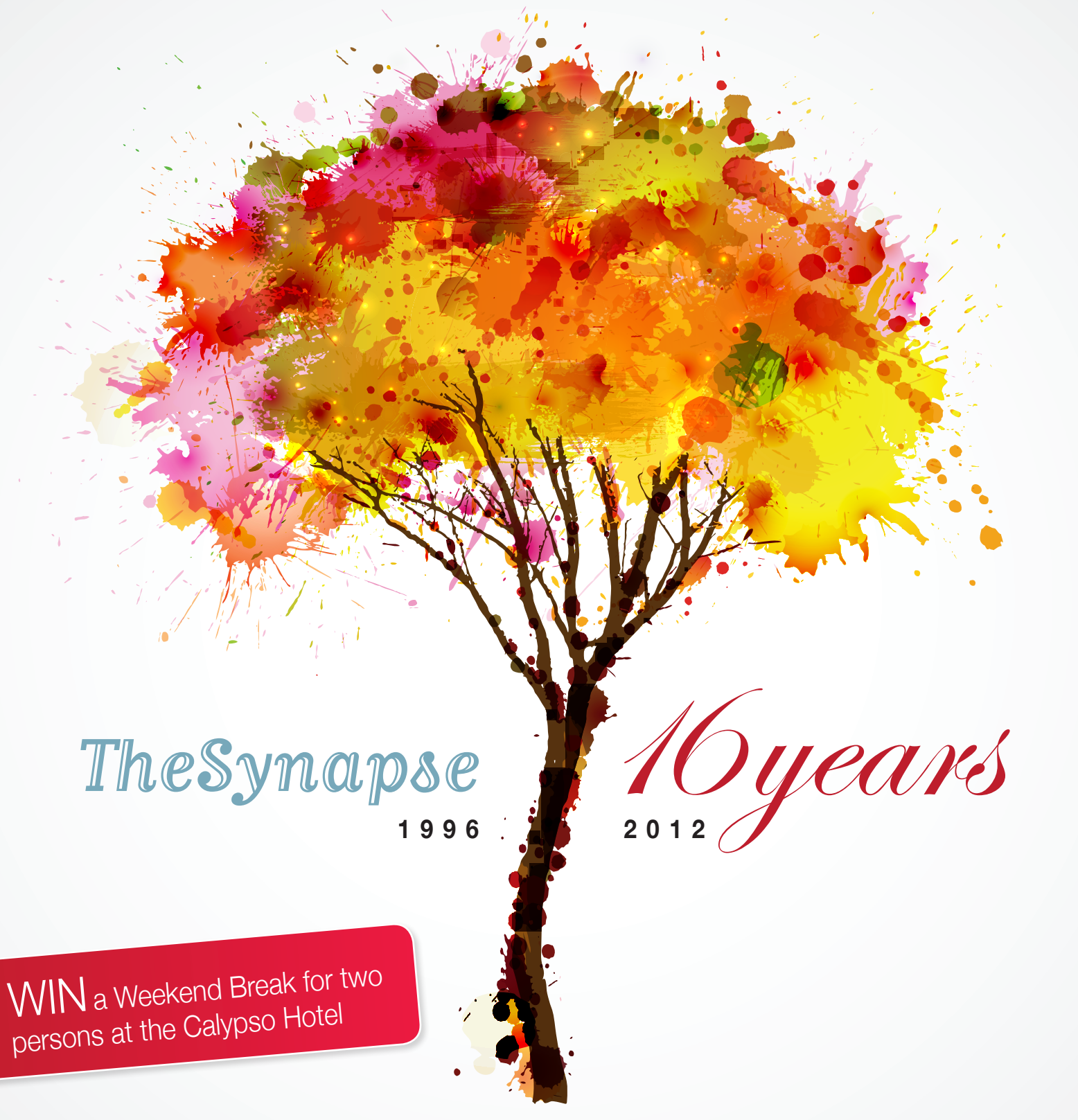
NEWSPAPERPOST

TheSynapse

The Medical Professionals' Network

Issue 05/12



TheSynapse 1996 . 2012 16 years

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Onbrez® Breezhaler®

The only Ultra[1] - LABA — offers patients[2]:

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- ✔ Rapid onset of action within five minutes from the first dose
- ✔ Significant reduction in the use of and need for rescue medication
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- ✔ Available in 150µg and 300µg: two dose strengths allowing flexibility when treating patients with COPD
- ✔ Onbrez® Breezhaler® allows patients to hear, feel and see that they have taken the full dose correctly

Onbrez Breezhaler (indacaterol) inhalation powder, hard capsules
PRESENTATION: Onbrez Breezhaler 150mcg and 300mcg inhalation powder hard capsules containing indacaterol maleate, and separate Onbrez Breezhaler inhaler. INDICATIONS: For maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD). **DOSAGE AND ADMINISTRATION:** Recommended dose is the inhalation of the content of one 150mcg capsule once a day, administered at the same time of the day each day, using the Onbrez Breezhaler inhaler. Capsules must not be swallowed. Dose should only be increased on medical advice. The inhalation of the content of one 300mcg capsule once a day has been shown to provide additional clinical benefit with regard to breathlessness, particularly for patients with severe COPD. Maximum dose is 300mcg once daily. No dose adjustment required in elderly patients, for patients with mild and moderate hepatic impairment or for patients with renal impairment. No data available for use in patients with severe hepatic impairment. No relevant use in the paediatric population. If a dose is missed, the next dose should be taken at the usual time the next day. **CONTRAINDICATIONS:** Hypersensitivity to the active substance, to lactose or to any of the other excipients. **WARNINGS/PRECAUTIONS:** *Asthma:* Onbrez breezhaler should not be used in asthma.. *Paradoxical bronchospasm:* If paradoxical bronchospasm occurs Onbrez Breezhaler should be discontinued immediately and alternative therapy substituted. D*eterioration of disease:* Not indicated for treatment of acute episodes of bronchospasm, i.e. as rescue therapy. *Systemic effects*: Indacaterol should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension), in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2-adrenergic agonists. *Cardiovascular effects:* Indacaterol may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms, ECG changes. In case such effects occur, treatment may need to be discontinued. *Hypokalaemia:* $Beta_2$-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce cardiovascular effects. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment which may increase the susceptibility to cardiac arrhythmias. *Hyperglycaemia:* Inhalation of high doses of $beta_2$-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Onbrez Breezhaler plasma glucose should be monitored more closely in diabetic patients. During clinical studies, clinically notable changes in blood glucose were generally more frequent by 1.2% on Onbrez Breezhaler at the recommended doses than on placebo. Onbrez Breezhaler has not been investigated in patients with not well controlled diabetes mellitus. *Pregnancy and Lactation:* No data available from the use of indacaterol in pregnant women. Onbrez Breezhaler should only be used during pregnancy if the expected benefits outweigh the potential risks. Not known whether indacaterol / metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or discontinue Onbrez Breezhaler therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Immediate hypersensitivity reactions have been reported after administration of Onbrez Breezhaler. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, Onbrez Breezhaler should be discontinued immediately and alternative therapy instituted. **INTERACTIONS:** Concomitant administration of other sympathomimetic agents may potentiate the undesirable effects of Onbrez Breezhaler. Onbrez Breezhaler should not be used in conjunction with other long-acting beta2-adrenergic agonists or medicinal products containing long-acting beta2-adrenergic agonists.Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta2-adrenergic agonists, therefore use with caution. Indacaterol should not be given together with beta-adrenergic blockers (including eye drops) as these may weaken or antagonise the effect of beta2-adrenergic agonists. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, does not raise any safety concerns given the safety experience of treatment with Onbrez Breezhaler. Indacaterol has not been shown to cause interactions with co-medications. **ADVERSE REACTIONS**: The most common adverse reactions with Onbrez Breezhaler are: dizziness, nasopharyngitis, upper respiratory tract infection, sinusitis, , headache, , cough, , rhinorrhoea, respiratory tract congestion, muscle spasm, peripheral oedema. Common: Chest Pain, Oropharyngeal pain including throat irritation, Uncommon: Myalgia, Musculoskeletal pain, Pruritis/rash, Paradoxical bronchospasm, tachycardia, palpitations, hypersensitivity, diabetes mellitus and hyperglycaemia ,paraesthesia, atrial fibrillation and non-cardiac chest pain, ischaemic heart disease. Please refer to SmPC for a full list of adverse events for Onbrez Breezhaler. LEGAL CATEGORY: POM **PACK SIZES:** Onbrez Breezhaler 150mcg - carton containing 10 or 30 capsules and one Onbrez Breezhaler inhaler. Onbrez Breezhaler 300mcg - carton containing 30 capsules and one Onbrez Breezhaler inhaler **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/09/593/001, 002, 007 **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta P.O Box 124, Valletta, VLT 1000 Malta. Tel: +356 22983217/+35621222872 - 2012-MT-ONB-02-Aug-2012

References:
1. Cazzola M, Matera MG. Novel long-acting bronchodilators for COPD and asthma. Br J Pharmacol. 2008;155:291-299.
2. Novartis Europharm Ltd. Onbrez® Breezhaler® Summary of Product Characteristics.

NOVARTIS

Once Daily
onbrez®
breezhaler®
indacaterol inhalation powder

ONB Ad1 09/12 MT

Money matters

It has been calculated that to market a novel drug a pharmaceutical company has to fork out up to a staggering Euro10,000,000,000 (Source: www.forbes.com/forbes/2012/0312/strategies-pharmaceuticals-lilly-stagger-cost-inventing-new-drugs.html). It is also becoming increasingly difficult to find new moieties and this is driving the expenses further up. Furthermore, the recession does not help. However as the saying goes, necessity is the mother of invention. And one Darwinian lesson which mankind has learnt is, precisely, how to adapt. In fact pharma companies are increasingly starting to explore alternatives to increase profits. After all, profit making is a very simple formula. You either increase income from sales or decrease production costs and examples to reach these goals range from additive printing to nanotechnology to medicinal chemistry. Such techniques are being discovered or rather, rediscovered, as methods by which one can either make existing medicines cheaper, thus making them more accessible resulting in increased sales, or more effective. This editorial will discuss two novel, albeit different strategies to produce more effective medicine.

The first example revolves around Daniel Anderson, a chemical engineer hailing from the Massachusetts Institute of Technology who has recently developed a simplified, artificial version of a living cell (although without the capacity to reproduce). In the right conditions (by mixing ribosomes, DNA, a supply of raw materials and enzymes) the cell has been able to produce a green fluorescent protein. The next phase was to control the 'factory', in order to switch it on at will, and thus act only where and when needed. Thus the team enclosed the DNA in a chemical cage before encapsulating it. This cage was designed to break down when illuminated by UV light. Only once this happens can the DNA become active. This also proved to a success since mice so illuminated produced green fluorescent proteins.

The third phase involved quantifying the the yield of these tiny factories. Dr Anderson created them in a range of sizes, from 400 nanometres to 100 nanometres. The 400 nanometre version turned out an average of 190 protein molecules per vesicle whilst the 170 nanometre version managed 81 molecules. This means that the smaller the size the better the results (proportionally speaking). This also means that by making the vesicles smaller they can travel through blood capillaries more easily, and would thus be simpler to deploy. However interestingly the 100-nanometre vesicles produced no protein whatsoever. The last phase which now remains to be explored is testing the nanofactories with DNA that makes proteins which might actually act as drugs, example anticancer antibodies. Theoretically this should not pose any problems since from a ribosome's point of view, one protein is similar to another. However the challenge is the validation of the drug delivery technique. Needless to say, if successful, this will mean that a new and valuable weapon will have been added to our current armamentarium.

The second example which I am including uses the diversification strategy, by which old drugs are used for new indications. Everyone is familiar with minoxidil, first used as an antihypertensive and now used as a hair growth product, or thalidomide, first used as an anti-emetic (which the notorious phocomelia cases) and now deployed for multiple myeloma. Such switching greatly saves companies' time, as well as R&D money. Nevertheless pharma companies still have to conduct additional testing as part of such a registration process. This includes investigations as to what other proteins the drug in question is interacting with and this itself is a costly business. However a method proposed by Sivanesan Dakshanamurthy, a molecular biologist at Georgetown University in Washington, DC, is being proposed to drive such costs down.

Dr Dakshanamurthy's initial study of the method, published last August in *Medicinal Chemistry*, started from the observation that the shapes of most drug molecules are well known and publicly available. Besides there are various publicly accessible databases which are populated with information about many of the proteins found in the human body as well as what type of receptors they interact with. His team managed to build a computer model which compares information on the structures of drugs with information on the structures of human proteins, in order to find the best fit between the two. To test their model, the team used information on 3,671 drugs already approved by FDA, together with data on the structures of 2,335 proteins found in the human body. This proved to have a 91% success matching rate.

What his team are now investigating are cases where the model predicts an interaction not yet observed in clinical practice. Given the model's successful matching rate, it is hypothesised that some of these previously unknown interactions might be worth investigating. For example, the model suggests that mebendazole, currently used to combat worms, also interacts with tubulins. Since tubulins are associated with angiogenesis it might herald research on the role of mebendazole in cancer. The model also suggested that celecoxib should bind with CDH11, a protein which plays an important role in the development of both rheumatoid arthritis and metastatic breast cancer.

Nearly 27,000 molecules are approved for pharmaceutical use, and the human genome project has shown that there are at least 23,000 human proteins. Even though not all of those proteins are adequately understood to be used in the model, that still means that there are a lot of potential interactions. Furthermore screening in a computer is faster and cheaper than in a laboratory. And even if only a few new significant interactions are discovered it would have been a worthwhile exercise!

Ian C Ellul

GALVUS and EUCREAS

COMPREHENSIVE POWER TO ADVANCE TYPE 2 DIABETES TREATMENT

GALVUS is a DPP-4 inhibitor that improves glycemic control through powerful islet enhancement[1]

EUCREAS is the combination of a DPP-4 inhibitor, GALVUS, and metformin[2]

Galvus® 50mg (vildagliptin) tablets

PRESENTATION: Each tablet contains 50 mg of vildagliptin **INDICATIONS:** For the treatment of type 2 diabetes mellitus in adults: As monotherapy ♦ in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance. As dual oral therapy in combination with ♦ metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin ♦ a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance ♦ a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate. **DOSAGE:** When used as monotherapy or in combination with metformin or thiazolidinedione the recommended daily dose of vildagliptin is 100mg, administered in two divided doses of one 50 mg in the morning and one 50 mg in the evening. In combination with sulphonylurea, 50 mg once daily in the morning. Galvus can be administered with or without a meal. Doses greater than 100 mg are not recommended. Galvus is not recommended for use in children and adolescents less than 18 years old. The recommended dose for patients with moderate/severe renal impairment is 50mg once daily. If a dose of Galvus is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. No dose adjustments are necessary in elderly patients *(≥ 65 years)* **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients **WARNINGS / PRECAUTIONS:** ♦ Galvus should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. ♦ Galvus is not recommended in patients with moderate or severe renal impairment or in haemodialysis patients with end-stage renal disease. ♦ Galvus is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x the ULN. Liver function tests should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3xULN or greater persist, withdrawal of Galvus therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus. ♦ There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class III-IV and therefore use is not recommended in these patients. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Galvus should not be administered during pregnancy or lactation since no studies on the effect on human fertility have been conducted for Galvus. ♦ Should be used with caution in patients with renal impairment. **INTERACTIONS:** ♦ Vildagliptin has a low potential for drug interactions. ♦ No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin.♦As with other oral antidiabetic medicines, the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angioedema, abnormal liver function tests, hepatic dysfunction (including hepatitis). *Monotherapy:* Common (>1/100 to <1/10): dizziness, Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. *Combination with metformin:* Common: tremor, headache, dizziness, nausea, hypoglycaemia. Uncommon: fatigue. *Combination with sulphonylurea:* Common: tremor, headache, dizziness, asthenia, hypoglycaemia. Uncommon: constipation. Very rare: nasopharnyngitis. *Combination with Thiazolidinedione:* Common: weight increase. oedema peripheral, Uncommon: headache, asthenia, hypoglycaemia. Frequency not known: urticaria, pancreatitis, hepatitis and abnormal liver function tests (reversible upon discontinuation of the medicinal product), bullous or exfoliative skin lesions **LEGAL CATEGORY:** POM PACK SIZES: 7, 28 tablets **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBERS:** EU/1/07/414/001, 003. Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 124, Valletta, VLT 1000, Malta. Tel +356 22983217. 2012-MT- GAL-02-Aug- 2012

Eucreas® (vildagliptin/metformin hydrochloride) Film-coated tablets

PRESENTATION: Each 50 mg/850 mg film-coated tablet contains 50 mg of vildagliptin and 850 mg metformin hydrochloride. Each 50 mg/1000 mg film-coated tablet contains 50 mg of vildagliptin and 1000 mg metformin hydrochloride. **INDICATIONS:** Eucreas is indicated in the treatment of type 2 diabetes mellitus in adult patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets. **DOSAGE:** The recommended daily dose should be based on the patient's current regimen of vildagliptin and /or metformin hydrochloride. The usual dose is 50 mg/850 mg or 50 mg/1000 mg twice daily one tablet in the morning and the other in the evening. Eucreas should be taken with or just after food since this may reduce the gastrointestinal symptoms associated with metformin. Doses of vildagliptin greater than 100 mg are not recommended. As metformin is excreted via the kidney, elderly patients have a tendency to decreased renal function. Patients > 65 taking Eucreas should have their renal function monitored regularly. Eucreas is not recommended for use in patients less than 18 years old. The safety and efficacy of Eucreas in children and adolescents (< 18 years) have not been established.For use in renal or hepatic impairment, see contraindications and precautions below or refer to the SmPC for more information. **CONTRAINDICATIONS:** Hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients. Diabetic ketoacidosis or diabetic pre-coma. Renal failure or renal dysfunction defined as creatinine clearance < 60 ml/min. Acute conditions with the potential to alter renal function e.g. dehydration, severe infection, shock or intravascular administration of iodinated contrast agents. Acute or chronic disease which may cause tissue hypoxia e.g. cardiac or respiratory failure, recent myocardial infarction, shock. Hepatic impairment. Acute alcohol intoxication, alcoholism, Lactation **WARNINGS / PRECAUTIONS:** Eucreas should not be used in patients with type 1 diabetes. Due to the risk of lactic acidosis, renal function could be monitored at least once yearly in patients with normal renal function and at least two to four times/year in patients with serum creatinine at the upper limit of normal and in elderly patients. Eucreas is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST >3x the ULN. LFT's should be performed prior to treatment initiation, at three month intervals during the first year and periodically thereafter. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of Eucreas therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Eucreas. There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class III-IV and therefore use is not recommended in these patients.. Metformin is contraindicated in patients with heart failure, therefore Eucreas is contraindicated in this population. Routine monitoring of diabetic patients for skin disorders such as blistering or ulceration is recommended. As Eucreas contains metformin, treatment should be discontinued 48 hours before elective surgery with general anaesthesia and not usually resumed earlier than 48 hours afterwards. The IV administration of iodinated contrast agents can lead to renal failure. Therefore due to metformin active ingredient, Eucreas should be discontinued prior to or at the time of the test and not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal.Eucreas should not be administered during pregnancy or lactation since no studies have been conducted on the effect of human fertility. **INTERACTIONS:** Vildagliptin has a low potential for drug interactions. No clinically relevant interactions with other antidiabetics (glyburide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin. Interactions with metformin hydrochloride that are not recommended include alcohol, cationic active substances e.g. cimetidine and intravascular administration of iodinated contrast media. Combinations requiring caution include metformin hydrochloride with medicines tending to produce hyperglycaemic activity e.g. glucocorticoids, beta agonists and diuretics. The dose of antihyperglycaemic medicinal products may need to be adjusted in combination with ACE inhibitors. **ADVERSE REACTIONS:** Rare cases (>1/10,000 to <1/1,000) angiodema,abnormal liver function tests, hepatic dysfunction (including hepatitis) have been reported with vildagliptin. *Vildagliptin Monotherapy:* Common (>1/100 to <1/10): dizziness, Uncommon (>1/1,000 to <1/100): headache, constipation, arthralgia, hypoglycaemia, oedema peripheral. Very rare (<1/10,000): URTI, nasopharyngitis. *Metformin monotherapy:* Very common (>1/10) Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. Common: metallic taste. *Combination vildagliptin with metformin:* Common: tremor, headache, dizziness, nausea, hypoglycaemia. Uncommon: fatigue. Frequency not known: urticaria, pancreatitis, hepatitis abnormal liver functions tests, (reversible upon discontinuation of the medicinal product), bullous or exfoliative skin lesions For a full list of Adverse reactions, please refer to the SmPC. **LEGAL CATEGORY:**POM **PACK SIZES:** 30, 60 film-coated tablets **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION** NUMBER: EU/1/07/425/002–003, EU/1/07/425/008-009. Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available upon request from: Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 124, Valletta VLT 1000, Malta. Tel +356 22983217/ +35621222872 2012-MT- EUC-26 Jul- 2012

NOVARTIS

Galvus® vildagliptin

1. Novartis Europharm Ltd. Galvus® Summary of Product Characteristics
2. Novartis Europharm Ltd. Eucreas® Summary of Product Characteristics

Eucreas® vildagliptin/metformin

GAL Ad1 09/12 MT

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Professor Albert Cilia-Vincenti MD FRCPath
is a scientific delegate to the European Medicines Agency (London), chairman of the Academy of Nutritional Medicine (UK) and a private surgical pathologist. He is a former pathology teacher at London and Malta Universities, and pathology services director to the British and Maltese health services. He trained at London's Royal Marsden, Royal Free, St George's, Charing Cross and The Middlesex hospitals.

Dr Sarah Cuschieri MD
Is a 2nd year foundation trainee at Mater Dei Hospital. She graduated as a doctor from the University of Malta in 2011.

Dr Tania van Avendonk MD DCH MSc MMCFD
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specialised in radiology at the Institute of Clinical Radiology at the University of Muenster, Germany and the Memorial Sloan-Kettering Cancer Center, New York, US. He is currently Consultant Radiologist and Managing Director at DaVinci Hospital, Malta.

Dr Charmaine Gauci MD MSc Dip(Fit&Nut) PhD FRSPH FFPH
is the Director of the Health Promotion and Disease Prevention Directorate. She is a senior lecturer with the University of Malta and delivers lectures in the field of public health with special interest in Epidemiology and Communicable Diseases. She is active in the field of public health and is currently also the President of the Malta Association of Public Health Medicine.

contents

COVER:
TheSynapse has recently celebrated 16th Anniversary from launch. TheSynapse was one of the first Maltese portals launched on the Internet just two months after the introduction of the Internet in Malta. It has continued to develop over the years and is the leading news, service and resources portal for the medical community.

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DID YOU KNOW

Counterfeit medications are a big problem in sub-Saharan Africa. Thus a Clinical Global Initiative member created Sproxil, a company which helps African and Indian people to check whether medicines which they are going to buy are counterfeit, by simply using their mobile phones to text a code found on the medicines.

(Source: The Economist, 1st October 2012)

TANIA VAN AVENDONK

The role of Phytoestrogens in the management of menopausal symptoms

Menopause reflects a change in the woman's physiological hormonal status and is regarded as a pivotal point in a woman's life. The commonest symptoms experienced by women during the menopause are hot flushes and night sweats. Although HRT remains the gold standard for the treatment of menopausal symptoms, certain controversial studies have led to a shift against the regular use of HRT. Many physicians and women have turned to alternative 'natural' products, hoping that these can substitute the need for HRT. The evidence base for the efficacy and safety of phytoestrogens, in particular isoflavones, will be discussed.

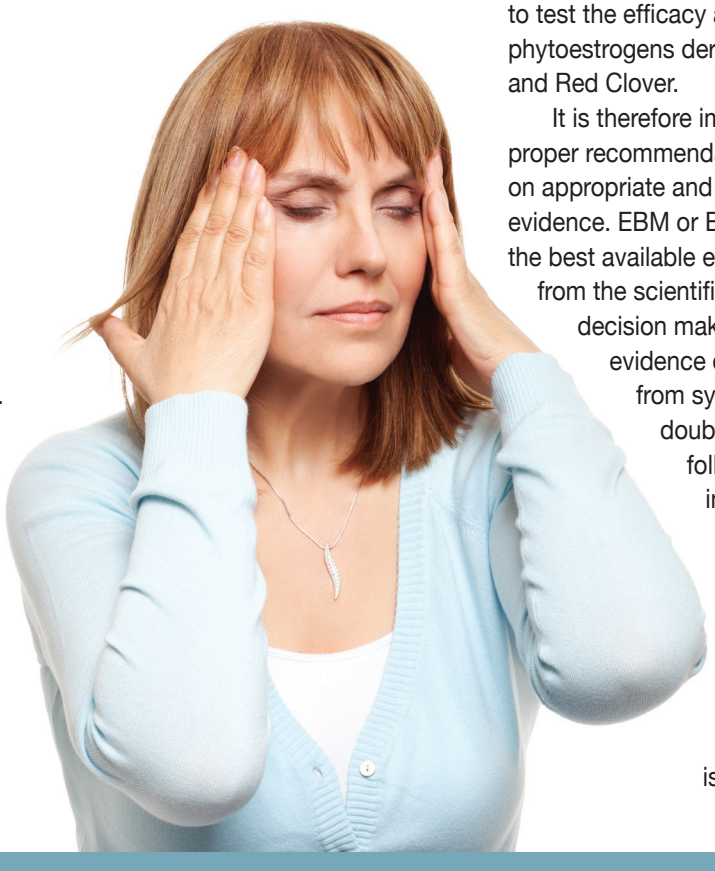
Introduction

Menopause reflects a change in the woman's physiological hormonal status, and although not equivalent to an illness, it is regarded as a pivotal point in a woman's life. Its management should not be neglected because while some women may go through it without noticing, it is generally accompanied by a variety of disorders. Top of the list in 40% to 80% of Western women are hot flushes and night sweats which can result in decreased quality of life.[1] Increased public expectations and awareness of health issues have contributed to an increased demand for products related to menopausal symptoms.

The gold standard for the treatment of menopausal symptoms is the conventional HRT that actually corrects the underlying lack of female hormones. Results of major RCTs including the Women Health Initiative[2], Heart Estrogen/Progestin Replacement Study II[3] and the large British observational study the Million Women Study[4] have demonstrated an increased risk of cardiovascular disease and cancer of the breast with HRT use. Following these controversial studies over 90% of family physicians in Malta have changed their prescribing habits of HRT.[5] Due to the fear of these adverse effects and possible long-term risks of HRT, many women are reluctant to use HRT and have turned to alternative 'natural' products hoping that these can substitute the need for HRT.

A number of epidemiological studies suggest that the female populations in Asian nations like Japan, China and South-east Asia, are less burdened by menopausal symptoms than those of Western countries. It has been postulated that these differences may be due to the traditional Asian diet that is rich in Soy, which contains substances that are structurally similar to estrogen and bind to ER and hence have been called phytoestrogens. Since their binding affinity to ER is preferential, i.e. stronger binding affinity to ERβ than to ERα, they are better classified as SERMs.

Media coverage has led to an increased consumer awareness of soy, which has resulted in skyrocketing sales of soy products and supplements. Many advertising campaigns have specifically targeted females and depicted soy and other phytoestrogens as the alternative to conventional HRT for menopausal symptoms with the added benefits of possible protective properties against breast cancer and heart disease. These products are classified under CAM and not as medicinals. Although they are freely available in health shops and pharmacies as over-the-counter products, many women request information and advice from their GP and other health practitioners about the effectiveness, safety and tolerability of these products before purchase.



What is the evidence base to support the effectiveness of phytoestrogen therapy in menopausal women for the control of hot flushes?

CAM products tend to lack a research tradition and infrastructure, since funding is generally limited compared with the amount spent by the pharmaceutical industry on conventional drugs. However over the past 10 years several studies both of experimental animal type and clinical trials have been carried out to test the efficacy and tolerability of phytoestrogens derived from both Soy and Red Clover.

It is therefore important that proper recommendations are based on appropriate and good quality evidence. EBM or EBP aims to apply the best available evidence gained from the scientific method to clinical decision making. The strongest evidence quality is derived from systematic reviews of double/triple blind RCT followed by that of individual properly designed RCTs.

The evidence base from systematic reviews of studies about efficacy of phytoestrogens is sometimes

New

inoclim®

soy isoflavones

Initial management of postmenopausal vasomotor disorders

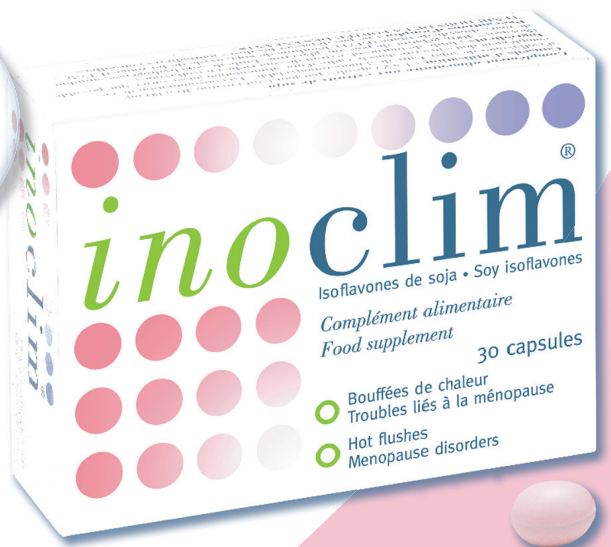
70% of postmenopausal women experience hot flashes(1)

Clinical effects of soy isoflavones supplement(1):

- Significant improvement of vasomotor disorders*
- No increase in endometrial thickness, breast density and vaginal cytology**

In postmenopausal women with distressing vasomotor disorders, initial management with isoflavones is reasonable(1)

40 mg soy isoflavones **per capsule**



- **Analytical quality control**
- **Easy to use: 1 capsule per day**
- **3-month program. Renewable**

(1) According to NAMS 2011 Isoflavones Report. The role of soy isoflavones in menopausal health: report of the North American Menopause Society/Wulf H. Utian Translational Science Symposium in Chicago, IL (October 2010). Menopause. 2011;18(7):772-53.

* In 11/14 more recent randomized controlled trials (RCTs) evaluating the efficacy of isoflavones versus placebo in the treatment of postmenopausal vasomotor symptoms.

** Not recommended for women with personal or family history of breast cancer.

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conflicting. Several reviews have evaluated the clinical evidence relating isoflavone treatment to the relief of menopausal hot flash symptoms. The majority of these reviews included a variety of isoflavone sources, often without differentiating between the identities of individual isoflavones contained in the study product. Hence reports concluding that isoflavone supplements do not significantly reduce hot flash symptoms may be incorrect. The lack of differentiation between individual isoflavones contained in heterogeneous isoflavone mixtures from differing sources can be misleading when designing studies, interpreting results, and conducting reviews.

One critical review conducted by Williamson-Hughes et al.[6] has demonstrated that a statistically significant reduction of hot flushes is achieved only in those studies which provided more than 15mg genistein (type of isoflavone). Another review by Bolanos et al[7] analyzed 19 RCTs and demonstrated an overall significant reduction in hot flushes with soy preparations. The systematic review and meta-analysis conducted by Taku et al[8] also concluded that soy isoflavone supplements, derived by extraction or chemical synthesis, are significantly more effective than placebo in reducing the frequency and severity of hot flushes.

As described, several double-blinded RCTs with particular standardised formulations of isoflavones have demonstrated positive effects in controlling hot flushes.[6,7,8,9] The strongest evidence is for formulations containing specifically genistein.[6,10] It was also suggested that genistein may have a favourable effect on some cardiovascular markers.[11] This positive effect of genistein without any adverse effects on the endometrium and vagina after 1 year treatment were also demonstrated by another RCT.[12] The safety concerns of isoflavones were also addressed in another RCT with no effects on the endometrium and the breast, demonstrated by biopsy specimens.[13]

Less evidence exists to address the effects of soy isoflavones on bone metabolism in postmenopausal women and their place in the prevention and treatment of postmenopausal osteoporosis. In vitro and animal studies have shown that they act in multiple ways to exert their bone-supporting effects by acting on both osteoblasts and osteoclasts. Epidemiological studies and clinical trials suggest that soy isoflavones have beneficial effects on bone mineral density, bone turnover markers, and bone mechanical strength in postmenopausal women.[14]

The North America Menopause Society in 2010 published a report stating that Soy-based isoflavones are modestly effective in relieving menopausal symptoms and supplements providing higher proportions of genistein (type of isoflavone) or increased S-equol content (isoflavan, metabolite of the soy isoflavonedaidzein) may provide more benefits. However larger studiesin younger postmenopausal women, and more research is needed to understand the modes of use of soy isoflavone supplements in women.[15]

Conclusion

There is enough evidence to support the use of isoflavones especially genistein, in the treatment of acute menopausal symptoms. Different sources and supplements of phytoestrogens are available on the market however many of them lack standardization of the content of the active ingredient which can seriously affect the bioavailability. Counseling of women regarding which preparations are most suitable and to avoid unrealistic expectations from these preparations is very important.

Abbreviations

CAM: Complementary and alternative medicine
EBM: Evidence-based medicine
EBP: Evidence-based Practice
ER: Estrogen receptor
HRT: Hormone replacement Therapy
RCT: Randomized controlled trials
SERM: Selective Estrogen receptor modulator

References

1. National Institute of Health (2005). NIH state-of-the-science conference statement: management of menopause-related symptoms. Annals of Internal Medicine. Vol.142;No.12:1003-1014.
2. Women's Health Initiative Steering Committee (2004). Effects of the conjugated equine estrogen in postmenopausal women with Hysterectomy: the Women's Health Initiative randomized controlled trial. Journal of the American Medical Association. Vol.291:1701-1712.
3. Grady D., Herrington D., Bittner V., Blumenthal R., Davidson M., Hlatky M., Hsia J., Hulley S., Herd A., Khan S., Kristen Newby L Waters D., Vittinghoff E. & Wenger N. (2002). Cardiovascular disease outcomes during 6.8 years of hormonal therapy. Heart and Oestrogen/progestin Replacement Study: follow up. (HERS II) Journal of American Medical Association. 288: 49-57.
4. Million Women Study Collaborators (2003). Breast cancer and hormone replacement therapy in the Million Women Study. The Lancet. Vol. 362:419-27.
5. Van Avendonk T.(2007). Menopausal management by Maltese family physicians and the role of Hormone replacement therapy in 2007. Dissertation submitted for MSc in Primary Care and General Practice from the University of Ulster.
6. Williamson-Hughes P., Flickinger B., Messina M., Empie M., (2006)Isoflavone supplements containing predominantly genistein reduce hot flash symptoms: a critical review of published studies. Menopause. Vol.13(5):831-839.
7. Bolaños R., Del Castillo A.,Francia, J.(2010). Soy isoflavones versus placebo in the treatment of climacteric vasomotor symptoms: systematic review and meta-analysis. Menopause: Vol. 17 (3):660-66.
8. TakuK., Melby M., Kronenberg F., Kurzer M.,; Messina M. (2012).Extracted or synthesized soybean isoflavones reduce menopausal hot flash frequency and severity: systematic review and meta-analysis of randomized controlled trials. Menopause. 19(7):776-790.
9. Faure E.D., Chantre P. & Mares P. (2002). Effects of a standardized soy extract on hot flushes: a multicenter, double-blind, randomized, placebo-controlled study. Menopause: Vol. 9 (5): 329-334.
10. CrisafulliA.,Marini H., Bitto A., Altavilla D.,Squadrito G., Romeo A., AdamoE., Marini R.,D'Anna R., Corrado F., BartoloneS., Frisina N., Squadrito F. (2004).Effects of genistein on hot flushes in early postmenopausal women: a randomized, double-blind EPT- and placebo-controlled study. Menopause: Volume 11 (4) :400-404.
11. CrisafulliA.,Marini H., Bitto A., Altavilla D.,Squadrito G., Romeo A., AdamoE., Marini R.,D'Anna R., Corrado F., BartoloneS., Frisina N., Squadrito F. (2005).Effects of the phytoestrogen genistein on cardiovascular risk factors in postmenopausal women Menopause: Vol. 12 (2):186-192.
12. D'Anna R., Cannata M.L., Marini H., Atteritano M.,Cancellieri F., Corrado F., Triolo O., Rizzo P., Russo S., Gaudio A., Frisina N., Bitto A.,Polito F., Minutoli L., Altavilla D.,Adamo E.B., SquadritoF.(2009). Effects of the phytoestrogen genistein on hot flushes, endometrium, and vaginal epithelium in postmenopausal women: a 2-year randomized, double-blind, placebo-controlled study. Menopause: Vol.16 (2): 301-306.
13. Cheng G.,Wilczek B., Warner M., Gustafsson J-A., Landgren B-M.(2007).Isoflavone treatment for acute menopausal symptoms. Menopause. 14(3):468-473.
14. Atmaca A., Kleerekoper M., Bayraktar M., Kucuk O.(2008). Soy isoflavones in the management of postmenopausal osteoporosis Menopause: Vol.15 (4): 748-757.
15. Clarkson T., Utian W.H., Barnes S., Gold E.B., Basaria S.,Aso T., Kronenberg F., Frankenfeld C.L., Cline J.M., Landgren B-M., Gallagher J.C., Weaver C., Hodis H., Brinton R.D., Maki P. (2011) The role of soy isoflavones in menopausal health: report of The North American Menopause Society/Wulf H. Utian Translational Science Symposium in Chicago, IL(Oct.2010. Menopause: Vol.18 (7):732-753.

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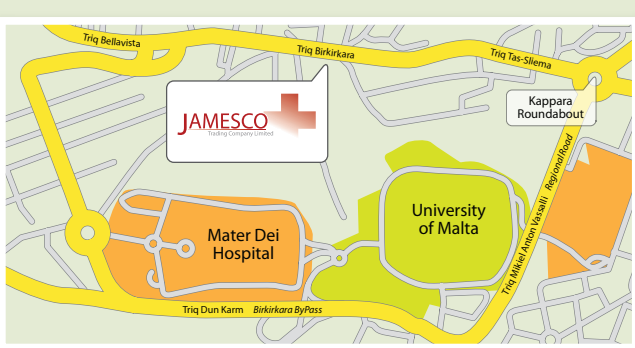

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MARIO J CACHIA

Testosterone deficiency in the adult males

Abstract

Testosterone deficiency leads to multiple problems but can be difficult to diagnose. However, replacement therapy can be rewarding and a life changer for the patient.

Throughout the ages, the search for eternal youth has led down many paths. The discovery of testosterone was, many believed the elixir which had, at long last, been found. The medical use of testosterone, however, proved to be very challenging indeed and not quite the epitome of eternal youth as had been hoped for.[1]

Physiological functions of testosterone include protein synthesis with anabolic effects on muscle, erythropoiesis and bone.[2] It also favourably alters glucose and lipid metabolism.[3] Testosterone promotes energy, drive, motivation, concentration and endurance. It is also important in promoting psychosexual health and activity. All these are very important in promoting the well-being of the male individual.

Men are usually considered not to be subject to andropause[4,5] but testosterone levels do decline with age (about 1.2% per annum from the age of 40, with about 12% of men above the age of 50 reaching 50% by 80 years of age). The level at which testosterone deficiency in adults occurs is a hotly debated issue. There are several reasons for this:

1. different testosterone assays can give very variable testosterone levels;
2. investigators use different assays in their studies whilst also taking different cut-off points;
3. decreased libido and erectile dysfunction can occur at testosterone levels which vary from one individual to another.

Matters are further complicated as testosterone levels, besides changing with age, are known to decrease with increasing body mass index; as well as increase for several hours after intercourse and also show diurnal variation.

Given all the above problems, it is surprising that testosterone replacement therapy is ever initiated.[6] Judicial use of testosterone replacement therapy will, however, improve the person's well being, decrease the person's cardiovascular risk parameters (although no large study has so far shown a decreased cardiovascular morbidity or mortality with therapy),[7] improve muscle bulk, increase libido, correct erectile dysfunction (if there are no other causes e.g. long standing diabetes with neuropathy) and halt the decline of, or even improve, bone mineral density.

Conditions which are increasingly being identified as associated with low testosterone levels include diabetes[8-11] and the metabolic syndrome,[8] increasing age,[5] heart failure,[12] and obesity.[13,14]

Given the variability of the assays and other variations as already mentioned above, the indiscriminate clinical testing for testosterone deficiency is inappropriate.[15] Targeting the correct, high risk individuals is the logical approach. Patients complaining of decreased libido and impotence should have a thorough history taking and examination looking for iatrogenic (e.g. beta-blocker therapy) or psychological causes prior to embarking on testosterone assay. High risk conditions include:

a. diabetes with another complaint e.g. impotence, decreased libido, decreased bone density, lethargy not explained by other causes;

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Interactions: Interactions reported with oral anticoagulants (requires dose monitoring), ACTH or corticosteroids, and thyroxin binding globulin in laboratory tests. **Pregnancy and lactation:** Not for use in women. **Effects on ability to drive and use machines:** None known. **Undesirable effects:** Common – injection site pain, acne, polycythaemia, increased weight, hot flush, increased prostate specific antigen, abnormal prostate examination, benign prostate hyperplasia and various injection site reactions. Serious side effects – *cf. CI/Warnings and Precautions* – in addition, hypersensitivity, cardiovascular disorder, depression, aggression, hypertension, liver function test abnormalities, urinary retention, prostatic intraepithelial neoplasia and prostatitis. Pulmonary microembolism of oily solutions can in rare cases lead to signs and symptoms such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia or syncope. 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References: 1. Minnemann T *et al.* Comparison of a new long-acting testosterone undecanoate formulation vs testosterone enanthate for intramuscular androgen therapy in male hypogonadism. *J Endocrinol Invest* 2008;**31**(8):718–723. **2.** Aversa A *et al.* Effects of testosterone undecanoate on cardiovascular risk factors and arthrosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. *J Sex Med* 2010;**7**(10):3495–3503. **3.** Saad F *et al.* An exploratory study of the effects of 12 month administration of the novel long-acting testosterone undecanoate on measures of sexual function and the metabolic syndrome. *Arch Androl* 2007;**53**(6):353–357. **4.** Giltay EJ *et al.* Effects of testosterone supplementation on depressive symptoms and sexual dysfunction in hypogonadal men with the metabolic syndrome. J *Sex Med* 2010;**7**(7):2572–2582.

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b. obese individuals with erectile dysfunction;
c. 'non-intermittent' impotence or lack of morning tumescence;
d. osteoporosis. In a male this should always lead to an evaluation of testosterone levels as part of the investigations.

Testosterone deficiency leads to multiple problems but can be difficult to diagnose. However, replacement therapy can be rewarding and a life changer for the patient

Most recent studies consider a total testosterone level of around 8 nmol/l as being the cut-off point for testosterone deficiency[16,17] if certain criteria are met i.e. the sample is taken at around 10am and the individual has refrained from sexual activity for the past 24 hours.

Once the diagnosis is made, then appropriate therapy has to be initiated. Testosterone replacement may not always be the appropriate therapy. For example, consider the case of a widowed 74 year old male with osteoporosis and prostate problems. The appropriate therapy here is treatment directed at the osteoporosis – testosterone therapy *may* exacerbate the prostate problem, and if he has no desire for sexual activity, may be totally inappropriate.

For patients for whom testosterone therapy has been considered appropriate, then there are several options available, not all of which are available locally. Testosterone by oral route, although once popular has now lost favour because of problems with hepatic first pass metabolism and erratic serum levels. Testosterone gels and patches utilise the cutaneous route of administration and are fairly popular, but require at least a daily application. The main problem is transfer of testosterone to a female partner (possibly also to minors in the family) if the proper precautions are not taken. Parenteral testosterone esters are perhaps the most popular, although not always legitimately used e,g, in body building and other performance sports. Most companies are now discontinuing most of these esters, causing supply and therapy problems. This has mainly arisen as a consequence to the 'hacking' of the Chinese undecanoate ester to the European market. This product only requires an injection at approximately three monthly intervals. Its rise in popularity has resulted in companies discontinuing production of other esters. Various other modes of administration are at present under review, such as implants.

Side effects are relatively few and mild if used appropriately. The most common is polycythaema, which often requires a decrease in dose and sometimes necessitates discontinuation of therapy. Liver dysfunction is probably the second most common side-effect. Uncontrollable rage and aggression has been reported, but is usually related to supra-pharmacological doses in abuse. Prostate problems, although often cited, are probably not an issue. No study has really shown an increase in prostate problems, including prostate cancer. In addition some studies have shown that the testosterone receptors on the prostate are easily saturated, so testosterone therapy does not really increase prostatic stimulation.[18]

Testosterone replacement can be a rewarding therapy, however, the pitfalls in diagnosis are such that specialist advice should be sought prior to initiation of any such therapy. S

References

1. Shalender Bhasin GRC, Frances J. Hayes. Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline. 2010.
2. Tuck SP, Francis RM. Testosterone, bone and osteoporosis. Frontiers of Hormone Research. 2009;37:123-32. PubMed PMID: 19011293.
3. Volpato S, Vigna GB, Fellin R. The benefit and risk of testosterone replacement therapy in older men: effects on lipid metabolism. Acta Bio-Medica de l Ateneo Parmense. 2010;81 Suppl 1:95-9. PubMed PMID: 20518198.
4. Wu CY, Yu TJ, Chen MJ. Age related testosterone level changes and male andropause syndrome. Chang Gung Med J. 2000 Jun;23(6):348-53. PubMed PMID: 10958037.
5. Leifke E, Gorenoi V, Wichers C, Von Zur Muhlen A, Von Buren E, Brabant G. Age-related changes of serum sex hormones, insulin-like growth factor-1 and sex-hormone binding globulin levels in men: Cross-sectional data from a healthy male cohort. Clinical Endocrinology. 2000;53(6):689-95. PubMed PMID: 2001037037.
6. Behre HM, Christin-Maitre S, Morales AM, Tostain J. Transversal European survey on testosterone deficiency diagnosis. Aging Male. 2012;15(2):69-77. PubMed PMID: 22380815.
7. Nigro N, Christ-Crain M. Testosterone treatment in the aging male: myth or reality? Swiss Medical Weekly. 2012;142:w13539. PubMed PMID: 22430839.
8. Stellato RK, Feldman HA, Hamdy O, Horton ES, McKinlay JB. Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: Prospective results from the Massachusetts Male Aging Study. Diabetes Care. 2000;23(4):490-4. PubMed PMID: 2000124275.
9. Schipf S, Haring R, Friedrich N, Nauck M, Lau K, Alte D, et al. Low total testosterone is associated with increased risk of incident type 2 diabetes mellitus in men: results from the Study of Health in Pomerania (SHIP). Aging Male. 2011;14(3):168-75. PubMed PMID: 21039324.
10. Ogbera OA, Sonny C, Olufemi F, Wale A. Hypogonadism and subnormal total testosterone levels in men with type 2 diabetes mellitus. Jcpsp, Journal of the College of Physicians & Surgeons - Pakistan. 2011;21(9):517-21. PubMed PMID: 21914405.
11. Li H, Kong XB, Zhang HL, Wu J. Testosterone Levels in Males with Type 2 Diabetes and Their Relationship with Cardiovascular Risk Factors and Cardiovascular Diseases. Journal of Sexual Medicine. 2011 April;8(4):1260. PubMed PMID: 2011184024.
12. Florvaag A, Oberle V, Fritzenwanger M, Kretschmar D, Betge S, Goebel B, et al. Testosterone deficiency in male heart failure patients and its effect on endothelial progenitor cells. Aging Male. 2012 September;15(3):180-6. PubMed PMID: 2012471670.
13. Biswas M, Hampton D, Newcombe RG, Rees DA. Total and free testosterone concentrations are strongly influenced by age and central obesity in men with type 1 and type 2 diabetes but correlate weakly with symptoms of androgen deficiency and diabetes-related quality of life. Clinical Endocrinology. 2012 May;76(5):665-73. PubMed PMID: 2012209658.
14. Mogri M, Dhindsa S, Ghanim H, Dandona P, Quattrin T. Testosterone concentration in obese young males. Diabetes. 2011 July;60:A345. PubMed PMID: 70629016.
15. Bain J. Testosterone and the aging male: to treat or not to treat? Maturitas. 2010;66(1):16-22. PubMed PMID: 20153946.
16. Anawalt BD, Hotaling JM, Walsh TJ, Matsumoto AM. Performance of total testosterone measurement to predict free testosterone for the biochemical evaluation of male hypogonadism. Journal of Urology. 2012 April;187(4):1369-73. PubMed PMID: 2012165588.
17. Crewther BT, Lowe TE, Ingram J, Weatherby RP. Validating the salivary testosterone and Cortisol concentration measures in response to short high-intensity exercise. Journal of Sports Medicine and Physical Fitness. 2010 March;50(1):85-92. PubMed PMID: 20308978.
18. Feneley MR, Carruthers M. Is Testosterone Treatment Good for the Prostate? Study of Safety during Long-Term Treatment. Journal of Sexual Medicine. 2012 August;9(8):2138-49. PubMed PMID: 2012455538.

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From a medical student to a doctor: a personal experience

SARAH CUSCHIERI

"I want to become a doctor" is expressed by many children; some do actually reach the stage where they enrol at a medical school. The journey as a medical student commences with over-enthusiasm and great anticipation to become a doctor. Few realise what really is in store for them; endless sleepless nights, anxiety and some even a degree of depression.[1]

Life as a Medical Student

The expectations of what becoming a medical student incorporates, is sometimes not met by the students and so, some experience disappointment. A good protective factor that a medical student needs to take on is the 'desire' to become a doctor. This would empower the student even if faced by multiple challenges, which are normal to come across during Medical school.[1]

On commencing the clinical years, the feeling of becoming part of the medical profession grows and is enhanced more on getting one's own stethoscope. Going around the wards, clerking and examining patients gives fuel to the longing to be a real doctor. As the student reaches final year, panic and anxiety sets in.[2] The hardship of the final year appears as an endless dark tunnel with a small dim light at the end. The fear of failing the finals and losing all those years of studying is a normal feeling among all medical students. Insomnia becomes second nature and the amount of coffee consumption increases drastically. Moral starts to diminish, as anxiety builds up when the exams start to creep. Nightmares may become a daily event and very commonly medical students begin to wish that this breathtaking experience comes to an end.

It is a normal anticipation among medical students that once they reach their goal to become a doctor, all problems and stress would disappear. This is a good strategy and aiming point in the last few weeks up to the final exams. Once the finals are over and a positive result is obtained, there is no turning back; the medical degree has been achieved! "So Goodbye medical school and Hello Hospital" is a common phrase expressed on the day results are out.

Life as a Junior doctor

The transition from a medical student to a junior doctor is over a short period of time.
This rapid change in status comes as a shock to the newly qualified doctor. It is a normal feeling amongst junior doctors, that during the first few weeks, they feel lost and incapable to cope with all the stress that the job holds as a foundation doctor. The feeling of security that one experienced as a medical student dissolves away. The senior doctors might not always be helpful or around on the wards, so most problems that arise in the wards are up to the junior doctor to solve. Nurses can be the doctors' best friend or their worst nightmare. It is important to get along well with the nurses from day one and be ready to listen to their advice especially in the beginning until one gets the hang of how it all works. There is a lot of knowledge that one can achieve from an experienced nurse, so one must ensure to get into their good books. It is important to maintain one's status but not to the degree of having one's ego overcome you, for that is the recipe for failure.

This rapid change in status comes as a shock to the newly qualified doctor.

It is very normal to feel like a secretary during the day, as junior doctors are responsible for ordering and taking bloods, running after radiologists, organising consultations with different medical professionals, calling patients, getting bombardments of questions from patients and their relatives ... questions that one may not always be in a position to respond, etc. There would be a point in time where one would "feel fed up" or "over-worked" or feel that "this is not what one has signed up for," but all of this would dissolve away when a patient comes up to say *thank you* for the work, or when one follows up a patient who had been admitted in a poor state and walks out of hospital as a brand new person. The satisfaction of being part of the medical team who managed the patient's health condition is what fuels the daily life as a foundation doctor. Night duties, when one is completely alone on the wards, are the time when one starts to consider onself as a 'real' doctor.

Night duties and consulting the seniors

The first night duty causes a lot of distress to the junior doctor. It is normal to feel as if one is trying to walk under water. The most important thing is to take a deep breath, keep calm and know one's limits. It is safer to call a senior if one is not sure or just wants to confirm the planned management rather than trying to deal with a patient alone. Preferably one always works along with another junior doctor, for two minds are much better than one, especially when an acute call is received.

The success in calling a senior doctor without having "the head chopped off,"

is to be well prepared before calling them. It is essential to have taken a good patient history, performed a physical examination, taken parameters (including body temperature, manual blood pressure, pulse, respiratory rate, arterial blood gases if the oxygen saturations are low, peripheral glucose test and ECG) as well as, basic blood tests (full blood count, renal profile, cardiac enzymes if patient presents with chest pain).

On calling the senior it is important to be calm and show that one is in full control of the situation, but would appreciate their expert advice. One should always present the case in an organised manner; giving the age and gender of the patient along with a brief medical history. This should be followed by the findings during the physical examinations and the parameters. If the patient would have already been started on any medication including oxygen, this should be stated to the senior. It is then up to the senior to ask any relevant questions if need be. It is vital to listen carefully to the instructions given out by the senior, and be sure to have everything ready and documented until the senior arrives to review the patient.

Becoming a doctor: the first step in the medical field

Once graduated as a medical doctor, it is the beginning of a new life routine; hospital and clinic responsibilities including night shifts. Now as a doctor one has the obligation to hand out any medical help needed for twenty-four hours every day. It is the doctor's responsibility to maintain a professional attitude, both at the work place and outside.

The first two years as a foundation doctor, are the toughest years since junior doctors are the first line to all the problems that arise in the wards. Also, during these two years, one needs to start thinking about the future career; to which basic specialist trainee (BST) post one would apply for at the end of the second year. This is not an easy task to perform. It is normal to feel frustrated, as generally one does not have an exact idea which area is best or worse yet. It is common for junior doctors to experience this dilemma.

On calling the senior it is important to be calm and show that one is in full control of the situation, but would appreciate their expert advice. One should always present the case in an organised manner

The essential thing to do during these two years, as a junior doctor, is to gain as much as possible, experience and knowledge while rotating in different departments. Making sure that one learns from one's mistakes and asks for help when needed. The seniors are there to help out, even if one might not realise it immediately. If a junior doctor convinces the seniors that s/he is hard working, eager to learn and ready to improve his or her medical practice, one will surely find all the support from the seniors. The most important thing of all is to enjoy these first two years, for although they might not appear to be enjoyable, these two years are the foundations towards a long life serving the community as a doctor. S

References

1 Karaoglu N, Seker M. Anxiety and Depression in Medical Students Related to Desire for and Expectations from a Medical Career. West Indian Medical Journal 2010; 59 (2): 196

2 Goodfellow PB. Claydon P. Students sitting medical finals – ready to be house officers? Journal of the Royal Society of Medicine 2001; 94: 516 – 520.

CHARMAINE GAUCI

Breast cancer awareness

The incidence of breast cancer is rising among women in many European countries, affecting up to 1 in 16 women and has become the most common cause of cancer in European women. In Malta breast cancer is the commonest oncological cause of death in females. In fact 5.2% of all deaths in females in 2010 was from breast cancer.

The most common breast cancer statistic you have probably heard is that "1 in 8 women will develop breast cancer in their lifetime." What it should really read is "If everyone lived beyond the age of 70, 1 in 8 of those women would get or have had breast cancer." This statistic is based on everyone in the population living beyond the age of 70. Since breast cancer risk increases as you age, your lifetime risk changes depending on the age. The American Cancer Society has estimated the risk per age group as follows:

Age 20-29: 1 in 2,000
Age 30-39: 1 in 229
Age 40-49: 1 in 68
Age 50-59: 1 in 37
Age 60-69: 1 in 26
Ever: 1 in 8

Apart from age, other risk factors for breast cancer include factors related to parity, reproductive history, endogenous and exogenous hormones, breast density, previous history of neoplastic disease, family history, body weight, physical inactivity and consumption of fat.

As in many countries, cancer is rapidly gaining public health importance in Malta. It is encouraging to know that the major types of malignancies in our population are either preventable or curable if detected early. The World Health Organisation has suggested that two components of early detection have been shown to improve cancer mortality:

Education - to help people recognize early signs of cancer and seek prompt medical attention for symptoms;

Screening programs - to identify early cancer or pre-cancer signs before these are recognisable, including mammography for breast cancer.

Appropriate attention must also be given to rehabilitation and palliative care. Primary prevention here refers to promotion of healthy lifestyles, especially with regards to a diet that is rich in fruits and vegetables and low in saturated fats, promotion of physical activity and maintaining a healthy weight, whereas secondary prevention refers to early detection and treatment.

The dire consequences of breast cancer can be significantly reduced if these diseases are detected early, when effective treatment can considerably improve life expectancy.

October is pink to remind people of the importance of raising awareness on breast cancer during which the Health Promotion and Disease Prevention Directorate launched a campaign with the collaboration of NGOs on breast cancer awareness.

Professionals who would like a copy of the material are kindly asked to call on 2326 6000 or email healthpro@gov.mt

Bibliography

1. Breast Cancer facts and figures, American Cancer Society. 2005-2006.
2. European Code against cancer and scientific justification. Association of European Cancer Leagues. 2003..
3. National mortality register, Department of Health Information and Research. 2010.

The European Code against Cancer is a key prevention tool, based on scientifically proven evidence. Certain cancers may be avoided – and health in general can be improved – by adopting a healthier lifestyle:

- Do not smoke; if you smoke, stop doing so. If you fail to stop, do not smoke in the presence of non-smokers;
- Avoid obesity;
- Undertake some brisk, physical activity every day;
- Increase your daily intake and variety of vegetables and fruits: eat at least five servings daily. Limit your intake of foods containing fats from animal sources;
- If you drink alcohol, whether beer, wine or spirits, moderate your consumption.

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  - patients with infections of the skin and soft tissue

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Therapy over at least 10 days is indicated in the treatment of infections with beta-haemolytic streptococci in order to prevent late complications (e.g. rheumatic fever, glomerulonephritis). However, Forcid Solutab should not be used for more than 14 days without assessing the liver function of the patient. **Adults and children over 40 kg body weight:** The usual posology of 500/125 mg is 3 times a day (every 8 hours). For severe, chronical and relapsing infections, this dosage may be doubled. The usual posology of 875/125 mg is 2 times a day. The single dose should be taken at regular intervals throughout the day; ideally at 12 hours interval. **Elderly patients:** Posology as for adults. **Patients with impaired renal function:** In patients with renal insufficiency the excretion of clavulanate and amoxicillin through the kidneys is delayed. Forcid Solutab 875/125 tablets may only be given to patients with a glomerular filtration rate > 30 ml/min. No dose adjustment is required then. **Patients with impaired liver function:** The combination amoxicillin/clavulanate should be administered cautiously to patients with liver impairment. The liver function should be monitored at regular intervals. There are, as yet, insufficient data on which to base a dosage recommendation. **Method of administration:** To prevent possible gastro-intestinal undesirable effects, Forcid Solutab should be taken at the start of the meal. Forcid Solutab tablets can be swallowed whole with a glass of water, or first dissolved in a 1/2 cup of water (at least 30 ml) and stirred thoroughly before swallowing. **Contraindications:** Hypersensitivity to amoxicillin, clavulanic acid or to any of the excipients. Hypersensitivity to any other ß-lactam antibiotic like penicillins and cephalosporins. A previous history of amoxicillin/clavulanate associated jaundice or hepatic dysfunction. Patients with infectious mononucleosis (glandular fever) and patients with lymphatic leukaemia have a higher risk of exanthema and consequently amoxicillin/clavulanate must not be administered in these diseases for concomitantly occurring bacterial infections. **Special warnings and precautions for use:** Serious and occasionally fatal cases of hypersensitivity (anaphylactic reactions) have been reported for patients on penicillin treatment. These reactions are more common for patients with a history of hypersensitivity. Treatment with Forcid Solutab must be stopped immediately and replaced by another suitable therapy. Suitable therapy to treat symptoms of an anaphylactic reaction may be necessary, such as immediate administration of epinephrine, intravenous steroids and the treatment of respiratory insufficiency. Forcid Solutab should be used with caution in patients with known severe allergies or asthma since such patients are more likely to respond with allergic reactions. Cross-hypersensitivity and cross-resistance between the penicillins and cephalosporins can exist. As is the case for other broad spectrum antibiotics, superinfections may occur, particularly in patients with chronic diseases and/or dysfunctioning immune responses. Mucocutane candida infections have been observed. If superinfections occur, the medicinal product should be discontinued and/or an appropriate therapy should be initiated. Patients with severe gastrointestinal disturbances with vomiting and/or diarrhoea should not be treated with Forcid Solutab since adequate absorption can not be guaranteed. In case of severe and persistent diarrhoea, the possibility of pseudomembraneous colitis must be considered and if not refuted, therapy should be discontinued and appropriate measures should be taken. The necessary measures should also be taken if haemorrhagic colitis occurs. The use of antiperistaltics is contraindicated in such cases. Administration of the amoxicillin/clavulanate combination to patients with a disturbed liver function should be approached with caution. Liver function should be monitored on a regular basis. Forcid Solutab 875/125 is not recommended for patients with a glomerular filtration rate ≤ 30 ml/min. In case of long-term treatment regular checks of renal and hepatic function and haematological studies are indicated. Amoxicillin/clavulanate should be used with care in patients on anti-coagulation therapy, since prolongation of the prothrombin time has been observed rarely. The presence of high urinary concentrations of amoxicillin can cause precipitation of amoxicillin in urinary catheters. Therefore, the catheter should be checked at regular interval in such cases. Forcid Solutab contains the following quantities of potassium per tablet: Forcid Solutab 500/125: 24.53 mg, Forcid Solutab 875/125: 25 mg. **Pregnancy and lactation:** Following administration of amoxicillin/clavulanic acid to pregnant women, no detrimental effects in the foetus or neonate could be observed. However, a single study in women with premature rupture of the amnion reported that prophylactic treatment with amoxicillin/clavulanic acid can be associated with an increased risk of necrotising enterocolitis in neonates. As a precautionary measure, Forcid Solutab should only be used during pregnancy after benefit/risk assessment by the physician in charge. Forcid Solutab should be avoided during the first trimester of pregnancy. Both substances reach the embryo/foetus via the placenta and are excreted in maternal milk. (Nothing is known about the effects of clavulanic acid on the breast-fed infant). Therefore, diarrhoea and fungus infections of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitising should be born in mind. **Marketing authorization holder:** Astellas Pharma International BV., Elisabethhof 19, 2353 EW Leiderdorp, The Netherlands. 12-FOR-004

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MARIKA AZZOPARDI

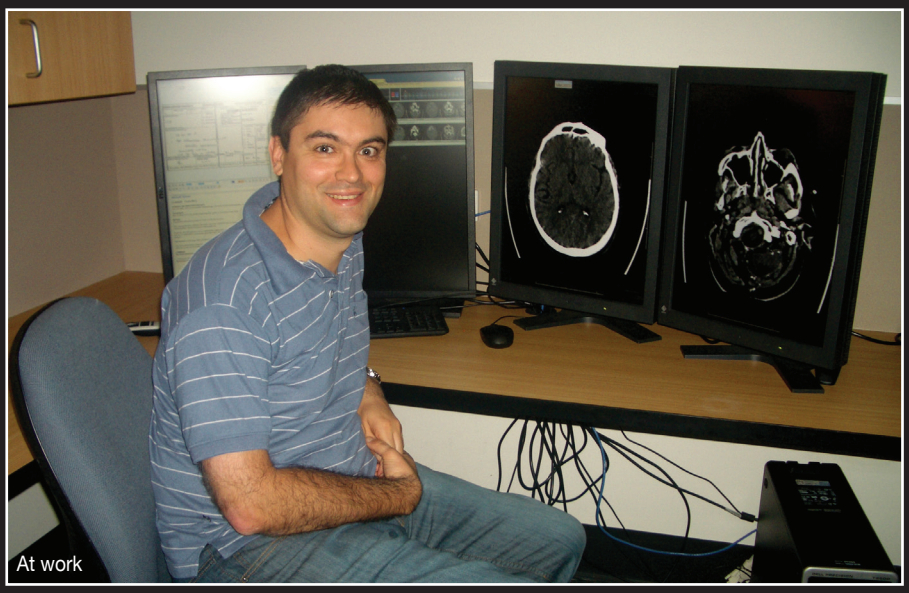
Doctoring down under

It is well known that Maltese professionals have taken flight and landed in far-flung countries around the world and most often made success for themselves. Catching one such professional during his yearly break in Malta provided me an inkling into what it is like to be a contemporary immigrant down under.

Dr Mark Fiorentino is only 33 years old but has been residing in Australia for the past five and a half years. A 2002 graduate, he underwent his housemanship in Malta and proceeded with surgical training. However today he is specialising in a completely different line – radiology. So how did Australia come into the picture?

"I had always wanted to specialise and live overseas and for some time had been seeking employment abroad. At one point I had the opportunity of choosing between employment in the UK or in Australia. From the onset a series of circumstances seemed to indicate we should proceed down under rather than anywhere else in Europe."

Now an Australian citizen Mark (like most Ozzies, he prefers to be called by his first name only) and his wife Lisa, also a doctor, moved to Sydney in 2007 and were lucky enough to be recruited at the same hospital. He started off as a surgical trainee whilst she continued to build on her anatomical pathology training initially started in Malta. The job offers were advantageous, but the downside was the lengthy acceptance process every foreign trained doctor has to go through. "It is becoming very difficult to emigrate to Australia but being a professional and especially a doctor allowed both of us to travel there and be granted practicing rights practically immediately. Most definitely we had to achieve the Australian equivalent of certain qualifications but these we got pretty quickly. Then there were several health checks to contend with and detailed procedures to acquire permission to live in Australia permanently. Had I known about the extremely complicated procedure one needs to go through, I would have probably given up on it all."



At work

What helped the newly wed Fiorentinos to find their feet in a new country that much easier was the fact that their income arrived straight away and so they could proceed to purchase a house and settle down. Eventually Mark moved on to train in radiology and is presently in his third year of training. In the meantime the couple moved to Tasmania and had a son, who is now three years old.

"In about two years' time, if we keep working hard, we will both be consultants." They were pleasantly surprised at the high level of professionalism in the medical field. "Meritocracy is very strong and if you are good at what you do and hard working, you will succeed. Then again, at work, every procedure or decision that is taken must have a reason and a scientific background to back it up. The doctors in Australia base their relationship with their patients on direct discussion and involvement."

Is there a comparison between Malta's level of radiology techniques

Presenting at the RANZCR annual meeting

and those in Australia? He claims that whilst in Malta the field of radiology is quite advanced, in Australia, scans and MRIs are more readily available both within the public and private sectors. What about comparing the kind of diseases witnessed in Australia and those seen in Malta or in Europe? He explains how the Australian experience has exposed him to a vast range of diseases which he had never witnessed before. "Australia is a huge country with a variety of climatic conditions, and therefore a variety of disease manifestations. I travelled around Australia extensively, especially in the first few years, often going to the country and outback. It was there that I came across diseases that I'd never seen before, like rheumatic fever and trachoma in the aboriginal population, as well as venomous snake and spider bites. However apart from these, the range of common diseases present in the Australian populace is practically the same spectrum of illnesses found in the West."

"Why did we move to Tasmania? Tasmania has a cooler climate but it is cleaner and much less hectic, particularly during winter ... a very vague comparison can be made to the Malta – Gozo equation. The Australians consider it as their holiday island because it is greener, enjoys a lot of wildlife and while it is approximately the size of Ireland, its population is just a little over the Maltese population. Which makes for great open spaces and large areas of unspoilt natural beauty."

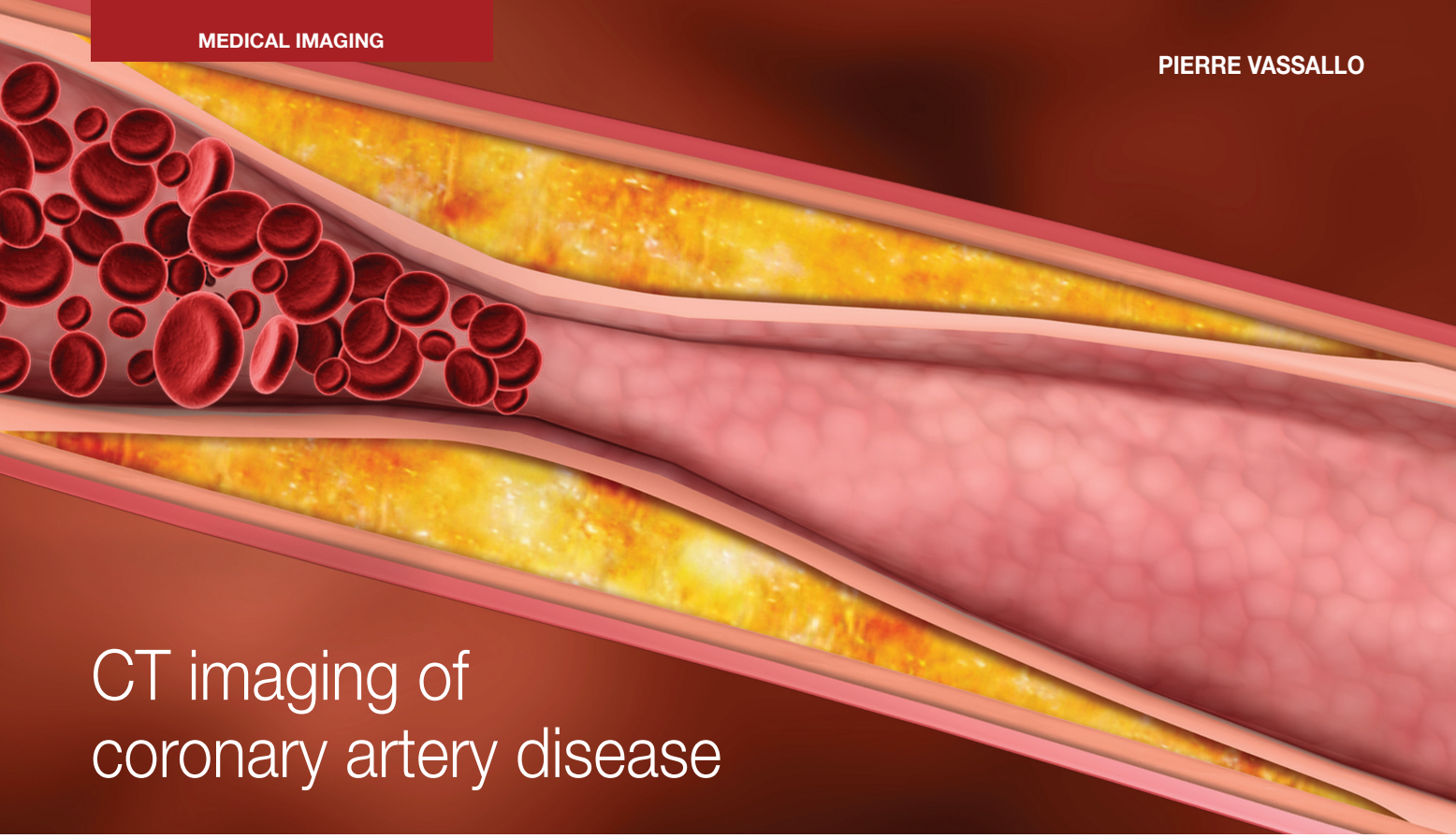
Whilst the Fiorentinos know they will probably return to Sydney eventually, they are happily enjoying their Tasmanian stay at the moment. The Australian experience also brought out unexpected characteristics in their life. He discovered an unknown love of cooking, something he had never done back home in Malta.

Would he move back to Malta now? Mark admits he probably wouldn't – "Our life is here now. We enjoy a good quality of life and the great thing is we have enough vacation time between us to visit family and friends for a good chunk of time every year. Our respective families visit pretty often and distance is bridged regularly so that Malta does not feel as far away as it really is. I certainly don't regret my decision...!" S


Obtaining Australian citizenship


Cradle Mountain, National Park Tasmania

PIERRE VASSALLO



CT imaging of coronary artery disease

Cardiovascular disease is the most common cause of death in developed countries. Particularly with regard to coronary artery disease, approximately 19 million people yearly worldwide either have acute coronary syndrome or die of sudden cardiac death. Thus, early identification and an accurate risk assessment of atherosclerotic disease are mandatory for improvement in the early identification, management, and prevention of acute coronary syndrome.

The coronary artery lumen diameter primarily assessed by invasive coronary angiography has been considered to be the gold standard for assessing risk of an acute coronary event. However histopathologic data have shown that plaque composition and vunerability may have a greater influence on the risk of acute coronary syndrome and cardiac death.

With the advent of non-invasive CT coronary angiography, it is now possible to accurately and safely screen for coronary artery stenosis particularly for individuals with risk factors as assessed by the Framingham and Reynolds classifications in a cost efficient manner.

CT coronary calcium scoring is an additional method that allows assessment of the extent of coronary artery disease by non-invasively measuring intramural calcium (Fig 1). This score is an indicator of your level of hard plaque burden. A very low score suggests that there is virtually no obstructive disease in the coronary arteries, whereas a high score indicates that the level of hard plaque burden is extensive and the risk of a future cardiac event is significant. The following chart outlines the specific ranges of scores and their significance.

A CT coronary calcium score >400 should prompt further evaluation with

Score Level	Hard Plaque Burden	Level of Significant Risk of CAD	Recommendations
0	None	Extremely low	Patient should maintain a healthy diet that is low in saturated fat and cholesterol, refrain from smoking, maintain ideal body weight, and exercise regularly.
1–10	Minimal	Very unlikely	All of the above PLUS close control of diabetes and high blood pressure, and possibly the use of statins for high cholesterol.
11-100	Mild	Mild to moderate	All of the above PLUS daily aspirin, statins for high cholesterol, and estrogen for postmenopausal women.
101–399	Moderate	Moderate to high	All of the above PLUS use of folic acid, and possibly stress testing for further risk assessment.
400 or greater	Extensive	High to very high	All of the above PLUS stress testing to assess extent of obstructive disease, and possibly cardiac angiography

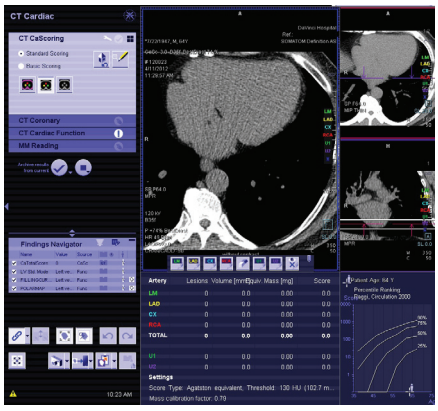


Figure 1. CT coronary calcium scoring: A 0 calcium score indicated that there are no measurable calcium deposits in the coronary arteries with a corresponding low risk for coronary artery disease.

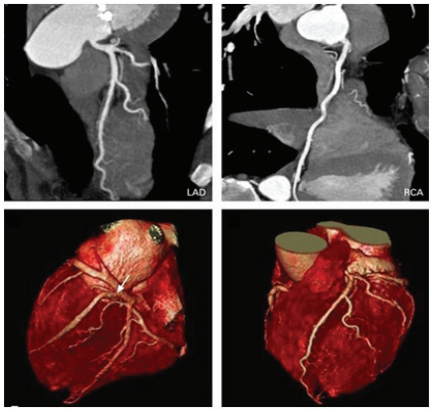


Figure 2. CT coronary angiography accurately and non-invasively assesses arterial diameter and mural irregularity.

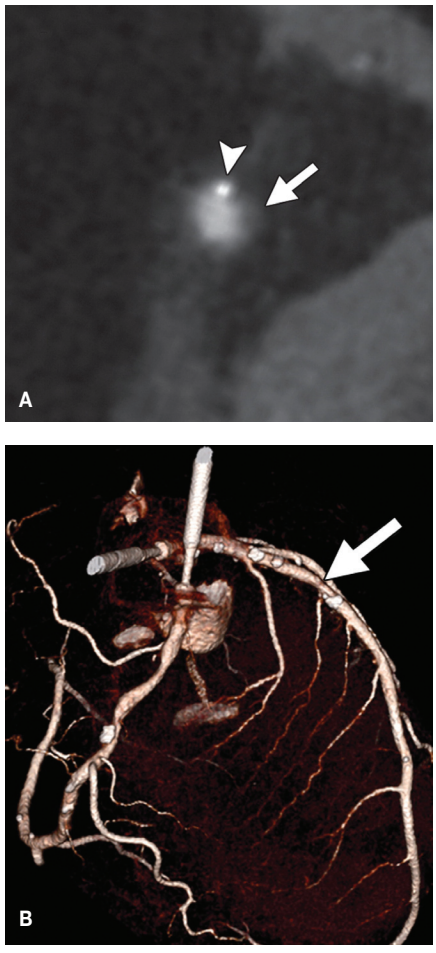


Figure 3. (A) Early fibroatheroma cross-sectional CT image clearly depicts mixed coronary artery plaque with noncalcified (arrow) and calcified (arrowhead) components. (B) Volume-rendered CT image shows location of the plaque (arrow).

invasive coronary angiography as there is a strong likelihood that one would need to proceed to angioplasty or stenting. In addition, heavy intramural calcium load interferes with accurate assessment of luminal diameter on CT coronary angiography. With a CT coronary calcium score <400 one should proceed to CT coronary angiography, which will guide further follow-up or intervention (Fig 2).

CT coronary angiography is technically more challenging than other CT applications because of the continuously moving heart. In this matter, the development of electrocardiographically synchronized CT scanning and reconstruction techniques have allowed cardiac imaging with the reduction of motion artifacts. In addition, fast volume coverage and high spatial and temporal resolution represent further prerequisites for artifact-free imaging. In this regard, 64-section CT systems have met the technical conditions for high-quality cardiac and coronary artery imaging. The submillimeter section collimation (circa 0.6 mm) and high temporal resolution of current CT technology result in excellent diagnostic accuracy for the identification of significant stenosis, compared with conventional coronary angiography.

During recent years as stated earlier, plaque composition has been receiving a lot attention on the research front, as plaque stability or vulnerability (as opposed to relatively stable luminal stenosis) is likely to play a very important role in acute cardiac events. Findings from multiple clinical trials and invasive imaging with optical coherence tomography and intravascular ultrasonography, have contributed to a better understanding of the relative importance of stenosis for risk prediction and have led to a change of focus from luminal narrowing to structural, haemodynamic, and metabolic assessment, including evaluation of plaque morphology and composition, fractional flow reserve, and the degree of inflammation and metabolic activity.

The earliest stage of atherosclerosis is characterized by endothelial dysfunction that results from endothelial injury. Endothelial dysfunction is associated with a reduction in the bioavailability of nitric oxide, which in turn reduces the anti-thrombotic properties of the endothelial surface and promotes adhesion and subsequent transmigration of leukocytes. Subsequent intimal thickening and later formation of fatty streaks characterize this early lesion, which contains lipid-filled macrophages (foam cells) and T lymphocytes. Inflamed fatty streaks represent a precursor of atherosclerotic plaque formation.

The atherosclerotic plaque classification scheme of the American Heart Association (AHA) implies an orderly linear pattern of lesion progression, whereas the modified AHA scheme is a comprehensive morphologic classification scheme that does not imply that there is a single sequence during the lesion progression and is able to deal with a wide spectrum of morphologic variations. On the basis of the modified AHA scheme, atherosclerotic plaque

During recent years ... plaque composition has been receiving a lot attention on the research front, as plaque stability or vulnerability (as opposed to relatively stable luminal stenosis) is likely to play a very important role in acute cardiac events

can be differentiated into early and advanced lesions: Early lesions include (a) adaptive intimal thickening, (b) fibrous plaques, and (c) pathologic intimal thickening. More advanced lesions include (a) early fibroatheromas, (b) late fibroatheromas, and (c) thin-cap fibroatheroma, which is defined as a fibrous cap overlying the necrotic core in a fibroatheroma with a cap thickness of less than 65 µm.Most major adverse cardiovascular events result from plaque rupture in thin-cap fibroatheromas. The histologic characteristics of these vulnerable plaques include a thin fibrous cap, an underlying lipid-rich necrotic core, and an abundance of inflammatory cells.

In addition to the delineation of the coronary artery lumen and the identification of coronary stenosis, coronary CT permits the accurate detection of atherosclerotic plaque.

Early fibroatheroma may be visualized on cross-sectional CT image as a mixed coronary artery plaque with noncalcified and calcified components (Fig 3). Abnormal intimal thickening appears as concentric thickening of the arterial wall on a cross-sectional CT image (Fig 4), and is distinguished from coronary artery plaque as the latter is eccentric (Fig 5).The appearance of a core of low CT attenuation surrounded By a rim-like hyperattenuating area (also known as the "napkin-ring sign") has been correlated with the presence of a necrotic core in vulnerable plaques (ie, thin-cap fibroatheroma) (Fig 6).

Recent research demonstrated that due to increased metabolic activity within vulnerable plaques, PET FDG (positron emmission tomography with fluoro-deoxyglucose) may have a role to play in plaque imaging. Increase FDG uptake occurs mainly due to the presence of activated macrophages in inflammed unstable plaques that are strongly avid for glycogen. Cardiac motion and the high metabolic activity of adjacent myocardium, presently pose limitations to this technique. However, the technique has been shown to clearly demonstrate increased plaque metabolic activity and consequently vulnerability (Fig 7).

New technologies are now available to evaluate a patient's risk for coronary events. Although not all the above techniques mentioned above are clinically available, a basic screening procedure with non-invasive imaging can easily be implimented in our daily practice. CT coronary calcium scoring and CT coronary angiography are easily accessible and will allow selection of patient's who require invasive diagnostic and therapeutic procedures.

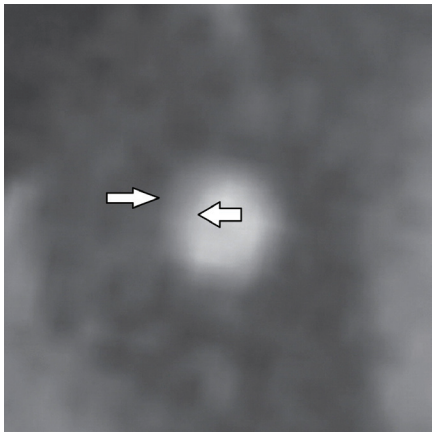


Figure 4. Abnormal intimal thickening (arrows) seen on a cross-sectional CT image of the middle portion of the right coronary artery; there is no coronary artery plaque.

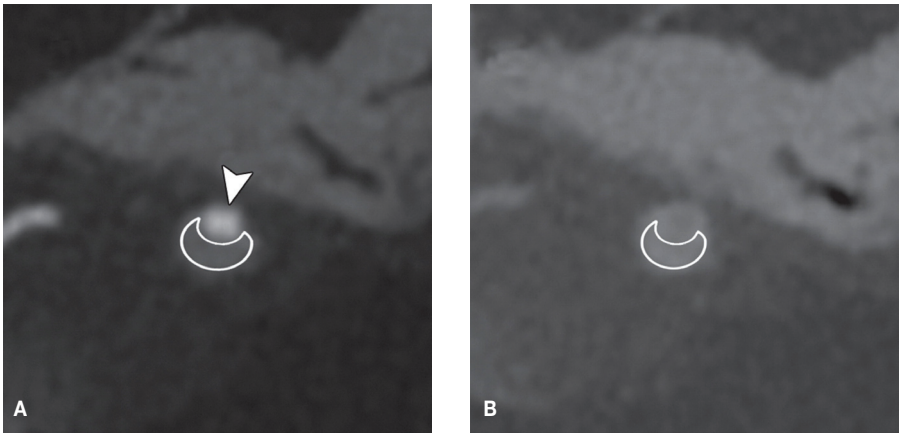
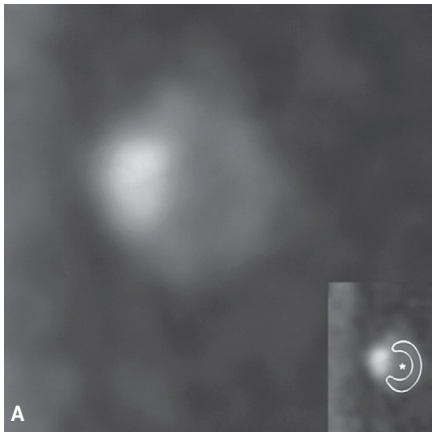


Figure 5. (A) Late fibroatheromais seen on cross-sectional contrast-enhanced **(a)** and nonenhanced (B) CT images. No calcification is seen within the plaque (outlined area). Arrow head incidates contrast material in the perfused lumen.



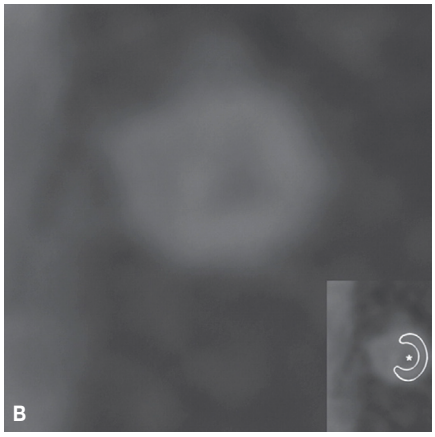


Figure 6. Vulnerable plaque seen on cross-sectional contrast-enhanced (A) and non-enhanced (B) CT image depicts plaque with the napkin-ring sign; there is a low density area (*) surronded by a denser rim located in the arterial wall (outlined area in insets). The area of high density in (B) represents the contrast agent filled arterial lumen.

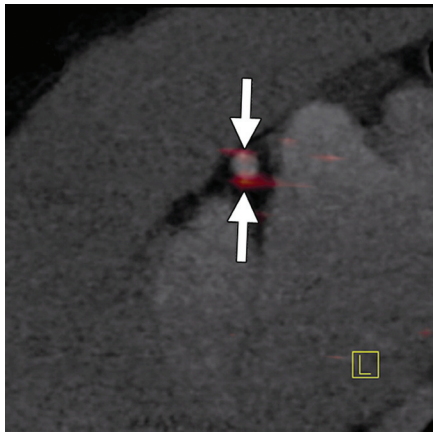


Figure 7. FDG uptake of coronary atherosclerosis is depicted on a co-registered sagittal PET/CT image.

ALBERT CILIA-VINCENTI

THE SERIES

Healing & Disease Reversal

This series reviews Dean Ornish's evidence-based claims of healing & disease reversal by dietary and lifestyle changes. He is a California University Professor of Medicine in San Francisco. This instalment discusses tea intake.

Tea is the most widely consumed beverage worldwide, other than water. Tea contains a variety (possibly thousands) of powerful protective antioxidant polyphenols, especially flavonoids such as catechins, that may help reduce the risk of the most common chronic diseases.

All teas have been shown to have health benefits, however green tea appears to be the best. For example, black tea was found to be less protective than green tea. This is not surprising because green tea is unfermented (so retains original tea leaf colour), and black tea is fermented (which makes it black). The fermentation process reduces the protective effect of the flavonoids, the level of which is highest in green tea and lowest in black tea. In fact the concentration of protective catechins in the blood after drinking green tea is three times higher than after drinking black tea. On the other hand, the caffeine level is highest in black tea and lowest in green tea.

A study which followed more than 49,000 Japanese men and women over a 7 to 11-year period, found that green tea consumption was associated with reduced mortality due to all causes except cancer. The more tea they drank, the lower their risk of dying early. After a 7-year follow-up, researchers found that their overall risk of premature death due to illness was 26% lower among those who consumed 5 or more cups of green tea a day than among those who drank less than one cup per day.[1]

Interestingly, the effects of green tea on reducing risk of cardiovascular disease were not caused only by changes in traditional risk factors, such as cholesterol levels or blood pressure – the polyphenols in green tea appear to have powerful antioxidant properties. These polyphenols may directly beneficially affect coronary artery atherosclerosis by dilating arteries, reducing thrombus formation, and reducing arterial wall inflammation.

In addition, researchers from the Harvard Boston Area Health Study have also shown that men and women who consumed one or more daily cups of green tea in the previous year had a 44% lower heart attack risk than non-tea drinkers.[2] Other studies indicate that regular green tea drinkers may reduce high blood pressure risk. Tea increases the body's nitric oxide production, which dilates arteries and reduces blood pressure.

Although the Japanese researchers did not find that tea drinking reduced cancer risk, other studies have. Animal studies have shown that green tea may inhibit cancer formation in the skin, lung, mouth, oesophagus, stomach, liver, kidney, prostate, and other organs. Human studies also suggest that tea drinking may reduce the risk of gastrointestinal tract cancers.

Some (but not all) studies with varying degrees of rigour suggest that tea may reduce risk of early-stage breast, prostate, ovarian and lung cancers. In one study, green tea extract was claimed to stimulate prostate cancer cell death (apoptosis), and the American National Cancer Institute is conducting a phase II study of green tea extract in men with metastatic prostate cancer.

On the whole, animal studies have tended to show greater value of tea in preventing cancers than in human studies, perhaps due to dietary, environmental and genetic differences.

Researchers from the Harvard Boston Area Health Study have also shown that men and women who consumed one or more daily cups of green tea in the previous year had a 44% lower heart attack risk than non-tea drinkers.[4] Other studies indicate that regular green tea drinkers may reduce high blood pressure risk. Tea increases the body's nitric oxide production, which dilates arteries and reduces blood pressure.

Green tea catechins have also been reported to have antibacterial, antiviral and antifungal activity, especially in early infective stages, involving some salmonella types, *Helicobacter pylori*, influenza and herpes simplex viruses, and *Candida albicans*. In addition, green tea consumption has also been associated with increased bone density and fewer hip fractures.

Furthermore, some studies suggest that tea may help regulate the blood sugar and possibly reduce diabetes risk since tea flavonoids may have both insulin-like and insulin-enhancing activities. Chinese medicine also claims that tea helps control obesity by increasing metabolism, reducing fat absorption, activating enzymes and reducing appetite.

If that's not enough, green tea may additionally reduce risk of dental caries by inhibiting bacterial growth and potentially harmful enzymes in the mouth. Also, both green and black teas contain natural fluoride.

White tea has recently appeared on supermarket shelves, even in Malta. It is said to be made from only the unopened bud and first leaves of the tea plant, and to possibly contain even higher levers of antioxidants than green tea. S

References

1. Kuriyama ST, Shimazu K, Ohmori N, Kikuchi N, Nakaya Y, Nishino Y, Tsubono Y, Tsuji I. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: The Ohsaki Study. JAMA 2006; 296 (10): 1255-65.
2. Sesso HJM, Gaziano J, Buring J, et al. Coffee and tea intake and the risk of myocardial infarction. Am J Epidem 1999; 149 (2): 162-7.

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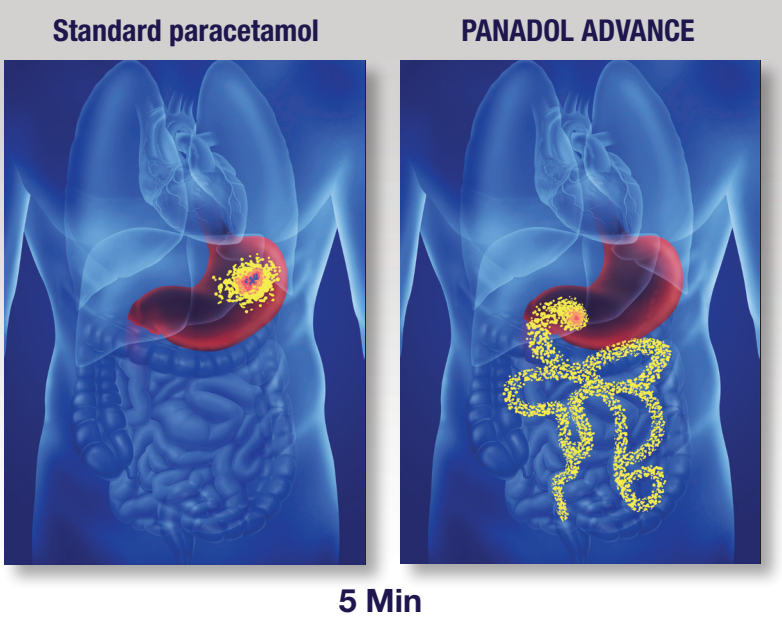

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*Representation of actual gamma scintigraphy images of paracetamol in the gastrointestinal (GI) tract.

References

1. Wilson CG, Clarke CP, Starkey YY, Clarke GD. Comparison of a novel fast-dissolving acetaminophen tablet formulation (FD-APAP) and standard acetaminophen tablets using gamma scintigraphy and pharmacokinetic studies [Epub ahead of print January 11, 2011]. *Drug Dev Ind Pharm.* 2. GSK. Data on file. Bioequivalence Studies A1900260, A1900265. 3. Clarke GD, Adams IM, Dunagan FM. Using suitability profiles to better inform consumers' choice of commonly used over-the-counter analgesics. *Int J Pharm Pract.* 2008;16(5):333-336. 4. Singh G. Gastrointestinal complications of prescription and over-the-counter nonsteroidal anti-inflammatory drugs: a view from the ARAMIS database. Arthritis, Rheumatism, and Aging Medical Information System. *Am J Ther.* 2000;7(2):115-121.

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