms account for a portion of the variability in dose-response. The pharmacokinetics of warfarin are also influenced by dietary vitamin K intake, other medications, alcohol use, age, body weight, and various diseases states, necessitating regular coagulation monitoring and dose adjustment to ensure that patient's international normalised ratio (INR) remains within the narrow therapeutic window. Failure to maintain the INR in the therapeutic range can either reduce its benefit or increase the risk of major haemorrhage. Thus, clinicians and patients have been eager to use alternative OAC that are equally efficacious but easier to administer. New OACs that are selective for one specific coagulation factor, either thrombin or factor Xa, have recently become available for stroke prevention in patients with AF.

Dabigatran etexilate

The first new OAC approved by the US Food and Drug Administration (FDA) for the prevention of stroke and systemic embolism in non-valvular AF is Dabigatran etexilate. It is an oral prodrug that is converted to dabigatran, a competitive direct thrombin inhibitor. Dabigatran is not metabolised by the cytochrome P450 enzymes. Peak plasma concentrations are reached 1 to 2 hours after administration, and its mean terminal half-life is around 9 hours and 13 hours in younger and older healthy individuals, respectively. About 80% of the drug is cleared renally. Dabigatran etexilate has relatively few drug interactions, but p-glycoprotein transporter inhibitors, like amiodarone, verapamil, or quinidine increase drug exposure; use of the drug with rifampin, a p-glycoprotein inducer, should be avoided as it reduces the drug's anticoagulant effect. There is no specific antidote to reverse the anticoagulant effect of dabigatran. Haemodialysis is effective in removing dabigatran in the blood and can be used to treat dabigatran toxicity. The RE-LY trial (**R**andomised **E**valuation of **L**ong-Term Anticoagulation Therap**Y**) compared dabigatran etexilate to warfarin in 18 113 patients with non-valvular AF[7]. Two doses of dabigatran etexilate, 110 or 150 mg twice daily administered in a blinded fashion, were compared with adjusted-dose warfarin administered in an unblinded manner. The stroke or systemic embolism rate was significantly lower with dabigatran etexilate at a dose of 150 mg twice daily (1.11%, RR 0.66; 95% CI 0.53–0.82; P < 0.001 for superiority) compared to warfarin, and the 110 mg BID dose was noninferior (1.53%; RR 0.91; 95% CI 0.74–1.11 P < 0.001 for noninferiority) compared to warfarin (1.69%). The rate of major bleeding with the 150 mg dose was not different to that with warfarin (3.11% vs. 3.36%; RR 0.93; 95% CI 0.81–1.07 P = 0.31), while it was significantly lower with the 110 mg dose compared with warfarin (2.71% vs. 3.36%; RR 0.80; 95% CI 0.69–0.93; P = 0.003). The rates of haemorrhagic stroke with the 110 and 150 mg dabigatran etexilate doses (0.12% and 0.10%) were both significantly lower than with warfarin (0.38%). A side effect of dabigatran etexilate was dyspepsia, which occurred significantly more commonly with dabigatran etexilate (11.8% and 11.3% in 110 and 150 mg dabigatran group) than with warfarin (5.8%) (P < 0.001

for both). The use of a proton pump inhibitor can relieve this side effect. Myocardial infarction (MI) also occurred more commonly with dabigatran (0.72% and 0.74% with 110 and 150 mg of dabigatran etexilate, respectively), compared to 0.53% with warfarin (P = 0.07 and 0.048, respectively). This was no longer statistically significant with the inclusion of newly identified events that were indentified after the database was originally locked (P = 0.12) [8]. Based on the results of the RE-LY trial, dabigatran etexilate has been approved in many countries for the prevention of stroke and systemic embolism in non-valvular AF as an alternative to warfarin. While both the 110 and 150 mg twice-daily dosing schedules have been approved in some countries, only the 150mg dose was approved in the U.S and a dose of 75 mg twice daily was approved for patients with renal dysfunction[9]. Patients should have their renal function evaluated prior to treatment initiation. In patients older than 75 or with renal impairment, renal function should be assessed at least yearly. Given the drug is mainly excreted renally, it should not be prescribed to patients with severe renal impairment (creatinine clearance less than 30 ml/min) as recommended by the European Medicines Agency [10].

Rivaroxaban

Rivaroxaban is the second new OAC approved by the US FDA for the prevention of stroke and systemic embolism in nonvalvular AF. Rivaroxaban is distinguished by being the first oral anticoagulant available in the US for the AF indication that can be given once daily without anticoagulation monitoring. Rivaroxaban is a synthetic small molecule that binds competitively to the active site of factor Xa. It is not a prodrug. It is rapidly absorbed after ingestion with about 80% bioavailability and maximal plasma concentrations are achieved in 2.5 to 4 hours[11]. Rivaroxaban has a half-life of 7 to11 hours and a dual mode of elimination; one-third is excreted unchanged by the kidney and two-thirds is converted by the liver (CYP 3A4) to inactive metabolites. Strong inhibitors of both CYP 3A4 and p-glycoprotein, are not recommended. ROCKET AF (**R**ivaroxaban **O**nce daily oral direct Factor Xa inhibition **C**ompared with vitamin **K** antagonism for prevention of stroke and **E**mbolism **T**rial in Atrial Fibrillation) was a double-blind global Phase III study of rivaroxaban compared with warfarin for stroke prevention involving over 14000 high risk AF patients[12]. In ROCKET AF, once-daily rivaroxaban (20 mg, or 15 mg for patients with moderate renal impairment) met the primary efficacy outcome (the prevention of stroke and non-CNS systemic embolism) and was shown to be non-inferior compared with warfarin, with a 21% relative risk reduction in stroke and non-CNS systemic embolism. Though superiority was not achieved in the intention-to-treat analysis, the 'on-treatment' analysis did show superiority. The principal safety outcome – the composite of major and non-major clinically relevant bleeding events – was similar in both treatment arms. Patients on rivaroxaban experienced significantly fewer fatal bleeding. Importantly, patients on rivaroxaban also showed significantly fewer intra-cranial haemorrhages compared with warfarin. Rivaroxaban was associated with favourable cardiovascular outcomes while patients were on treatment, with a statistically significant 15% relative risk reduction in the composite of stroke, systemic embolism, myocardial infarction and vascular death – a pre-specified composite secondary endpoint. Rivaroxaban has also been studied in other conditions. Rivaroxaban has been shown to have non-inferior efficacy compared to enoxaparin followed by warfarin in the treatment of acute deep vein thrombosis[13]. Rivaroxaban may offer a simple and convenient single-drug oral approach to the initial treatment of venous thrombosis. Low dose rivaroxaban has also been tested in the ATLAS ACS 2 TIMI 51 trial and has shown promising results, with a reduction in overall and cardiovascular mortality versus placebo in patients with recent acute coronary syndrome[14].

Apixaban

Like rivaroxaban, apixaban is not a pro-drug and binds to the active site of factor Xa. It has > 50% oral bioavailability and maximal plasma concentrations are achieved within 3 hours. It has a half-life of 8–15 hours and is metabolised by the liver (partially by CYP 3A4); 75% is eliminated in the faeces and 25% by the kidneys[15]. Strong inhibitors of both CYP 3A4 and p-glycoprotein can raise plasma levels of apixaban. Apixaban at a dose of 5 mg twice daily was compared to aspirin (81–324 mg daily) for stroke prevention in atrial fibrillation (AVERROES trial)[16]. This study included 5599 patients, who had failed or were deemed unsuitable for warfarin, was stopped early because of a clear benefit in favour of apixaban. The rates of stroke and systemic embolism were 1.6% and 3.7% per year in patients on apixaban and aspirin, respectively (hazard ratio with apixaban 0.45; 95% CI 0.32– 0.62, P < 0.001). The annual rates of major bleeding were similar at 1.4% and 1.2% per year in the apixaban and aspirin arms, respectively. Apixaban (5 mg twice daily) has also been compared with dose-adjusted warfarin (INR 2.0-3.0) in over 18,000 patients with AF in the randomised, double-blind **A**pixaban for the p**R**eventIon of **ST**r**O**ke in subjects with a**T**ria**L** fibrillation (ARISTOTLE) trial[17]. Apixaban was noninferior and superior to warfarin for the primary outcome, reducing the risk of stroke or systemic embolism by 21% (P<.001 for noninferiority, P=.01 for superiority). The primary safety outcome of major bleeding occurred less frequently in the group receiving apixaban. Rates of intra-cranial haemorrhages were also lower with apixaban. This drug is not yet available in Hong Kong and is under consideration by the US FDA for this indication.

Conclusion

Warfarin has been the treatment of choice to reduce the risk of stroke among moderate to high-risk patients with AF but is significantly underutilised. Oral direct thrombin and factor Xa inhibitors offer many advantages over warfarin. The availability of an immediately acting OAC with no food interaction that does not require laboratory monitoring and cause less intra-cranial bleeding will simplify care for the patient and physician, leads to improved quality of life for the patient. However, there are important issues that must be recognised with the new OACs. The lack of a requirement for regular coagulation monitoring may limit the determination of overdose or treatment failure

and limit detection of medication non-adherence. Other disadvantages include contraindication in severe renal dysfunction and absence of specific antidotes when patients develop major bleeding. Finally, the long term side effects of these new OACs remain unknown. Warfarin will remain an important option for patients who fail or develop thrombotic events while taking one of these new agents or have contraindications to the new OACs.

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Dermatological Quiz

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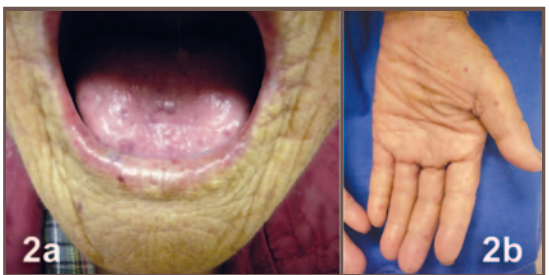

Fig. 2 : Skin lesion at (a) face, especially around the lips and tongue and (b) close-up of right hand

This 70-year-old woman was admitted because of recurrent episodes of gastrointestinal (GI) bleeding. She also had a long-standing history of recurrent epistaxis. Physical examination showed these non-itchy red spots around her face, lips and tongue (Fig. 2a), as well as both hands (Fig. 2b). She claimed that the red spots had been there since her early age. In addition, she mentioned that his son also had this rash on his face and hands.

Questions:

1. What is your provisional diagnosis or differential diagnoses?
2. What other investigations would you like to order?

(See P.42 for answers)

Fever and neck pain in a middle age lady

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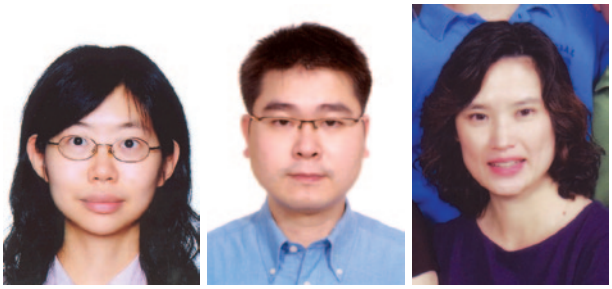


Dr. Flora CW HO Dr. Yin-Kwan LAM Dr. Grace YW KAM

Ms. Wong, a 47-year-old woman presented with fever for 2 weeks. She also had headache, vomiting and sore throat. She had visited her general practitioner three times and was treated with panadol, mefenamic acid and gastrocaine. Fever persisted and so she attended the Accident and Emergency Department. Physical examination reviewed a soft goitre which was tender at the left lower pole. She did not have any signs of thyrotoxicosis and no thyroid eye disease. She did not have any neck rigidity, no neurological deficit. Examination of major systems was unremarkable. CXR was clear. In view of fever and headache, lumbar puncture was done. Cerebrospinal fluid was sent for cell count, biochemistry and microscopy which did not suggest inflammation of the central nervous system. The patient complained of posterior neck pain after lumbar puncture. XR C-spine did not reveal any bony lesion. CT spine was done after orthopaedics consultation which was normal and the neck pain was attributed to lumbar puncture. Blood result showed normal white cell count, liver and renal function tests. Anti-nuclear antibodies were negative. Blood culture and urine culture were negative and sputum culture grew commensals. TSH was suppressed < 0.03 (0.27-4.2) mIU/l and free T4 was raised 65.2 (12.0-22.0) pmol/l. Anti-thyroglobulin antibodies and anti-microsomal antibodies were undetectable. Inflammatory markers were raised including erythrocyte sedimentation rate of 108 (<12) mm/hr and c- reactive protein of 17.6 (<5.0) mg/l. CT of the neck did not show any neck abscess. Clinical diagnosis of subacute thyroiditis was made. She was discharged with propranolol, ibuprofen and panadol.

Her subsequent thyroid function test, which was 8 weeks from discharge, showed hypothyroidism with TSH 32.6 mIU/l and free T4 7.7 pmol/l. Thyroxine was withheld due to upcoming thyroid scan. Technetium scan of the thyroid 2 months after discharge showed homogenous uptake of the thyroid gland at lower normal limit. Her thyroid function recovered spontaneously. Her latest TSH (4 months after discharge) was 5.97mIU/l and free T4 was 13.0pmol/l.

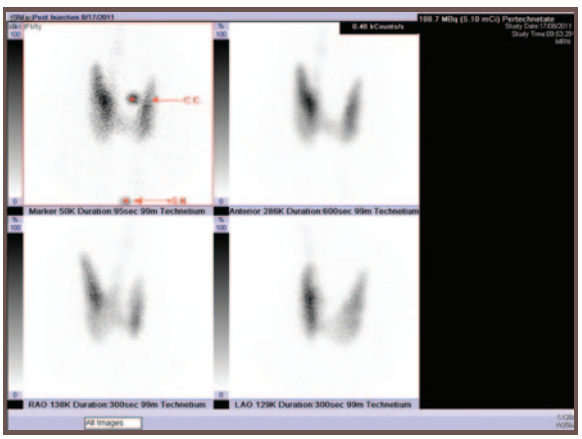
Discussion

Subacute thyroiditis is recognised as a differential diagnosis of pyrexia of unknown origin (PUO). Other more common causes include infection, neoplasm and connective tissue disease. History of fever, sore throat, anterior neck pain, prior upper respiratory tract infection and tender thyroid gland are commonly found in subacute thyroiditis.

This case illustrated the three phases in subacute thyroiditis. In the initial inflammatory phase, the patient has transient hyperthyroidism for two to eight weeks but without thyrotoxic symptoms. Clinical course is then followed by transient hypothyroidism for several weeks. Most patients will have recovery of thyroid function. 5-30% of patients with subacute thyroiditis have permanent hypothyroidism requiring long term thyroxine replacement.

Differential diagnoses for subacute thyroiditis include infectious thyroiditis and thyroid abscess. Imaging may be needed for diagnosis if the patient has high fever, leukocytosis and appeared toxic.

Treatment in subacute thyroiditis is mainly symptomatic. Non-steroid anti-inflammatory drug (NSAID) is used as first line. If pain control is not achieved with NSAID, short course of corticosteroid may be needed. Anti-thyroid medication is not required as hyperthyroidism is transient. Beta blockers such as propranolol can be given to control thyrotoxic symptoms.



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A lady with thyroid carcinoma diagnosed during pregnancy

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Madam X has a history of thyrotoxicosis treated in the Mainland in 2004. She received antithyroid drugs for 6 months but then defaulted further treatment. She remained asymptomatic. She experienced palpitation at 7th week of gestation of her first pregnancy in 2008. Her thyroid function test (TFT), was checked with Thyroid Stimulating Hormone (TSH), <0.03mIU/L and Free Thyroxine level (FT4), 34.9pmol/L. She was given Propylthiouracil (PTU),50mg bd by her family doctor. Her TFT was rechecked at 16th week (TSH <0.03mIU/L and FT4 17.3pmol/L). She was euthyroid at that time and a diagnosis of Gestational Thyrotoxicosis was made. PTU was stopped. At 19th week, her TFT reported TSH <0.03mIU/L and FT4 12.2pmol/L. She remained euthyroid and delivered on 10/7/2009. Rechecked thyroid function at 4th week postpartum was normal. Physical examination revealed a small goitre without any thrill or bruit.

5 months after delivery, she developed toxic symptoms with TSH <0.03mIU/L and FT4 60.7pmol/L. Despite symptoms relieved after starting Carbimazole, she complained of progressive increase in goitre size with prominent right lobe. There was no cervical lymph nodes palpable. Ultrasonography of thyroid US revealed a 2.5cm solitary right thyroid mass. US guided fine needle aspiration of cytology FNAC arranged which reported cells suspicious of malignancy. She was referred to the Head and Neck surgeon for operation. At that moment, she was pregnant again and antithyroid drug was switched to propylthiouracil. Repeated US thyroid showed a 16X17mm irregular right lobe nodule but there was no lesion found in the left lobe.

She received a right hemithyroidectomy and right paratracheal lymph nodes dissection under general anaesthesia in the second trimester. Histology reported Papillary Thyroid Carcinoma with a clear resection margin. Right paratracheal lymph nodes were excised and histology was consistent with metastatic papillary carcinoma. Her staging of thyroid carcinoma was pT2pN1a(TNM, AJCC 7th edition). Post operation, PTU was stopped and the patient was put on thyroxine replacement T4 50microgram o.m. Her TFT reported TSH 0.96mIU/L. The calcium level was normal and the patient did not have any hypocalcaemic symptom.

In view of the clear resection margin, complete thyroidectomy or radioactive iodine ablation was not mandatory or feasible. US performed by the gynaecologist revealed a single viable foetus at 21-24 weeks gestations. The patient was happy to continue the pregnancy with regular monitoring and follow up by the Head and Neck Surgeon and Gynaecologist.

Discussion:

The patient has autoimmune thyrotoxicosis as evidenced by her high anti-microsomal ab 1:6400 and postpartum flared up of thyrotoxicosis. Despite biochemically controlled with carbimazole, she noticed asymmetrical enlargement of the right thyroid lobe at 11 months after her first delivery. US thyroid confirmed a right lobe nodule and FNAC showed cells suspicious of malignancy. However she was pregnant again and no radioisotope scan was performed.

FNAC is the most accurate and cost effective method for evaluating thyroid nodules[1,2]. The aspirates can be nondiagnostic, malignant, indeterminate or suspicious for neoplasm and benign. "Indeterminate cytology", "suspicious," "follicular lesion," or "follicular neoplasm" amount to 15%–30% of FNAC specimens[8]. For cystic nodules, nondiagnostic aspirates are common. If the nondiagnostic aspirate lesion is a solid nodule, surgical excision is advised.

Sonographic characteristics such as microcalcifications, hypoechogenicity of a solid nodule, and intranodular hypervascularity are superior to nodule size for identifying nodules that are more likely to be malignant but still not 100% specific[4]. These nodules with a suspicious sonographic appearance should be aspirated preferentially.

If none of the nodules has a suspicious sonographic appearance, the largest nodules usually more than 1 cm should be aspirated. Even if benign aspirate, these nodules should be followed up because of a false-negative rate of up to 5% with FNAC. Repeat FNAC is indicated if a nodule grows in size as defined by a 15% increase in nodule volume or a 20% increase in nodule diameter at least 2mm in two or more dimensions[3-8].

A low or low-normal serum TSH concentration may suggest the presence of autonomous nodules. A radioactive iodine scan should be performed and directly compared to the ultrasound images to determine the functionality of each nodule larger than 1–1.5 cm. FNAC should be considered for those isofunctioning or nonfunctioning nodules.

Thyroid nodules in pregnant women behave similar to those in non-pregnant women. However, during pregnancy a radionuclide scan is contraindicated. For euthyroid and hypothyroid pregnant women with thyroid nodules, FNAC should be performed. For women with suppressed serum TSH levels that persist after the first trimester, FNAC may be deferred until

after pregnancy[1]

A nodule with malignant cytology discovered early in pregnancy should be monitored sonographically and if it grows substantially by 24 weeks' gestation, surgery should be performed at that point. However, if it remains stable by midgestation or if it is diagnosed in the second half of pregnancy, surgery may be performed after delivery[1].

There is no consensus about whether surgery should be performed during pregnancy or after delivery. Thyroid cancers discovered during pregnancy do not behave more aggressively. There is no difference in either recurrence or survival rates between women operated on during or after their pregnancy[10-12]. Retrospective data suggest that treatment delays of less than 1 year from the time of thyroid cancer discovery do not adversely affect patient outcome.[23]

Madam X had right hemithyroidectomy and right paratracheal lymph nodes dissection under general anaesthesia in the second trimester. Her staging of thyroid carcinoma was pT2pN1a (TNM, AJCC 7th edition).

Differentiated thyroid Carcinoma DTC is the second most frequent tumour diagnosed during pregnancy with an incidence of 14 per 100,000 live births[13-14]. DTC complicating pregnancy is defined as DTC diagnosed during pregnancy or in the first 12 months postpartum. Physiological hormonal changes in pregnancy including Oestrogen and Human chorionic gonadotrophin (hCG) have been postulated as culprits for the development of DTC. Thyrotrophic activity of hCG may be implicated in the pathogenesis of DTC complicating pregnancy[15-20].

Differentiated thyroid carcinoma involves cervical lymph nodes in 20%–50% of patients (20-90% for papillary Ca of thyroid). Papillary carcinoma is typically unencapsulated, multifocal and bilateral in 30%. It is slow growing with micro-metastases approaching 90% at presentation, initially to cervical LNs and later to the lungs. Tall cell or columnar cell has more aggressive courses. Preoperative ultrasound identifies suspicious cervical adenopathy in 20%–31% of cases. Mulitfocal (2 foci) papillary cancers in the ipsilateral lobe have a higher rate of cancer in the opposite lobe as opposed to unifocal. Metastatic disease does not obviate the need for surgical excision of the primary tumour. Preoperative neck ultrasound for the contralateral lobe and cervical (central and bilateral) lymph nodes is recommended for all patients[23].

The surgical risks of two-stage thyroidectomy (lobectomy followed by completion thyroidectomy) are similar to those of a near-total or total thyroidectomy. Completion thyroidectomy is not needed for those with small (1 cm), intrathyroidal, node-negative, low-risk tumours. Radioactive iodine ablation in lieu of completion thyroidectomy is not recommended. RAI is indicated to patients with larger tumours (1.5 cm), or with residual disease after surgery, while lower risk patients do not show evidence for benefit[24].

Radioactive iodine ablation is recommended for patients with stages III and IV disease (AJCC sixth edition), all patients with stage II disease younger than age 45 years and most patients with stage II disease 45 years or older, and selected patients with stage I disease, especially those with multifocal disease, nodal metastases, extrathyroidal or vascular invasion, and/or more aggressive histologies[24].

Cervical ultrasonography is highly sensitive in the detection of cervical metastases in patients with differentiated thyroid cancer. This should be performed at 6 and 12 months and then annually for at least 3–5 years[24.]

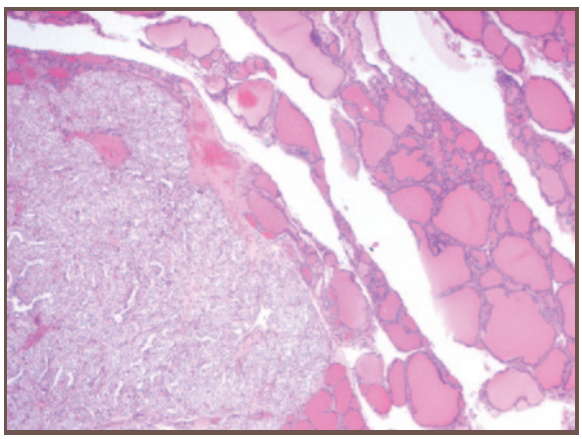
For patients with persistent disease, the serum TSH should be maintained below 0.1mIU/L indefinitely. For those who are clinically free of disease but who present with high risk disease, consideration should be given to maintaining TSH suppressive therapy to achieve serum TSH levels of 0.1 to 0.5mIU/L for 5–10 years. In patients free of disease, especially those at low risk for recurrence, the TSH may be kept within the low normal range (0.3 to 2mIU/L) [24.]

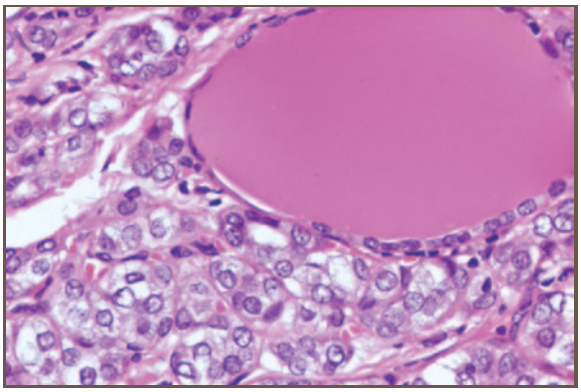
There was no difference in overall survival in patients with pregnancy-related DTC compared with other DTC. However, there were contradicting results reported with regard to the rate of recurrent or persistent disease in DTC related to pregnancy [23].

Few studies gave base to the policies about pregnant patients with DTC.

Data obtained through systematic review show conflicting results when it comes to observed outcomes in this population. The impact on overall survival in the long term appears to be unaltered[23.]

Previous study had suggested that pregnancy might promote growth of thyroid carcinoma but recent studies refuted the suspicion. There is no evidence to support termination of pregnancy when the diagnosis of DTC is made. The guidelines of the endocrine society for pregnancy-related DTC recommend thyroidectomy after delivery for patients with no evidence of advanced disease or without rapid progression, and thyroidectomy in the second trimester of pregnancy for the others (USPSTF recommendation level B). Radioactive iodine should only be given after delivery and the ending of breastfeeding[22.]





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Radiation Induced Thyroid Cancer

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Introduction

Radiation exposure of the thyroid gland during childhood is the most clearly defined environmental factor associated with thyroid cancer. The recent nuclear reactor accident in Japan due to the earthquake and tsunami, and the proximity to the nuclear power reactors in southern China has raised fears of radiation exposure in Hong Kong. The purpose of this review is to provide a better and up-to-date understanding of the effects of radiation to the thyroid gland.

Radiation and Thyroid Cancer

The risk of thyroid cancer had been investigated in many radiation-exposed groups, including the survivors of atomic bombing in Japan, and children exposed during therapeutic external radiation therapy for medical conditions. A pooled analysis of seven studies of external radiation exposure had proven that the thyroid gland was among the most radiation-sensitive tissues in the body, and there was a linear dose-response curve, with no evidence of a threshold at low doses[1]. This observation was confirmed by a nested case-control study from the Childhood Cancer Survivor Study cohort, which reported a linear dose-response curve with maximal risk of thyroid cancer at radiation doses between 20-29 Gy and a fall in risk with doses >30 Gy (consistent with a cell-killing effect)[2]. Studies on children following external radiation therapy for Hodgkin's disease demonstrated an inverse association between age at the time of radiation exposure and the risk of thyroid cancer, i.e. the younger the age at the time of radiation exposure the higher the risk[3,4]. A survey study of 4091 Hiroshima and Nagasaki atomic bomb survivors showed the effects of radiation persisted for several decades and then eventually wane[5,6]. Persistent elevation of risks had also been demonstrated in a study of 10,834 individuals irradiated in Israel for tinea capitis as children in the 1950s. The excess relative risk of thyroid cancer per Gy peaked after 20 to 29 years, and then fell substantially, but was still significant after more than 40 years[7].

Chernobyl Accident

The most recent evidence for such an association between radiation exposure and an increased thyroid cancer risk came from the Chernobyl power plant accident in 1986, which resulted in a substantial increase in thyroid cancer incidence among those exposed as children or adolescents in the three republics (the whole of Belarus and Ukraine, and the four most affected regions of the Russian Federation). Amongst those under aged 14 and 18 years in 1986, 5,127 and 6, 848 cases of thyroid cancer were reported between 1991 and 2005, respectively[8]. There was no evidence of a decrease in the excess incidence of thyroid cancer up to 2005 (Figure 1). Part of the increase was related to the normal age pattern of disease occurrence but the majority of the increase was attributed to the radiation exposure. In Belarus, the relative incidence of thyroid cancer per one million children younger than 15 years ranged from 1 to 3 from 1986 to 1989 and increased to 12 -35 between 1990 and 1995. In the region of Gomel, which had been contaminated most heavily by radioactive fallout containing iodine -131 and short-lived radioisotopes of iodine, the relative incidence of childhood thyroid cancer increased from 3-10 per one million between 1986 and 1989 to 33-135 per one million between 1990 and 1996[9].

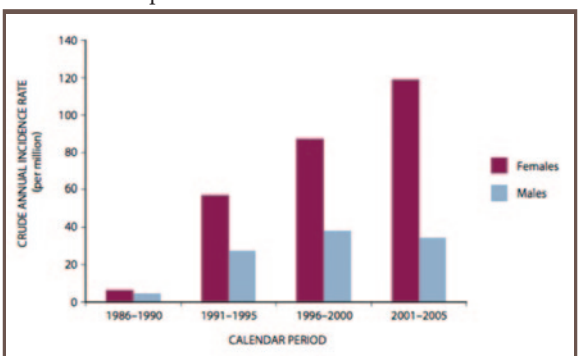

Figure 1. Thyroid cancer incidence rate among those exposed as children and adolescents (age under 18 years in 1986) in Belarus

The exposure was likely due to the high levels of radioactive iodine released from the Chernobyl reactor in the early days after the accident. Radioactive iodine was deposited in pastures, eaten by cows that then concentrated it in their milk, which was subsequently drunk by the children. This was further exacerbated by a general iodine deficiency in the local diet causing more of the radioactive iodine to be accumulated in the thyroid. Since radioactive iodine is short lived, if people had stopped giving locally supplied contaminated mild to children for a few months following the accident, it is likely that most of the increase in radiation-induced thyroid cancers would not have resulted.

One of the concerns about these findings was attributed to the undertaken screening programmes following

the Chernobyl accident, by ultrasonography and fine-needle aspiration biopsy. However, subsequent screening of children born after the accident in the same regions demonstrated the absence of cancer in this age group (Figure 2). Furthermore, because everyone in the prospective studies was screened regardless of dose, confounding by screening intensity is unlikely by demonstrating a linear dose-response relationship from recent prospective studies[10,11].

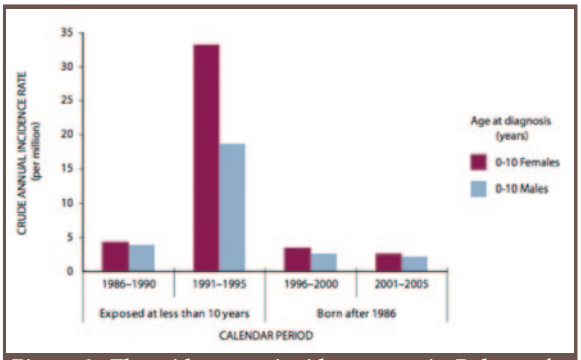

Figure 2. Thyroid cancer incidence rate in Belarus for children under 10 years old at diagnosis

In addition to the demonstration of a strong, consistent association between radiation dose and risk of thyroid cancer, this cohort study suggested that thyroid cancers attributable to I-131 exposure continued to occur two decades after exposure. There was no indication of diminishing the excess relative risk (ERR) per Gy with increasing time since exposure. Moreover, the trend for increasing ERR per Gy with decreasing age at exposure was also proved in this studies that the ERR per Gy for 0-4 years of age at exposure was ten times more than that for 12-18 years at exposure (7.43 vs 0.69)[11].

There was some indications that nutritional iodine deficiency at the time of exposure might increase the risk of developing thyroid cancer after incorporation of radioiodine[12]. On the other hand, prolonged stable iodine supplementation in the years after exposure might reduce this risk[8]. While the modification of the I-131 related thyroid cancer risk by iodine prophylaxis or intake of stable iodine was important in view of the mild-to moderate iodine prevailing in northern Ukraine, it is difficult to study since data on iodine status at the time of the accident, the most relevant time period, were not readily available.

Clinicopathological Aspects

Studies of early Chernobyl-related tumours by several groups found that a very high proportion showed RET rearrangement, predominantly RET/PTC3[13-16]. It was speculated that this rearrangement might be a marker for radiation-induced tumours. However, more recent papers have suggested that this may be related more to the young age of the patients in the study, because frequent RET/PTC3 rearrangements have also been observed, with similar prevalence, in sporadic papillary carcinomas form children and young adults[17,18]. These findings may therefore reflect more the association between the solid morphological subtype with RET/PTC3 rearrangement and the age of the patient at diagnosis, rather than the aetiology of the tumour.

Papillary carcinoma accounted for over 90% of thyroid cancers after the Chernobyl accident. Similar to sporadic childhood papillary carcinoma, they were generally more aggressive, and associated with a higher frequency of cervical nodes and lung metastases as compared with adult cases[19]. Farahati et al. reported an inverse association between the age at exposure and severity of the disease in children from Belarus with thyroid cancer. Compared with older children, the younger group (2-4 years of age) showed more frequently extra-thyroidal invasion of tumours, more lymph node involvement and distant metastases[20].

Treatments of papillary thyroid cancer with or without radiation exposure are similar. Surgery and radioiodine ablation remain the principal treatment of Post-Chernobyl thyroid cancers. However, most patients remained very young at the age of treatment, and the prognosis of this disease in most cases was excellent, issues such as quality of life and long term complications of the treatment should be addressed. The extent of surgery has been a matter of debate for many years. Total or near-total thyroidectomy may be associated with a higher incidence of life-long voice disability or calcium replacement at young age. The availability of Vitamin D analogues in these areas might also be considered. However, a safe surgical procedure frequently results in recurrence in the thyroid remnants or lymph node involvement. In the Belarusian series every fourth patient had to undergo completion thyroidectomy for local relapse or residual tumour after primary lobectomy or subtotal thyroidectomy[21].

Radioiodine ablation of thyroid remnants and lung metastases was found to be more difficult to achieve in this particular category of patients due to their young age, and the use of relatively less radical surgical procedures[22]. The use of repeated fractionated radioiodine therapy for complete remission of lung metastases should be discussed critically, since the risk of radiation induced pulmonary fibrosis in these patient groups has to be seriously taken into consideration[23].

Role of Potassium Iodide (KI)

In addition to evacuation, sheltering (staying in an unventilated room with the doors and windows closed), and avoiding contaminated food, milk, and water, Potassium iodide should be included in the emergency plan during a nuclear event, if radioactive iodine is released. Potassium iodide (KI) is the same form of iodine used to iodise table salt. KI floods the thyroid with iodine, thus preventing radioactive iodine from being absorbed. If taken at the proper time, KI protects the thyroid from radioactive iodine from all sources – air, food, milk, and water.

The benefit of KI is based on the experiences from Poland, immediately adjacent to Belarus and Ukraine, that distributed KI to 18.5 million people after exposure to the Chernobyl fallout and does not appear to have had an increase in thyroid cancers[24].

The World Health Organization endorses KI, and the U.S. Food an Drug Administration (FDA) has published general recommendations for KI doses: a full 130-mg pill for adults, 65 mg for children 3-18 years old, 32 mg for babies 1 month to 3 years old, and 16 mg for newborns up to 1 month old. Taken 6-12 hours before exposure to radioactive iodine, KI fills the thyroid cells and prevents the gland from absorbing radioactive iodine. KI is also protective if taken within the first few hours after exposure to radioactive iodine. People should take one dose a day, only while they are being exposed to radioactive iodine and one day afterwards. However, an April 2002 FDA statement says that "absolute precision in dosing is generally not critical to safety or efficacy" and "the overall benefits of KI far exceed the risks of overdosing, especially in children." Side effects of KI are rare. The only people who should not take KI are those who have had a major allergic reaction to iodine. If taken for long enough, KI can cause temporary hypothyroidism.

Conclusion

Available data make the relationship between radiation exposure in childhood and adolescence and thyroid tumourigenesis incontrovertible. Although post-radiation thyroid cancers appear to be more aggressive, over 90% of patients survive the disease, but they will always remain at risk for recurrences and require lifelong medical care. Likewise, people who were exposed to radioactive iodine from the nuclear accident but have not developed thyroid cancer remain at risk for life and must continue to be monitored. The demands of regular testing and care for this large population are putting a heavy burden on both patients and health care systems, and the impact in economic, social and psychological aspects is enormous.

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of nonfatal MI + fatal CHD in patients with hypertension (p=0.0005)[1]

Diabetes

37% RRR

time to first occurrence of major CV events in patients with diabetes (p=0.0005)[2]

High Risk

CHD

59% RRR

of nonfatal MI in patients with CHD (p=0.0001)[3]

CHD

22% additional RRR

of major CV events in patients with CHD (p<0.001)[4]

Highest Risk

ACS

16% RRR

of major CV events in patients with ACS (p=0.005)[5]

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Practical Approach : The Diabetic Foot & Podiatry

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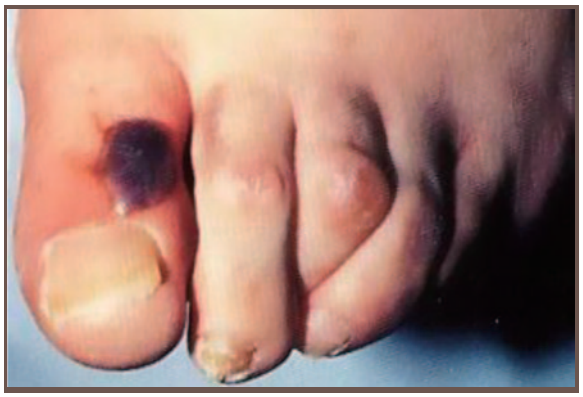
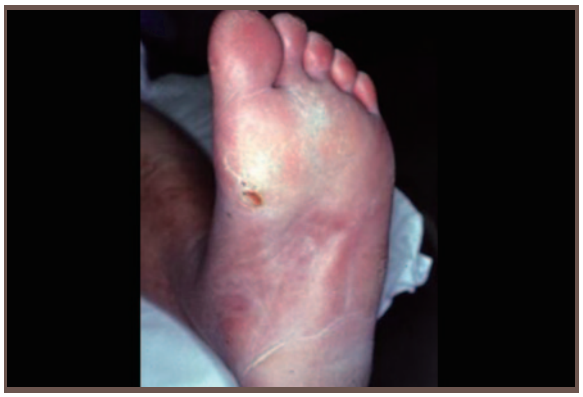
Podiatrist (Private Practice)

Mr. Peter WH KOO

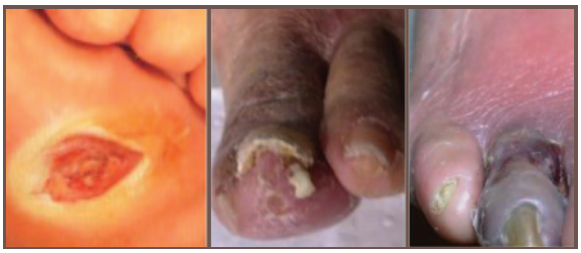
- Symptoms of the chronic diabetic foot with foot-at-risk for ulceration / amputation
  - Weakness, tiredness & poor concentration
  - Reduced self foot care ability / self neglect
  - Itchy skin / skin scratching induced lesions
  - Swollen ankles / abrasion / with difficulties to fit shoes



- Pragmatic findings about the diabetic foot-at-risk for ulceration & amputation
  - Increased risk of trauma
  - Foot ulcers are common in older diabetic patients
  - Ulcers on the foot less likely to heal quickly
  - More likely to become infected and to spread
  - More likely to result in amputation
  - Diabetic associated foot-at-risk factors
  - Peripheral arterial disease is the most prevalent condition linked with limb ischaemia in renal failure patients



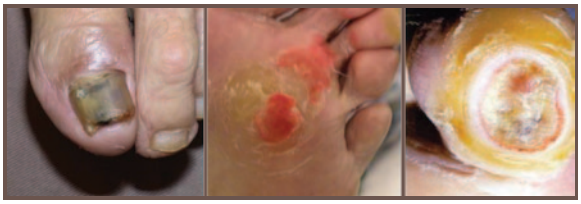
- Pathogenesis of foot lesion
  - Factors put a certain individual "at risk"
  - Event leads to an actual break in the skin
  - Factors delay healing & lead to complications
    - Ulcers on the feet of diabetic patients are worrying because they are slow to heal and quick to become complicated.
    - Once an ulcer is infected, healing is delayed even further and underlying ischaemia is worsened.



- Foot care team for diabetic patients
  - Patient
  - DM Nurse
  - Podiatrist
  - Primary Care Physician
  - Diabetologist
  - Vascular Surgeon

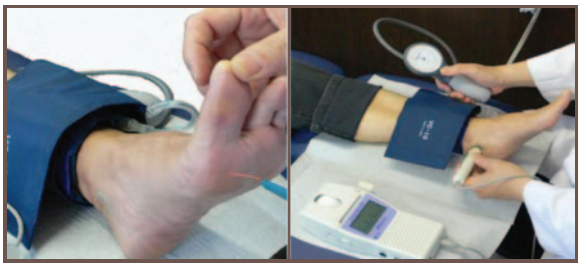
- Roles of podiatrists in diabetic foot care
  - Podiatrists are those members of the multidisciplinary team who provide regular and routine foot care.
  - They are often the first to notice potential problems, to detect ulcers that have occurred as a consequence of trauma, and to observe when an ulcer has become infected.
  - Podiatrists are also in an ideal position to teach the patients about the relationship between diabetes and foot problems, emphasising the need for regular inspections and a sensible approach to hygiene.
  - Thus they can give general advice in washing, changing socks regularly and drying between the toes in order to prevent the accumulation of moist debris in the toe, which provides an excellent climate for fungal invasion.

- Treatment : Preventive Foot care for Foot-at-risk by Podiatrists



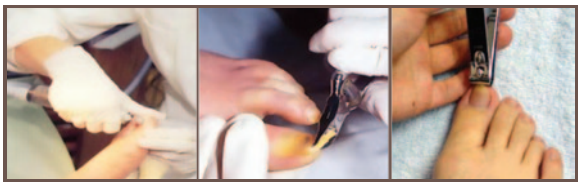
- Podiatric treatment principles for diabetic foot problems
  - Primary foot assessment
  - Classification of foot-at-risk for ulceration & amputation
  - Foot & leg skin condition & wound management
  - Dressing prescription
  - Mechanical offloading of ulcers or severe complications
  - Minor surgery under local anaesthetic

- Screening and assessment for diabetic foot-at-risk conditions
  - Common diabetic foot-at-risk classification systems for reference
  - Common diabetic foot-at-risk classification systems place individuals into five different categories : normal, high risk, ulcerated, infected and the most critical stage, necrotic.
  - Sensory Test Vascular Assessment

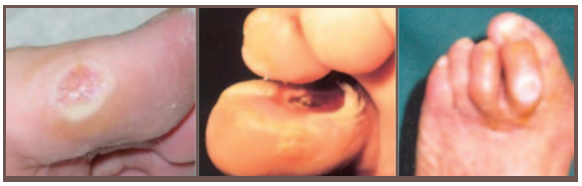


- Common self foot care problems contributing to diabetic foot ulceration
  - Toe nail problems

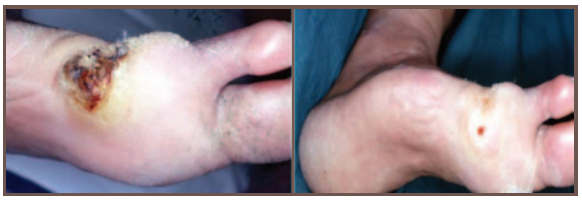
    - Preventive routine nail care and advice for nail trimming technique



    - Other self foot care problems contributing to diabetic foot ulceration
  - Blisters, Corns & Calluses

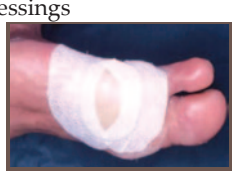


- Purpose of debridement
  - The purpose of debridement is to create the best possible environment for wound healing.



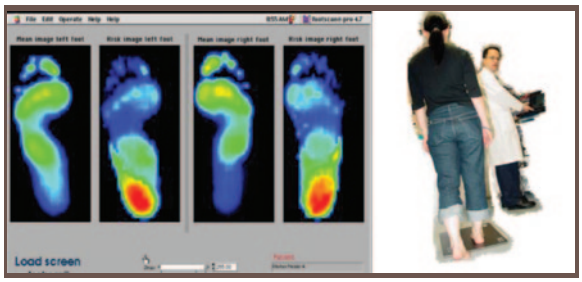
- Treatment considerations by podiatrists in the management of the diabetic foot
  - Preventive Podiatric treatment
  - Periodic Podiatric follow-ups
  - Fit shoes properly
  - Control leg biomechanics
  - Offer patient foot care education
  - Referral to experts for further management
    - People with diabetic disease should be advised to wear high-quality, cushioned soled running or sports shoes rather than ordinary shoes.
    - People with high-risk feet, deformity, or previous amputation, custom-built footwear or orthotic insoles should be used to reduce callus severity and ulcer recurrence.
    - Treatment : Self foot care abilities
    - The ability of the person to undertake regular self foot care and self-assessment should also be assessed by the health care practitioner.

- Treatment : Applications & Dressings
  - Conventional / Protective
  - Antiseptics
  - Promote healing dressings
  - Applications of Special Dressings

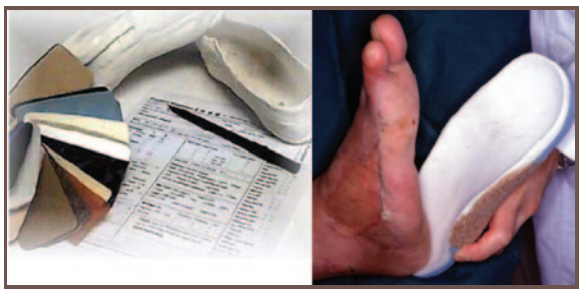


    - Selection of suitable footwears for Foot-at-risk

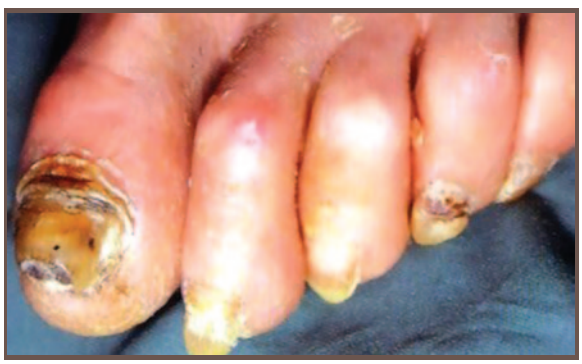
- Identification of Peak Pressure Loading



- Custom Made Shoes & Foot Orthotics for Diabetic Patients
  - Foot Orthotics & Appliances
  - Foot Orthotics
  - Appliances used in shoes
  - May be in the form of cushioned insoles, and arch supports etc.
  - They can be purchased over the counter or they can be custom made



- Patient / Caregiver Education to Include Daily Inspection for the Following:
  - Cracks in skin
  - Sores
  - Toenail changes
  - Skin temperature changes
  - Blisters
  - Odour
  - Change in foot shape
  - Swelling
  - Corns/Calluses
  - Redness



- Practical tips for diabetic patients
  - NEVER walk barefoot, or wear sandals which leaves the toes exposed
  - Wear only well fitting shoes made of soft leather, with lace-up or velcro fasteners which hold the feet firmly in place & prevent them from slipping forward, putting pressure on the toes.
  - If it is necessary to put on extra orthotics into your shoes, make sure the shoes have enough space.
  - New shoes shouldn't be worn for more than two hours on the first occasion, after which the feet should be inspected for any signs of redness which might indicate rubbing

- Six Steps to a pair of Healthier Feet
  - Wear comfortable shoes & socks that fit the feet
  - Wash & dry feet thoroughly, especially between the toes
  - Keep your toenails trimmed short & straight across
  - Apply cream or lotion to the feet to keep the skin smooth
  - Wear clean socks or stockings & avoid wearing the same shoes two days in a row
  - See Podiatrist for preventive foot care or any persistent foot problem

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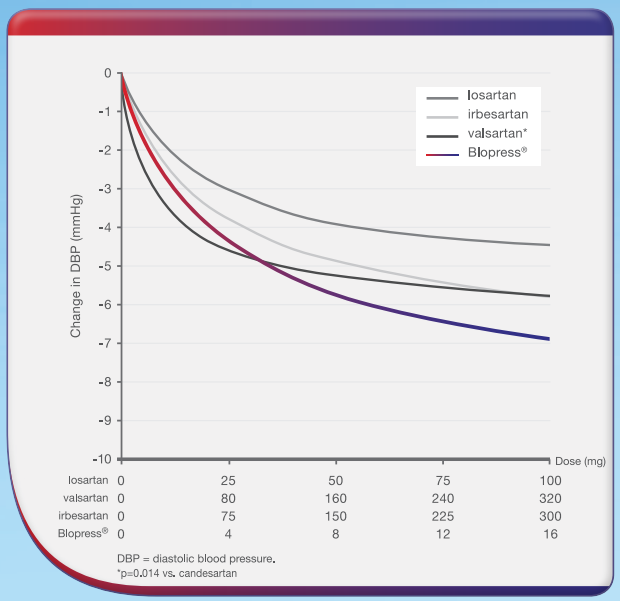

DBP = diastolic blood pressure.
*p=0.014 vs. candesartan

A meta-analysis of randomised, double-blind, placebo-controlled, parallel-group studies in adult men and women with mild to moderate primary diastolic hypertension, using data submitted to the US FDA, to assess the dose-response relationship for the first four AT1-receptor blockers (ARBs). Adapted from Elmfeldt D, *et al.*[1]

1. Elmfeldt D, *et al. Blood Press* 2002; 11: 293-301.

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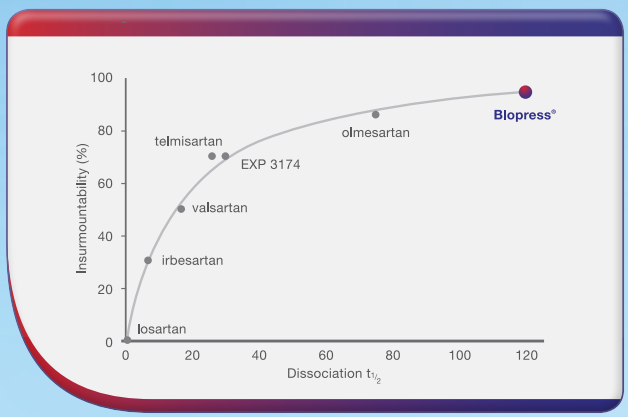

Correlation between the degree of insurmountability and the corresponding experimental dissociation half-lives from the AT1 receptor of different ARBs.

2. Van Liefde I and Vauquelin G. *Mol Cell Endocrinol* 2009; 302: 237-243.

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Treatment for Diabetic Peripheral Neuropathy

Dr. Edward HC WONG

MBChB (Auckland), MRCP (UK), FHKCP, FHKAM (Medicine)
Specialist in Neurology

Diabetic peripheral neuropathy is a common clinical problem. More than 50% of diabetic patients will develop peripheral neuropathy over time and 14% will have severe symptoms.[1] The most common subtype is distal symmetrical sensorimotor polyneuropathy. Clinical manifestation reflects the gradual loss of integrity of both large and small myelinated and unmyelinated nerve fibres. Loss of vibratory sensation and altered proprioception reflect large-fibre loss. Impairment of pain, light touch and temperature are secondary to loss of small fibres. These can be further divided into so-called "positive" symptoms, including persisting burning or dull pain, paroxysmal electric shooting pain, hyperalgesia and numbness, as well as "negative" symptoms such as hypoalgesia, and reduction of thermal or pressure sensation.

Treatment for diabetic peripheral neuropathy can be categorised into pathogenesis-orientated and symptomatic treatment. The goal of pathogenesis-oriented treatment is to slow the progression of neuropathy. It includes optimisation of glycaemic control and specific pharmacological therapy. For symptomatic treatment, the main focus is pain control with the use of analgesics, antidepressants and anticonvulsants.

Pathogenesis-oriented treatment

Glycaemic and risk factor control: Tight glycaemic control is the most important component to slow down the progression of diabetic neuropathy. This benefit was confirmed by the Diabetes Control and Complication Trial (DCCT), in which the development of clinically-evident neuropathy was reduced by 64% with intensive insulin therapy.[2] Its beneficial effect persisted for at least 8 years during follow-up. Patients with established neuropathy at baseline were also found to have improved nerve conduction study parameters with good glycaemic control.[3] The treatment target for HbA1C should be <7%.

Oxidative stress reduction: One of the mechanisms implicated in the pathogenesis of diabetic neuropathy is increased oxidative stress. Benfotiamine, a lipophilic pro-drug of thiamine pyrophosphate, has been shown to block the four major pathways related to oxidative stress, impaired vascular function and formation of glycation end-products. It achieves this by activation of transketolase, the rate-controlling enzyme of the reductive pentose phosphate pathway.[4,5] It has been shown a 3-6 weeks therapy of 400-600mg/day resulted in improvement of neuropathy and pain scores in small-scale studies.[6]

Alpha-lipoic acid (ALA) is another potent antioxidant to diminish the oxidative stress from enhanced superoxide production in diabetic peripheral neuropathy. In the SYDNEY trial, 120 diabetic patients with symptomatic polyneuropathy were treated with either a three-week course of intravenous ALA at 600mg/day versus placebo. Significant improvement was found in each component of Total Symptom Score (TSS): lancinating and burning pain, numbness and prickling.[7] The efficacy of different oral ALA dosages at 600mg, 1200 or 1800mg/day was investigated in the SYDNEY II trial. 50-62% of patients receiving ALA achieved reduction in TSS of at least 50%, compared to 26% of the placebo group. Higher dosages (1200mg and 1800mg) were associated with side effects of nausea and vertigo, but a favourable safety profile was shown in the 600mg/day group with similar efficacy.[8]

Symptomatic treatment

Antidepressants: Randomised controlled trials have shown that amitriptyline, duloxetine and venlafaxine are effective in reducing pain in diabetic neuropathy.[9,10] Tricyclic antidepressants act centrally to reduce perception of pain, but not selective serotonin reuptake inhibitors. Patients who received amitriptyline was almost twice as likely to achieve reduction in pain symptoms compared to placebo. Common side-effects of tricyclics are dry mouth and somnolence, and they are contraindicated in patients with ischaemic heart disease. Similar efficacies in pain reduction were observed for duloxetine and venlafaxine (a serotonin-norepinephrine reuptake inhibitor) with nausea and somnolence being their common side-effects.[10]

Anticonvulsants: Pregabalin appears to be a presynaptic inhibitor of the release of excitatory neurotransmitters including substance P, glutamate and calcitonin gene-related peptide.[11] At 300-600mg/day, its effectiveness in symptomatic treatment of diabetic neuropathy was confirmed in a pooled-analysis of seven randomised clinical trials, with twice as many responders compared to placebo.[12] Gabapentin (900-3600mg/day) and sodium valproate (500-1200mg/day) are possibly effective as well. Sedation, dizziness and ataxia are potential side effects of these anticonvulsants. The evidence to support the use of other anticonvulsants, such as topiramate and carbamazepine, are less conclusive.[13]

Analgesics: Opioids are effective in pain relief for diabetic neuropathy patients. The use of tramadol, oxycodone, and dextromethorphan are supported by clinical trial evidence.[14-16] Limitations for their use are the high frequency of side effects and concerns of dependence.

Foot care: Patients should be instructed to check for signs of early infection, skin breaks and callus formation on a daily basis. Feet should be cleansed with mild soap and lukewarm water, pat dried and followed by application of skin moisturiser. Properly-fitted, but not overly-tight shoes are essential. Inspection of feet should be carried out at each doctor's visit, with access to podiatry input if needed.[17]

Conclusion

The symptoms of diabetic peripheral neuropathy have a detrimental effect on patients' quality of life. They are also more prone to develop foot ulceration and infection leading to limb amputation. Glycaemic control, pathogenesis-oriented and symptomatic treatment, as well as general foot care are integral to the lowering of the long term impact of diabetic peripheral neuropathy.

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Moving Stills and Flowing Energy

Ms. Simone BOON

Photography, Ceramics & Sculpture and Multimedia

Ms. Simone BOON

Photographs are often called memento mori, since the moment captured does not exist anymore when looking at the image. In these series of photographs, made over the last two years, a different view is given. The aim was to capture the becoming not the being, and it was a way for me to reflect on the essence of human (female) identity. Not the moment here and now, but the inclusion of the moment of before and -after.

"In reality the body is changing form at every moment, or rather there is no form, since form is immobile, and the reality is movement, What is real is the continual change of form. Form is only a snapshot view of a transition. (French philosopher Henry Bergson, Creative Evolution).

With these words as starting point I experimented with an alternative way in photography. When there is form in the images, it is the digital photographic capture of transitions in time, a record of more moments in one image, unveiling invisible patterns and shapes we could not have captured with our bare eyes.

Personal note:

Life is unfathomable and includes mortality. Living with a chronic disease, (brittle type 1 diabetics) makes me even more aware of this.

I am not great in accepting my disease, and do not place it on the for-ground or as first priority automatically. To get me controlled is not an easy job for an endocrinologist. It goes so easily out of my focus that I could use repeated rehabilitation programs to get me on track again… understanding and guidance of a doctor is very helpful for the diabetic control and I would advise others to try to keep better control than I manage, to avoid complications.

Art can take me completely away and asks my 100% attention, while in the process of making it, I find great fulfillment in doing art, it is like swimming as a fish in the water, is for why I was born.

The advantage is that I live life to its full, and do not let me turn down or get me off track too much.

My relatives are not controlled constantly by the demands of my diabetics, and my social environment does not notice it that much. But sometimes I have to explain for own health sake, why certain symptoms or behaviour I have, when in a hypo, or why I have that remote control for my pump…

It is not easy to live with diabetics, it is with you every second of the day.

Nevertheless it does not mean you can't become a professional in your passion or interest, just go for it!

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Federation Annual Dinner 2011

On 31 December 2011, the Federation Annual Dinner 'Casablanca' was held. The evening was a fun and excellent entertainment with fabulous program arranged by Suzan Productions, and wonderful performances from Grammy award nominee Mr. Howard McCrary, joined by the glamorous Ms. Suzan Guterres and various other local artists.

The audience all had a great time with the exciting activities and programs like games booth, gaming tables for charity, wine tasting, portrait shooting, Chinese paintings display, table prizes, raffles, bingo game, song dedication and the climax of the evening – countdown to New Year 2012.

We would like to thank all our gift and table sponsors and especially our dinner sponsors: Lexus/Crown Motors, Mekim and Dr. Laurence HOU.

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Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1	* FMSHK Foundation Meeting 2	3	4
5	6	* FMSHK Officers' Meeting * HKMA Council Meeting 7	* HKMA CW&S Community Network – Endovascular Therapy for Varicose Veins & Peripheral Arterial Disease 8	* HKMA Hong Kong East Community Network -- Is it possible to Achieve the Aggressive LDL-C target Goals for Diabetic Patients? * HKMA NT West Community Network – Management of Atopic Dermatitis * HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2012 -- When should we think of a gynaecological cancer? 9	10	* HKMA Powerlifting subcommittee Training Session 11
12	13	14	15	* MPS Workshop – Mastering Adverse Outcomes 16	17	* HKMA Powerlifting Subcommittee Training Session * MPS Workshop – Mastering Professional Interactions 18
* MPS Workshop – Mastering Difficult Interactions with Patients * HKMAPS 1st Seasonal photo Competition 19	20	21	22	* FMSHK Executive Committee and Council Meeting 23	24	* HKMA Pwerlifting Subcommittee Training Session 25
26	27	28	* MPS Workshop – Mastering difficult Interactions with Patients 29			

Date / Time	Function	Enquiry / Remarks
2 THU 8:00 pm	**FMSHK Foundation Meeting** Organiser: The Federation of Medical Societies of Hong Kong, Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Sonia CHEUNG Tel: 2527 8898 Fax: 2865 0345
7 TUE 8:00 pm	**FMSHK Officers' Meeting** Organiser: The Federation of Medical Societies of Hong Kong, Venue: Gallop, 2/F., Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Sonia CHEUNG Tel: 2527 8898 Fax: 2865 0345
8:00 pm	**HKMA Council Meeting** Organiser: The Hong Kong Medical Association, Chairman: Dr. Kin CHOI, Venue: HKMA Head Office, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Christine WONG Tel: 2527 8285
8 WED 1:00pm	**HKMA CW&S Community Network – Endovascular Therapy for Varicose Veins & Peripheral Arterial Disease** Organiser: HKMA CW&S Community Network, Chairman: Dr. LAW Yim Kwai, Speaker: Dr. TSE Cheuk Wa, Chad, Venue: The Hong Kong Medical Association Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central	Mr. Alan LAW Tel: 2527 8285 1 CME point
9 THU 1:00pm	**HKMA Hong Kong East Community Network -- Is it possible to Achieve the Aggressive LDL-C target Goals for Diabetic Patients?** Organiser: HKMA Hong Kong East Community Network, Chairman: Dr. Yip Yuk Pang, Kenneth, Speaker: Dr. Norman Chan Venue: HKMA Head Office, 5/F Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Miss Candice TONG Tel: 2527 8285 1 CME point
1:00pm	**HKMA NT West Community Network – Management of Atopic Dermatitis** Organiser: HKMA NT West Community Network; Chairman: Dr. LEE Fook Kay, Aaron; Speaker: Dr. Steven LOO King Fan, Venue: Maxim's Palace Chinese Restaurant, Tuen Mun	Mr. Alan LAW Tel: 2527 8285 1 CME point
2:00 pm	**HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2012 -- When should we think of a gynaecological cancer?** Organiser: The Hong Kong Medical Association; Speaker: Dr. TAM Kar Fai; Venue: The Hong Kong Medical Association Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central	HKMA CME Department Tel: 2527 8452 1 CME point
11 SAT 1:00pm	**HKMA Powerlifting subcommittee Training Session** Organiser: The Hong Kong Medical Association, , Venue: HKMA Head Office, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Miss Alice TANG Tel: 2527 8285
2:30 pm	**Refresher Course for Health Care Providers 2011/2012** Organiser: The Hong Kong Medical Association; Speaker: Dr. Tin Sik CHENG; Venue: OLMH	HKMA CME Department Tel: 2527 8452 2 CME Points
16 THU 6:30pm	**MPS Workshop – Mastering Adverse Outcomes** Organiser: The Hong Kong Medical Association, Speaker: Dr. HUNG Chi Wan, Emily, Venue: Eaton Hotel	HKMA CME Department Tel: 2527 8452 2.5 CME Points
18 SAT 2:00pm	**HKMA Powerlifting Subcommittee Training Session** Organiser: The Hong Kong Medical Association, Venue: HKMA Head Office, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Miss Alice TANG Tel: 2527 8285
2:30pm	**MPS Workshop – Mastering Professional Interactions** Organiser: The Hong Kong Medical Association, Speaker: Dr. Hau Ka Lam, Venue: The Hong Kong Medical Association Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central	HKMA CME Department Tel: 2527 8452 2.5 CME Points
19 SUN 2:00pm	**MPS Workshop – Mastering Difficult Interactions with Patients** Organiser: The Hong Kong Medical Association, Speaker: Dr. Cheng Ngai Sing, Justin, Venue: Holiday Inn	HKMA CME Department Tel: 2527 8452 2.5 CME Points
2:00pm	**HKMAPS 1st Seasonal photo Competition** Organiser: The Hong Kong Medical Association, Venue: HKMA Head Office, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Miss Alice TANG Tel: 2527 8285
23 THU 7:00-10:00pm	**FMSHK Executive Committee and Council Meeting** Organiser: The Federation of Medical Societies of Hong Kong, Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Sonia CHEUNG Tel: 2527 8898 Fax: 2865 0345
25 SAT 2:00pm	**HKMA Pwerlifting Subcommittee Training Session** Organiser: The Hong Kong Medical Association, Venue: HKMA Head Office, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Miss Alice TANG Tel: 2527 8285
29 WED 6:30pm	**MPS Workshop – Mastering difficult Interactions with Patients** Organiser: The Hong Kong Medical Association, Speaker: Dr. CHENG Ngai Sing, Justin, Venue: The Hong Kong Medical Association Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central	HKMA CME Department Tel: 2527 8452 2.5 CME Points

Meeting

6/2/2012	**A small mass in a solitary kidney** Organiser: Hong Kong Urological Association, Venue: Multi-disciplinary Simulation and Skills Centre 4/F, Block F, QEH, Time: 7:30 – 8:30pm, Chairman: Dr. Yu Cheong, Associate Consultant, Speakers: Dr Lee Yue Kit Chris, Resident, CME Accreditation: 1 point, Enquiry: Dr HUNG Hing Hoi/ Ms Tammy Hung Tel: (852) 2958 6006/ 9609 6064, Fax: (852) 2958 6076/ 8344 5115
8/2/2012	**Hong Kong Neurosurgical Society Monthly Academic Meeting – Natural history and treatment of unruptured intracranial aneurysm** Organiser: Hong Kong Neurosurgical Society, Venue: Seminar Room, Ground Floor, Block A, Queen Elizabeth Hospital, Time: 7:30am, CME Accreditation: 1.5 point, College of Surgeons of Hong Kong, Chairman: Dr. CHENG Kin Ming, Speaker: Dr. TSANG Chun Pong, Registration & Enquiry: Dr. Gilberto Leung, Tel: (852) 2255 3368, Fax: (852) 2818 4350

Answer to Dermatological Quiz

1. This elderly woman presented with this asymptomatic quite discrete erythematous to dark red telangiectatic round papules on her face, lips, tongue, palms and fingers. Some had an ill-defined border and stellate appearance. Together with the history of recurrent epistaxis and GI bleeding and the positive family history of similar characteristic skin lesions, the diagnosis of hereditary haemorrhagic telangiectasia (HHT, also known as Osler-Weber-Rendu disease) can be made. The longstanding history of the cutaneous telangiectasia with episodes of GI/nasal bleeding and the positive family history had negated other less likely possibilities such as hereditary benign telangiectasia which did not have any visceral involvement.

   HHT is an autosomal dominantly inherited disorder with late-onset penetrance characterised by skin, mucous membrane and visceral telangiectases. These telangiectases represent small arteriovenous malformations with a tendency to bleed. The first manifestation of HHT is usually epistaxis onset in childhood and subsequently complicated by GI or genitourinary bleeding in adulthood resulting in iron deficiency anaemia. Cutaneous telangiectases appear most commonly on the face, lips, tongue, palms and fingers characteristically as shown by our patient.

2. In addition to the common GI involvement, an estimation of 30 % of HHT patients have hepatic arteriovenous fistulas and malformations (AVM), 30% have pulmonary AVM and 10-20% have cerebral AVMs. As a result, radiological imaging of the internal organs, as guided by clinical symptoms, to screen for any AVM is indicated.

Dr. Ka-ho LAU
MBBS(HK), FRCP(Edin, Glasg), FHKCP, FHKAM(Med)
Yaumatei Dermatology Clinic, Social Hygiene Service

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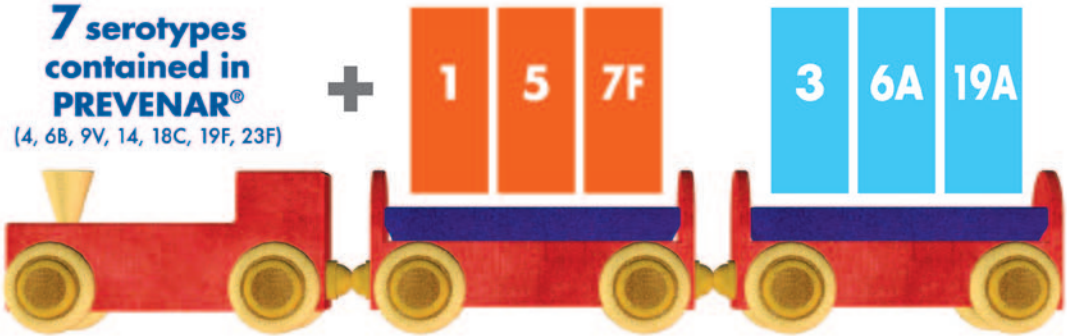

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