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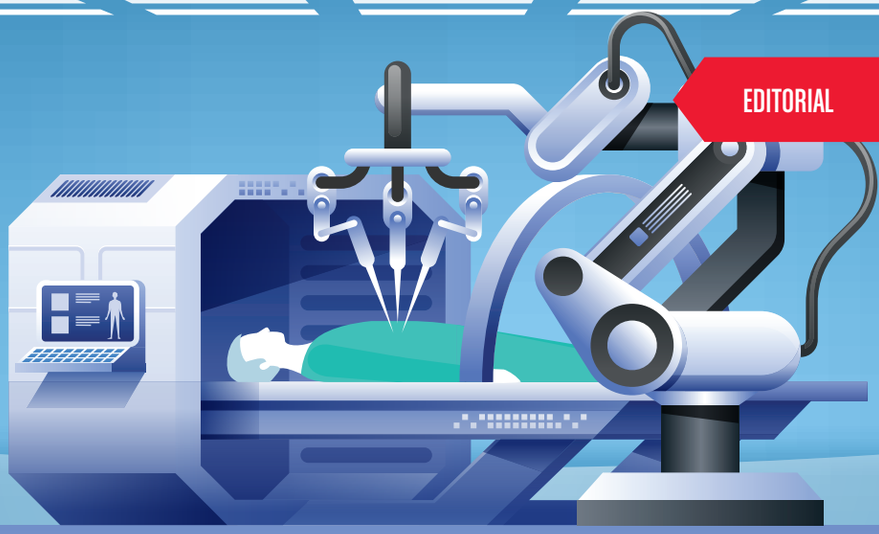
EDITORIAL

HEALTHCARE ADVANCEMENTS IN MALTA FOR 2019



If I were asked to pinpoint the main healthcare game changers in Malta for 2019, I guess I would mention the introduction of robotics at Mater Dei as well as the roll-out of blockchain technology and the related AI; obviously the ominous spectre of Brexit, which has already been discussed in the last editorial[1] will always be looming in the background.

Exactly three years[2] ago I have discussed the relevance of using robots in Maltese hospitals; so I was most happy that the last Budget discussed the introduction of robotic surgery in Malta in the forthcoming months, where their main use will initially be during laparoscopic procedures. In essence, robotic surgery uses miniaturized surgical instruments that fit through a series of quarter-inch incisions. These miniaturized instruments, together with a magnified high-definition 3-D camera, are mounted on separate robotic arms, allowing the surgeon maximum range of motion and precision. These arms are controlled from a console located in the operating room. Obvious advantages include less surgeon fatigue, less trauma on the body, minimal scarring and faster recovery time. However, as what happens with changes, resistance may be a challenge. To date only a handful of countries in the EU have adopted this technology so we are really at the forefront of this.

Challenge number two: blockchain. In 2018 the Maltese Parliament approved three laws on blockchain technology making Malta the first country in the world to create a legal framework, so that companies, which work with this technology, can start operating from Malta. Artificial Intelligence also has an important role to play in this ultra-secure store of information, which is blockchain, and its distributed ledger technology. Artificial intelligence [incorporating failsafe automation systems] within the realm of blockchain has a pivotal role in reducing the incidence of algorithm failures and thus optimising the implementation of blockchain within the realm of healthcare.

In 2017[3,4] I have already discussed the relevance of blockchain in healthcare. Important considerations include [1] Drug Supply Chain Integrity, ensuring provenance tracking; [2] Cyber Security, in line with Europe's new GDPR, where blockchain is poised to take its place at centre stage in today's economy, and [3] ensuring that blockchain-enabled, time-stamped records of clinical trials, protocols and results effectively address the selective reporting in clinical research - it has been estimated that as much as 50% of clinical trials conducted worldwide go unreported, often because the results are negative.

Not everything is rosy, of course. A major challenge which blockchain poses is the fact that medical data, especially images, are too large for current blockchain storage. But we can manage to overcome this, no?

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MADS Malta Association of Dental Students

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TheSynapse eLearning Module

RHEUMATOLOGY

Dr Michela Frendo

EARLY REFERRAL OF RHEUMATIC MUSCULOSKELETAL DISEASE - WHY?

LEARNING OBJECTIVES

- To recognise and appreciate the burden of rheumatic and musculoskeletal diseases which are often underestimated
- To understand the importance of early referral and diagnosis of rheumatic conditions since early diagnosis equates to better quality of life and improved outcomes
- To develop a structured approach to diagnosis and understand the importance of history and clinical examination
- To understand the importance of a multidisciplinary approach to rheumatic conditions and the role of the family doctor as a key player in the team

Dr Cecilia Mercieca

JUVENILE IDIOPATHIC ARTHRITIS

LEARNING OBJECTIVES

- To explain differential diagnosis and improve recognition of distinctive clinical features of JIA
- To increase awareness on the different clinical patterns of the condition
- To emphasize the importance of performing appropriate investigations
- To increase familiarisation with management and with the special considerations which need to be considered when managing young people with JIA

Dr Bernard Coleiro

RAYNAUD'S PHENOMENON

LEARNING OBJECTIVES

- To recognise and diagnose Raynaud's Phenomenon
- To differentiate between Primary and Secondary Raynaud's Phenomenon
- To counsel and treat patients with Raynaud's Phenomenon
- To appreciate when it is appropriate to refer patients with Raynaud's Phenomenon to a Specialist Centre

Prof Andrew Borg

DISENTANGLING FIBROMYALGIA

LEARNING OBJECTIVES

- To improve understanding of Fibromyalgia, including diagnosis, symptoms and the relationship between the condition, sleep disturbances and anxiety
- To discuss management options; both pharmacological and non-pharmacological including EULAR recommendations
- To increase appreciation of the importance of a multidisciplinary support structure in the pro-active management of patients affected by the condition

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ISSUE GUIDE

EPIDEMIOLOGY

A RETROSPECTIVE STUDY ON THE NATIONAL COLORECTAL SCREENING PROGRAMME: ANALYSIS OF PARTICIPATION AND FINDINGS

DR GABRIELLA BUTTIGIEG & DR RACHEL ABELA

ABSTRACT

Colorectal screening in Malta is a population-based screening programme using faecal immunochemical test as the primary screening tool. In this retrospective study, records and datasheets of patients undergoing screening colonoscopies at Gozo General Hospital in 2016 were inspected. The extracted data reflected national participation, as an integration between Mater Dei and Gozo General Hospitals was introduced, to reduce patients' waiting time. Both Maltese and Gozitan patients were eligible for screening at Gozo General Hospital. Outcomes were collected into excel spreadsheets and statistically analysed. Participation rates, positivity rates and detection rates for colorectal cancers were compared with other European Union countries. Comparison showed that Malta has a higher detection rate for colorectal cancer for asymptomatic patients;- however, a significant number of cancer-positive patients were retrospectively also found to have been symptomatic.

KEYWORDS

FIT, Colorectal cancer, Screening, Detection rate, Comparison to EU member states.

INTRODUCTION

Colorectal screening in Malta is a population-based screening programme modelled on the European Council guidelines of colorectal cancer management.[1,2] Screening aims primarily at an early diagnosis when treatment is more likely to work (secondary prevention) and also for tertiary prevention with detection and management of metachronous lesions.

The use of Faecal Immunochemical Tests (FIT) to detect blood in stools is the primary screening tool. It has good patient compliance as patients do not need to undergo dietary or medication restriction unlike the guaiac-based Faecal Occult Blood test where Aspirin, anti-inflammatory medications and vitamin C preparations have to be stopped 7 days prior to test, and also undergo dietary restrictions.[3,4]

In 2016, written invitations were sent to those born between 1957-1959 (aged 59-61 years), to perform a FIT. Those who scored above 100ng/ml were then invited to undergo colonoscopy.

METHOD

Patient records and Colorectal Cancer Screening Programme datasheets for colonoscopies done at Gozo General Hospital between January and December 2016 were accessed. Data fields inspected retrospectively included patient demographics, date of the pre-assessment at the Lascaris deparment, waiting time to and date of colonoscopy, medication history, surgical, medical and family history and, relevant symptoms (including diarrhoea, constipation, bleeding, rectal irritation, mucus, tenesmus, abdominal pain). Other data included histology results, FIT values, MCV value, platelet count, bowel cleansing preparations which were used, extent of colonoscopic examination, as well as any colonoscopic findings including lesions or tumours or diverticuli, inflammation, bleeding, number and type of polyps, their location and whether the polyps were resected or not during the colonoscopy. Data was entered in an excel sheet for statistical processing.

RESULTS

362 patients with a FIT result above 100ng/ml presented for colonoscopy at Gozo General Hospital.

GENDER

53.3% who had a positive FIT result were females while 46.7% were males.

SYMPTOMATIC VERSUS ASYMPTOMATIC PATIENTS

156 patients (43%) were asymptomatic while the remaining 206 patients (57%) were symptomatic. 11 from 362 patients (3%) cases were diagnosed with colorectal adenocarcinoma; only 2 of these were asymptomatic. Patients who were symptomatic included the following:

- 119 from 362 patients (33%) complained of bleeding
- 61 patients (17%) complained of tenesmus
- 71 patients (20%) complained of rectal irritation
- 48 patients (13%) complained of abdominal pain
- 30 patients (8%) complained of change in bowel habit – of which 10 patients suffered from diarrhoea and the remaining 20 patients suffered from constipation.

The following results show that each individual's histology may have fallen in more than one of the mentioned categories. During colonoscopy specific patients had polyps of a different histological nature.

POLYP TYPE	OVERALL	ASYMPTOMATIC	SYMPTOMATIC
Carcinoma	11	2 (0.6%)	9 (2.5%)
Metaplasia/Dysplasia	86	31 (8.6%)	55 (15.2%)
Adenoma	99	37 (10.2%)	62 (17.1%)
Other: Hyperplastic & Inflammatory polyps	300	110 (30.4%)	190 (52.5%)

Figure 1: Comparison of types of polyps identified in asymptomatic vs symptomatic patients as a percentage of a total of 362 patients undergoing colonoscopy. Patients in whom no polyps were identified were not listed in the above table.

POLYP TYPE	OVERALL	ASYMPTOMATIC	SYMPTOMATIC
Carcinoma	11	18%	82%
Metaplasia/Dysplasia	86	36%	64%
Adenoma	99	37.4%	62.6%
Other: Hyperplastic & Inflammatory polyps	300	36.7%	63.3%

Figure 2: % Asymptomatic vs % Symptomatic with positive findings at colonoscopy

AVERAGE FIT VALUES

The average FIT for asymptomatic patients was 184ng/ml.

AVERAGE FIT IN INDIVIDUAL CATEGORIES OF ASYMPTOMATIC PATIENTS

Carcinoma	827
Metaplasia/Dysplasia	629
Adenoma	713
Other: Hyperplastic & Inflammatory polyps	373

The average FIT for symptomatic patients was 166ng/ml.

AVERAGE FIT IN INDIVIDUAL CATEGORIES OF SYMPTOMATIC PATIENTS

Carcinoma	902
Metaplasia/Dysplasia	205
Adenoma	215
Other: Hyperplastic & Inflammatory polyps	288

FIT levels alone are not indicative of colonic tumours: whether benign or malignant. In fact this is why a patient with a positive FIT value is afterwards invited to undergo a colonoscopy. Latter will confirm the histological type of the polyps, as having an elevated FIT value, does not necessarily mean carcinoma. Patients with haemorrhoids or inflammatory bowel disease (IBD) can also have elevated FIT values. Sometimes FIT values are higher in these patients rather than in those patients with a colonic malignancy. The values obtained above could be due to the fact that most of the patients were asymptomatic at the time of screening but had either haemorrhoids or IBD or had both carcinomatous polyps and hyperplastic and inflammatory polyps.

OTHER FINDINGS

Average time gap between the pre-assessment and endoscopic date was 43 days. During the procedure, bowel abnormalities and caecal intubation rate of 360 patients (from 362 patients) were recorded. Colonoscopy exit time was 22 minutes. 26 colonoscopies did not have any exit time documented.

AVERAGE DURATION OF COLONOSCOPY

- Less than 10 min: 27 or 7.5%
- Between 11-30 min: 242 or 67%
- Between 31 and 60 min: 65 or 18%
- Over 1 hour: 2 or 0.6%
- Not recorded: 26 or 7%

DISCUSSION

In 2016, 14,844 letters were sent to the Maltese and Gozitan population, aged 59-61 years to participate in colorectal screening. 557 (3.8%) invites were returned back undelivered. Therefore the total number of eligible invites were 14,287 (96%). From the latter, 12,209 accepted the invitation and their stool kits were sent to the lab. Those who had a positive FIT test were then invited to have a colonoscopy. All patients were asked whether they prefer undergoing their colonoscopy at either Mater Dei Hospital or Gozo General Hospital. Screening colonoscopies in Gozo helped in reducing waiting time; in fact the majority of patients that participated in the screening programme at Gozo, resided in Malta.

COMPARISION OF DATA WITH OTHER EU COUNTRIES

The results of the Maltese population were compared to other European countries which either follow a non-population based colorectal screening i.e. Greece and Latvia, or a population-based screening i.e. Austria, Belgium, Croatia, Cyprus, Denmark, Finland, France, Hungary, Ireland, Germany, the Czech Republic, Italy, the Netherlands, Poland, Portugal, Slovenia, Spain, Sweden and the UK. Lithuania, which adopts a population-based colorectal screening, has been excluded from the analysis, as screening registries did not exist at that time and the call-recall system which ensures active invitation of the entire target population at regular intervals was not implemented. [5]

A) Positivity Rate: Rates of positive screening test results, reflect the cut-off level chosen in each member state for the adopted test. These rates are consistent across the member states using gFOBT, ranging between 1.8% and 4.1%. However higher variability can be observed across member states adopting FIT, ranging between 3.3% to 9.8%. 931 out of 12,209 (7.6%) Maltese and Gozitan patients had a positive FIT. This is similar to the EU average.[6]

B) Detection rates for colorectal cancers: Colorectal cancer detection rates across the member states ranged between 0.09 – 0.19 % using gFOBT and 0.12 – 0.47% using FIT based programmes.[6] In Malta and Gozo, patients who took part in the screening programme and who had a positive FIT (931) were then invited to undergo a colonoscopy. Out of 931, 723 (77.6%) patients accepted to undergo a colonoscopy. A total of 12 (1.7%) of these patients were diagnosed with colorectal cancer (Mater Dei and Gozo General Hospital; one was histologically diagnosed in Malta while the other eleven were diagnosed in Gozo. Of these eleven patients, two were Gozitan while the rest were Maltese).

Compared to the EU, a significant higher detection rate for colorectal cancer was noted. This could be due to the limited size of the gene pool as most people marry within the same population rather than foreigners.

Overall, the detection rate and the positive predictive value for colorectal cancers and adenomas are influenced by characteristics of the screened population and by the screening protocol adopted.[6,7]

In European countries, detection rate of colorectal carcinomas and advanced adenomas is similar, where endoscopy screening is adopted either by flexible sigmoidoscopy or total colonoscopy. Detection of any other type of adenomas is higher with total colonoscopy rather than with flexible sigmoidoscopy.

In general, the prevalence of target lesions is lower among screenees having previous negative examination reports. Independent of subjects' screening history, the prevalence shows an increasing trend with age, both among men and women.[6-8] In the Maltese islands the average age for both adenoma and colorectal carincoma detection was 61 years.

PARTICIPATION RATES

A) Gender: Women show a higher uptake than men in all countries using the faecal test while males show a higher uptake in those countries implementing endoscopy screening. [6,9] In this study, where the FIT test was used as the initial screening investigation, participation was highest amongst women (53.3% who had a positive FIT were females while 46.7% were males).

B) Age: In 2003, the EU Council recommended biennial screening with faecal occult blood testing to all subjects aged 50-74 or, based on national prioritization for a narrower age band. Recently, based on a comprehensive review of available evidence, the EU Council is recommending that programmes should start screening between age 50 and 60, with a 2-year interval, if the screening test is gFOBT or FIT, or a 10-year interval, or more, if the screening test is flexible sigmoidoscopy or total colonoscopy, and to continue sending invitations to screen up to the age of 70–75 years.[6,10] In 2016, the targeted age population in the Maltese islands included those between 59-61 years.

C) Screening Protocol: The type of screening protocol affects participation. Participation in a single invitation round is generally higher for programmes offering faecal tests as compared to programmes offering flexible sigmoidoscopy or total colonoscopy screening. However, a sigmoidoscopy or total colonoscopy can ensure a long lasting protection to those who attend.

From a public health point of view a proportion of non-responders will attend at least once over repeated invitations. But non-invasive faecal tests for primary screening will require colonoscopy assessments of positive subjects. Issues related to colonoscopy capacity are also influencing the choice of the method, as well as the target age range, in different countries. For example Italy is providing a choice of different methods for screening to improve participation rates. Ideally all countries should adopt this method for a more reliable comparison.[11] In 2016, 14,287 Maltese and Gozitan individuals received their invitation to undergo a FIT test. 12,209 (85%) accepted their invitation and participated. Participation rates across European countries exceeded the acceptable minimum of 45%, but neither country reached the desired target (>65%). Screening programs must employ specific strategies to attract the target population and encourage participation in screening programs.[5] Although the participation rate in the Maltese islands was approximately 85%, one must remember that 557 invites were not delivered. So if the latter 557 invites were to be considered with the total, the participation rate decreases to 82%. In screening methods that employ faecal tests, patients need to be followed up, while in endoscopic methods, no follow-up is needed. From the 931 (6.3%) patients who resulted FIT-positive, 208 patients (22.3% of the FIT-positive patients) did not undergo a colonoscopy. This clearly shows that with faecal tests there is the risk that patients do not undergo a colonoscopy and follow-up is lost.

The quality of screening reports has to be consistent and linked with the European health interview survey and national health interview surveys to obtain more precise information. Screening monitoring should be continuous and updated at regular intervals. Comparision of the data collected from various programmes needs to be enhanced. The coverage (by invitation and by examination) and the detection rates in different settings could be misleading unless due consideration is given to the different tests which are adopted, screening intervals and target ages that different programmes may adopt. Furthermore, opportunistic screening should also be accounted for.[6]

CONCLUSION

The high incidence of findings in asymptomatic patients and high percentage of symptomatic patients brings to question these patients' lifestyle, their awareness and their management in primary care. In keeping with the study results, it is suggested that symptomatic patients, particularly those who experience rectal bleeding should be fast-tracked to a colorectal investigation, skipping the immunochemical screening phase. Absence of fast-tracking may have led to the increased rate of colorectal cancer detection rate in the Maltese and Gozitan population. The increased detection rate of colorectal cancer may also be due to the limited size of the gene pool. Patients with a positive family history should seek medical advice for early screening even if asymptomatic.

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*Fluticasone/salmeterol 500/50 mcg BID. †Lung function trough FEV$_1$ (P<0.001).[1] **Health-related quality of life, SGRQ-C (P<0.01).[1] ‡Patients had at least one moderate or severe exacerbation in the previous 12 months.[1] §Annual rate reduction of all exacerbations (mild/moderate/severe): ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 11% (RR 0.89, P=0.003). Annual rate reduction of moderate or severe exacerbations: ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 17% (RR 0.83, P<0.001). Annual rate reduction of severe exacerbations: ULTIBRO® BREEZHALER® vs. Seretide® Accuhaler® was 13% (RR 0.87, P=0.23).[1] Seretide® Accuhaler® is a registered trademark by GSK.

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PRESENTATION: medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Refer to section 4.8 of the SmPC for how to report adverse reactions. **INDICATIONS:** Ultibro Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). **DOSAGE AND ADMINISTRATION:** The recommended dose is the inhalation of the content of one capsule once daily using the Ultibro Breezhaler inhaler. Ultibro Breezhaler is recommended to be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible on the same day. Patients should be instructed not to take more than one dose in a day. Ultibro Breezhaler can be used at the recommended dose in elderly patients (75 years of age and older). 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Patients should be informed about the signs and symptoms of acute narrow-angle glaucoma and should be informed to stop using Ultibro Breezhaler should any of these signs or symptoms develop. *Urinary retention:* No data are available in patients with urinary retention, therefore Ultibro Breezhaler should be used with caution in these patients. Patients with severe renal impairment: These patients should be monitored closely for potential adverse reactions. ***Cardiovascular effects:*** Ultibro Breezhaler should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension). ***Hypokalaemia:*** Beta$_2$-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias. Clinically relevant effects of hypokalaemia have not been observed in clinical studies of Ultibro Breezhaler at the recommended therapeutic dose. ***Hyperglycaemia*** Inhalation of high doses of beta2-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with Ultibro Breezhaler plasma glucose should be monitored more closely in diabetic patients. Ultibro Breezhaler should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2-adrenergic agonists. *Pregnancy and Lactation:* There are no data from the use of Ultibro Breezhaler in pregnant women available. Indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Therefore, Ultibro Breezhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus. It is not known whether indacaterol, glycopyrronium and their metabolites are excreted in human milk. The use of Ultibro Breezhaler by breast-feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. *Excipients:* This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. **INTERACTIONS:** Information on the potential for interactions is based on the potential for each of its two active substances. Beta-adrenergic blockers may weaken or antagonise the effect of beta$_2$-adrenergic agonists. Therefore, Ultibro Breezhaler should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution. The co-administration of Ultibro Breezhaler with other anticholinergic-containing medicinal products has not been studied and is therefore not recommended. Concomitant administration of other sympathomimetics(alone or as part of combination therapy) may potentiate the adverse events of indacaterol. Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or nonpotassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta$_2$-adrenergic agonists, therefore use with caution. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-glycoprotein (P-gp), raises the systemic exposure of indacaterol up to two-fold. The magnitude of exposure increases due to interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical studies of up to one year at doses up to twice the maximum recommended indacaterol dose. **ADVERSE REACTIONS:** The presentation of the safety profile is based on the experience with Ultibro Breezhaler and the individual active substances. Ultibro Breezhaler showed similar adverse reactions to the individual components. As it contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of these components may be expected in the combination. The most common adverse reactions with Ultibro Breezhaler are: Upper respiratory tract infections. Common: Pyrexia, chest pain, dyspepsia, dental caries, bladder obstruction and urinary retention, cough, oropharyngeal pain including throat irritation, dizziness, headache, nasopharyngitis, urinary tract infections, sinusitis, rhinitis, chest pain, hypersensitivity, diabetes mellitus and hyperglycaemia. Uncommon: Fatigue, peripheral oedema, muscle spasm, myalgia, pain extremity, dry mouth, pruritis, rash, glaucoma, myalgia, musculoskeletal pain, paradoxical bronchospasm, dysphonia, epistaxis, gastroenteritis, tachycardia, palpitations, insomnia. Please refer to SmPC for a full list of adverse events for Ultibro Breezhaler. **LEGAL CATEGORY:**POM **PACK SIZES:** Single pack containing 10x1 or 3x10 hard capsules, together with one inhaler. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. **MARKETING AUTHORISATION NUMBERS:** EU/1/13/862/003, EU/1/13/862/007 **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 4, Marsa, MRS 1000 Malta. Tel: +35621 222872

2019-MT-ULT-23-JUL-2019b

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NOVARTIS

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NYHA = New York Heart Association; HFrEF = heart failure with reduced ejection fraction.

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NOVARTIS

Start ENTRESTO sooner in NYHA Class II patients with HFrEF for superior protection

ENTRESTO helps patients stay out of the hospital, live longer, and feel better.[1-3]

Start ENTRESTO today

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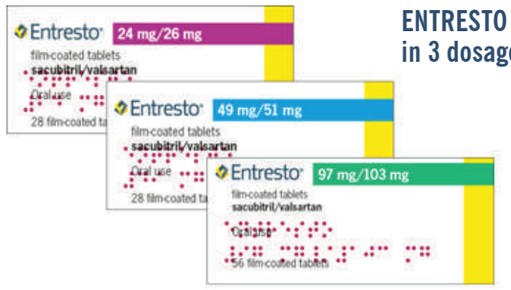
- The target dose is 97/103 mg twice daily[1]
- Stop using an ACE inhibitor for 1.5 days (36 hours) before starting ENTRESTO[1]



ENTRESTO is available in 3 dosage strengths[1]

ENTRESTO contains valsartan, and therefore should not be coadministered with another ARB-containing product.

Before your NYHA Class II patients with HFrEF leave your office, take action with ENTRESTO—and keep them on the right path.

ENTRESTO™▼(sacubitril/valsartan) Presentation: Each film-coated tablet of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex). Indications: In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction. Dosage & administration: The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. In patients not currently taking an ACE inhibitor or an ARB, or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3 - 4 weeks) are recommended. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg, moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. Contraindications: Hypersensitivity to the active substances or to any of the excipients. Concomitant use with ACE inhibitors. Do not administer until 36 hours after discontinuing ACE inhibitor therapy. Known history of angioedema related to previous ACE inhibitor or ARB therapy. Hereditary or idiopathic angioedema. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy. Warnings/ Precautions: Dual blockade of the renin angiotensin-aldosterone system (RAAS): Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Entresto must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with Entresto is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of Entresto. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co administered with another ARB containing product. Hypotension: Treatment should not be initiated unless SBP is ≥100 mmHg. Patients with SBP <100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with Entresto during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). Blood pressure should be monitored routinely when initiating or during dose titration with Entresto. If hypotension occurs, temporary down-titration or discontinuation of Entresto is recommended. Impaired or worsening renal function: Limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m2). There is no experience in patients with end-stage renal disease and use of Entresto is not recommended. Use of Entresto may be associated with decreased renal function, and down-titration should be considered in these patients. Impaired renal function: Patients with mild-moderate renal function are more at risk of developing hypotension while patients with severe renal impairment may be at a greater risk of hypotension. Entresto is not recommended in patients with end-stage renal disease. Hyperkalaemia: Entresto should not be initiated if the serum potassium level is >5.4 mmol/l. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If clinically significant hyperkalaemia occurs, consider adjustment of concomitant medicinal products or temporary down-titration or discontinuation of Entresto. If serum potassium level is >5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with Entresto. If angioedema occurs, discontinue Entresto immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. Entresto must not be re administered. Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Entresto is used in these patients. Black patients have an increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution is required and monitoring of renal function is recommended. Patients with NYHA functional classification IV: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. B-type natriuretic peptide (BNP): BNP is not a suitable biomarker of heart failure in patients treated with Entresto because it is a neprilysin substrate. Interactions: Contraindicated with ACE inhibitors, 36 hours washout is required. Use with aliskiren contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2). Should not be co-administered with another ARB. Use with caution when co-administering Entresto with statins or PDE5 inhibitors. No clinically relevant drug-drug interaction was observed when simvastatin and Entresto were co-administered. Monitoring serum potassium is recommended if Entresto is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on Entresto who are taking NSAIDs concomitantly. Interactions between Entresto and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of Entresto and furosemide reduced Cmax and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and Entresto was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone, no dose adjustment is required. Co administration of Entresto with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised. Co-administration of Entresto with metformin reduced both Cmax and AUC of metformin by 23%. When initiating therapy with Entresto in patients receiving metformin, the clinical status of the patient should be evaluated. Fertility, pregnancy and lactation: The use of Entresto is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. It is not known whether Entresto is excreted in human milk, but components were excreted in the milk of rats. Entresto is not recommended during breastfeeding. A decision should be made whether to abstain from breast feeding or to discontinue Entresto while breast feeding, taking into account the importance of Entresto to the mother. Undesirable effects: Very common (≥1/10): Hyperkalaemia, hypotension, renal impairment. Common (≥1/100 to <1/10): Anaemia, hypokalaemia, hypoglycaemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhoea, nausea, gastritis, renal failure, acute renal failure, fatigue, asthenia. Uncommon (≥1/1,000 to <1/100): Hypersensitivity, postural dizziness, pruritis, rash, angioedema. Packs sizes: Entresto 24 mg/26 mg – x28 tablets; Entresto 49 mg/51 mg – x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets. Legal classification: POM. Marketing Authorisation Holder: Novartis Europharm Ltd, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. Marketing Authorisation Numbers: Entresto 24 mg/26 mg film coated tablets EU/1/15/1058/001; Entresto 49 mg/51 mg film coated tablets EU/1/15/1058/002-004; Entresto 97 mg/103 mg film coated tablets EU/1/15/1058/005-007. Please refer to the 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 4, Marsa, MRS 1000, Malta. Tel: +356 21222872. 2018-MT-ENT-30-APR-2018

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CULOPLASTICS

DR MARIA DE BONO

HISTORY OF OCULOPLASTICS SURGERY

Oculoplastics surgery is a relatively "new" subspecialty within Ophthalmology which deals with disorders of the lids, lacrimal system and orbits. Like any other surgical subspecialty, oculoplastics was born out of a need to provide specialized surgical care and in this particular case, to people suffering from severe eyelid disease, trauma and watery eye problems. One can say that this particular line of surgery originated from a 'cross breed' between plastic surgery and ophthalmology.[1]

The influential British plastic surgeon Jack Mustardé*, way back in the 1960s, was beginning to hope that "in the future we might see a generation of surgeons arising who would be, fundamentally, either plastic surgeons or ophthalmic surgeons, but who would take specific training of some sort in the contralateral field."[2] He went on to say that "I had the honour to be invited to speak at conferences by both plastic surgeons and ophthalmic surgeons. The plastic surgeons didn't know enough ophthalmology to contradict me, and the ophthalmic surgeons didn't know enough plastic surgery to contradict me either!"[2]

A few years later - in 1969 - the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS) was founded with a view to establish a qualified body of surgeons with the required training and experience in this highly specialized field; the European Society (ESOPRS) was set up in 1982 and the British Oculoplastics Surgical Society (BOPSS) in 2000.

It is now standard practice internationally to have ophthalmologists trained in oculoplastic surgery because this allows them to apply the micro precision of ophthalmology to the aesthetic concepts of facial plastic surgery.

APPLICATIONS

The applications of oculoplastics surgery are diverse. These include any eyelid malposition including involutional or cicatricial ectropion (everted eyelid) and entropion (inverted eyelid), brow ptosis, blepharoptosis and dermatochalasis which all can cause a droopy eyelid. The commonest cause for blepharoptosis in adults is gradual, age-related stretching of the levator palpebrae aponeurosis tendon known as involutional ptosis. The levator muscle itself is not affected and so the movement of the eyelid from looking up to down remains normal. Long term contact lens wear can cause ptosis, possibly related to the repeated insertion and removal of the lens causes stretching of the tissues. Sometimes ptosis follows other eye surgery (such as cataract surgery) or an injury. If clinically significant, involutional ptosis can be treated surgically using different approaches, the most recent being the "posterior approach white line advancement" whereby the levator aponeurosis is approached from the underside of the eyelid and tightened to the superior edge of the tarsal plate. This is advantageous since it does not create any skin incisions. Another commonly used technique is the anterior approach aponeurosis advancement – this technique is favoured when a blepharoplasty is also needed to remove some excess eyelid skin – where a skin crease incision is created and the septum opened to isolate the levator aponeurosis which is then tightened to the tarsus.

Other conditions which are commonly treated include benign lid lumps including cysts, xanthelasma, seborrheic keratosis and chalazia. Removal of eyelid tumours with adequate margins, most commonly basal cell carcinoma, squamous cell carcinoma and melanoma are also carried out; lid reconstruction then involves direct closure, various flaps or full thickness skin grafting depending on the size and location of the primary defect.[3]

Patients with facial nerve palsy also fall under oculoplastic care. The aim is to protect the ocular surface until nerve function recovers in idiopathic cases or in the longer term in patients in whom the facial nerve had to be compromised during surgery to treat the underlying condition such as acoustic neuroma or parotid tumour. In these cases, if the cornea is at high risk of breakdown, an emergency tarsorrhaphy is carried out. However, in most cases we tend to partially join the lids [and not carry out a complete tarsorrhaphy] for a short period of time as patients find it cosmetically unacceptable and also because it decreases their field of view. Putting in an eyelid weight (gold or platinum) helps to improve their blink excursion and lid closure. Some patients also suffer a paralytic ectropion which can be corrected by doing an augmented lateral tarsal strip with or without a medial canthal tendon tightening.[4]

Oculoplastic surgeons also manage patients with Thyroid eye disease.[5] Thyroid eye disease can be sight threatening or non-sight threatening. Treatment is targeted depending on the severity of the condition. Ocular structures involved in the inflammatory process include the eyelids, ocular surface, extraocular muscles and intraorbital fat. Eventual scarring of the eyelid muscles and deposition of extra fat in the eyelids causes them to be puffy and retracts the eyelids away from the eye causing exposure of the eye. These changes alter a person's appearance in a disturbing way but also introduce a medical problem of exposure of the eye and cornea which can threaten vision. Many people will have exposure to the degree that it causes their eyes to be very gritty and watery and discomfort is their major problem. In some people, however, dry spots will actually form on the surface of the eye causing exposure keratitis which can lead to scarring and damage to the eye. In the mild inactive state of thyroid eye disease, selenium supplementation and maintenance of the euthyroid state have shown to be beneficial for non-progression of the condition. In the more severe active stages, intravenous methylprednisolone over a course of 12 weeks is necessary.[6] Upper eyelid lowering (temporarily using Botox or permanently by surgery) is necessary so that the eyelids are able to protect the eye more adequately and an improvement in appearance can also be obtained.

Other conditions include blepharitis and closely related meibomitis. There are two types of blepharitis: a) anterior blepharitis occurring at the outside front edge of the eyelid where the eyelashes are rooted, and b) posterior blepharitis affecting the inner edge of the eyelid that is in contact with the eyeball.[7] A diagnosis of the specific type of blepharitis can often be made based on the appearance of the eyelid margins. Blepharitis and meibomitis can be associated with chalazia and conjunctival concretions. Treatment depends on the specific type of blepharitis. The key to treating most types of blepharitis is keeping the eyelids

clean and crust-free by means of warm compresses and good lid hygiene; however, refractory cases of anterior blepharitis may require more complex treatment plans such as BlephEx™ which is a revolutionary new patented hand piece, used to very precisely and carefully spin a medical grade micro-sponge along the edge of the eyelids and lashes, removing scurf and debris and exfoliating the eyelids. For refractory posterior blepharitis, tetracycline antibiotics are used not only for their antimicrobial properties but also for their strong anti-inflammatory action when used in sub-antimicrobial concentrations. These antibiotics have been shown to inhibit the production of pro-inflammatory mediators, thus reducing the production of inflammatory compounds such as cytokines and chemokines, and in particular, matrix-metalloproteineases.[8]

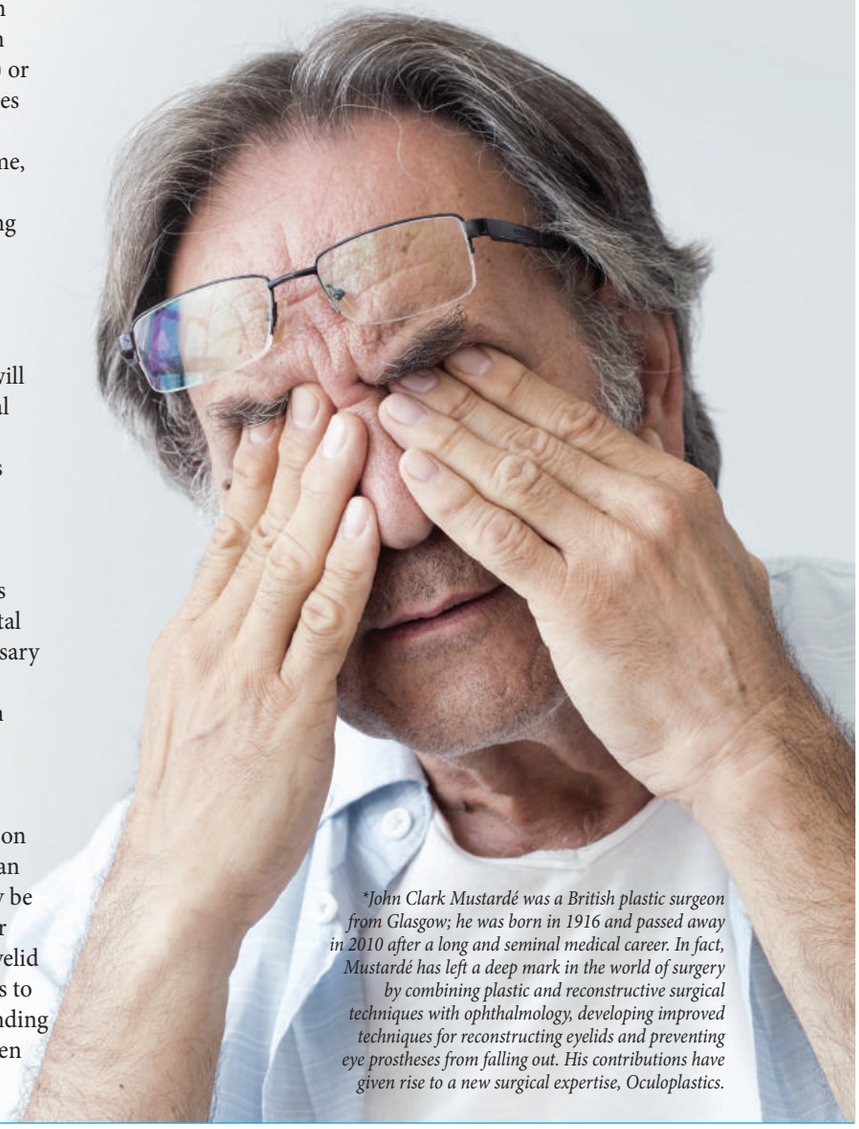
Extreme circumstances at times necessitate the removal of an eye, indicated when the eye becomes painfully blind or in cases of ocular tumours. This could be either an evisceration (removal of the eye's contents leaving the scleral shell intact) or enucleation (removal of the whole eye leaving the eye muscles and remaining orbital contents intact). These patients can then develop Post-Enucleation/Evisceration Socket Syndrome, including sunken appearance of the eye, usually years after removal of the eye; oculoplastic surgeons face the challenging task to try to achieve a symmetrical and natural look to the corresponding eye as much as possible.

ROLE OF OCULOPLASTIC SURGERY IN PAEDIATRICS

The commonest conditions that an oculoplastics specialist will deal with are congenital ptosis, dermoid cysts and congenital nasolacrimal obstruction. Historically congenital ptosis has been thought of as a disorder of levator palpebrae superioris development, however newer theories are more focused on disordered muscle innervation. Deprivational amblyopia (when vision fails to develop adequately) is the commonest association with ptosis in childhood – in the literature this is quoted as being present in 20-70% of children with congenital ptosis.[9,10] Close follow-up with orthoptists is therefore necessary to monitor visual development, since if this is seen as being adequate, then surgery can be postponed to a later age when surgical results are more predictable.

Dermoid cysts are generally the commonest periorbital mass presenting in childhood. These are developmental choristomas; in the periocular area they are often evident soon after birth, with parents raising concern about the lump, or an asymmetry of the eyelids or brows. More rarely the cyst may be asymptomatic until it presents with apparent enlargement or with inflammatory symptoms—such as pain, redness and eyelid swelling. These cysts are normally excised in childhood so as to avoid potential rupture which can lead to fibrosis to surrounding structures. Surgically a skin crease approach is normally taken so as to achieve the best cosmetic outcomes.

Congenital nasolacrimal duct obstruction is the commonest cause of childhood epiphora. It is most commonly due to failure of initial opening of nasolacrimal duct (NLD) into the inferior meatus by birth at the level of the valve of Hasner, stenosis of the opening from narrowed `NLD or hypertrophied inferior turbinate. Spontaneous resolution occurs in 96% of children in the first year without intervention and a further 60% will resolve in the second year of life.[8,11] Therefore management is normally conservative with parents being taught how to perform regular lid hygiene and lacrimal sac massage. Probing is reserved for cases which are persistent; current evidence suggests deferring this until the age of 18-24 months due to the natural history of this condition and the risks associated with general anaesthesia on neurodevelopment of the child under the age of 2 years.



**John Clark Mustardé was a British plastic surgeon from Glasgow; he was born in 1916 and passed away in 2010 after a long and seminal medical career. In fact, Mustardé has left a deep mark in the world of surgery by combining plastic and reconstructive surgical techniques with ophthalmology, developing improved techniques for reconstructing eyelids and preventing eye prostheses from falling out. His contributions have given rise to a new surgical expertise, Oculoplastics.*

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LATERAL EPICONDYLITIS

DANIELA MIFSUD

Lateral Epicondylitis or, as known by many, tennis elbow, is an overuse syndrome of the extensor muscles of the forearm that can affect anyone ranging from elite tennis players to house wives, musicians and manual labourers. Despite being linked with tennis players, hence the colloquial name, it also affects a wide array of athletes ranging from swimmers to baseball and squash players amongst others.

ASSESSMENT

Upon palpating the lateral epicondyle, and sometimes 1-2 cm distal to it, tenderness and discomfort are immediately elicited. Pain will be reproduced or increased on resisting wrist extension with the elbow extended and forearm pronation but the type of pain elicited can vary from sharp pain when the tendon is affected, to a duller pain when it's a muscular problem. The lateral epicondyle is the point of origin for the upper limb extensor muscles and thus, prolonged overuse of these extensors results in chronic eccentric overload on the tendon extensor carpi radialis brevis (ECRB). Other tendons in the proximity such as the extensor carpi ulnaris and extensor digitorum are also commonly affected. However, it's the degeneration of ECRB that has been noted as the primary culprit of this condition. A recent study carried out in 2017 established that the common extensor tendon is thicker in men and in the dominant elbow.[1] In their study, no tendon thickness was observed between study participants from different age groups. Bony spurs, which increase in prevalence exponentially with every decade of age, were another common finding in patients diagnosed with tennis elbow, while colour Doppler activity was positive in 1 in 10 asymptomatic patients.[1] This has to be kept in mind by the clinician when assessing patients.

However, the term epicondylitis is actually a misnomer as this condition is not characterized by inflammation but rather by degeneration, collagen disarray and angiogenesis,[2] and thus the term tendinosis rather than tendinitis is more appropriate. Tennis elbow is a clinical diagnosis and thus, most often, imaging is not necessary. However, if symptoms are not well-defined, diagnostic studies may be helpful.

Moreover, the differential diagnosis for the condition may include cervical radiculopathy, elbow overuse to compensate for a frozen shoulder, posterior interosseous nerve entrapment, degenerative changes, as well as inflammation and oedema of the anconeus muscle.[2]

BIOMECHANICS

Improper backhand hitting technique can immediately result in symptoms due to the force generated on the wrist in supination generating an irritation of the extensor tendons especially when done with just one hand.[3] Another possibility of injury is when the player hits the ball with a bent elbow rather than with a straight one. This is generally more common in novice players and will result in a force generated from the elbow rather than from the core. Moreover, a recent study explained that improper energy flow during the tennis serve can increase the risk of overuse injuries in all of the joints of the upper limb by creating a decrease in ball velocity and an increase in upper limb joint kinetics.[4]

Literature on tennis elbow in non-tennis players such as housewives, musicians, manual labourers and other athletes is still limited. However, the main culprit is a repetitive strain injury (overuse) of the ERCB tendon resulting in degeneration of this tendon.

TREATMENT

Conservative treatment should be attempted first. While rest from aggravating/inflammatory activity should be the first step of treatment, ice after activity as well as NSAIDs (oral and topical) may be used to aid pain relief.[5] The same authors also suggest that forearm counterforce straps may be used together with occupational therapy and physiotherapy aimed to strengthen the forearm muscles and tendons.

Physiotherapy aims to eccentrically load the tendon to the limit without surpassing it. Stability in the shoulder complex is also essential for correct elbow function and therefore exercises targeted at stabilising the rotator cuff and the scapular muscles are also require.[2]

If pain is still present, invasive techniques should be considered. The use of botulinum toxin, dextrose prolotherapy, corticosteroid injection and autologous platelet rich plasma, amongst others have been recently suggested as they showed positive end results.[5] Surgery should always be the last option in cases where functional disability and pain persist.[6]

Single administration of sodium hyaluronate injection has proved to be effective to manage moderate but not severe pain related to this condition.[7] On the other hand, other studies found that both extracorporeal shockwave therapy and acupuncture resulted in pain relief which however, persisted for just two weeks after treatment.[8]

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BEGINNINGS OF MALTESE VASCULAR SURGERY

Prof. Kevin Cassar

"I REMEMBER

Isaac Azzopardi meets Prof. Kevin Cassar.

TS: YOU ARE CREDITED WITH REVOLUTIONISING THE MANAGEMENT OF ARTERIAL PROBLEMS. WHAT DROVE YOU TO MAKE THESE CHANGES?

Vascular surgery emerged due to two main factors: advances in endovascular techniques and advances in technology, notably ultrasound, both of which required new skill sets.

I returned from Scotland in 2007, where I had been working as Consultant Vascular Surgeon and since I was the only consultant working purely in vascular surgery in Malta I was able to focus on implementing these developments, which led to drastic improvements. New minimally invasive procedures and new technology meant less risks for the patient, increased treatment options and ultimately a higher rate of success. A telling statistic is that locally, major amputations have gone down from an average of 130 a year to a little over 50 last year.

TS: CAN YOU TELL ME SOMETHING ABOUT THE SETTING UP OF THE VASCULAR LAB?

I remember having to borrow the ultrasound machines from the X-Ray department at St Luke's to conduct my work after hours, but as the vascular workload increased the need for dedicated vascular sonographers became more pressing.

In 2011, we introduced the Masters in Vascular Ultrasonography in collaboration with the University of Malta, which helped attract qualified radiographers to train in this field. On completion of their training the vascular lab was set up. This is now well-established and well-equipped with high quality ultrasound scanners and excellent sonographers. The lab offers vascular ultrasonography services covering carotid, aortic, venous and peripheral arterial scans. The lab also provides bypass graft surveillance and aneurysm surveillance programmes.

Today, along with my consultant colleagues Dr Pejkić and Dr Petrovic, we provide a comprehensive vascular service to the whole country.

TS: WHAT CAN YOU TELL ME ABOUT THE FOUNDATION PROGRAMME?

Led by Dr Tonio Piscopo and myself, the programme was launched in 2008. After reaching an agreement with the UK Foundation Programme Office we now have an affiliation to offer the same training programme in Malta and it is recognised as equivalent to that in the UK. As a result of this programme we have managed to retain the vast majority of local graduates allowing them to contribute to the local health service while receiving high quality training.

The Foundation Programme was introduced to tackle the brain drain that reached a peak between 2005 and 2007, but equally important to improve the quality of training. The Programme itself has brought about a lot of changes, but at its heart, it helped cultivate a culture of training and assessment where consultants and senior doctors contribute significantly to the training of junior doctors. I am sure that this culture change has contributed significantly to the whole of the health service.

The number of doctors who choose to join the Malta foundation programme and work in our health service after graduation has increased substantially, and the programme now also attracts foreign doctors. The foundation training inculcates in our trainees the concept of lifelong learning - an essential mindset in this day and age, where medicine is constantly changing. I believe that this is the best way of ensuring that doctors continue to develop their skills and competences to be able to provide the best care to our patients.

TS: CAN YOU TELL US SOMETHING ABOUT YOUR SCHEDULE?

My alarm goes at 5:15am. I do 15 minutes of exercise, and try to get to work by 6:30am. Since we are only three vascular surgeons, we are on 24/7 call on a 1:3 basis.

On theatre days we often work till about 7 or 8pm, and try to use all our disposable time … the truth is that I spend a lot of my time here, at the hospital - between my work with the Foundation Programme, surgery, university, and other activities. So, yes, I would like to take some time off for other interests.

I have three children, all of whom are now teenagers. Obviously I would like to dedicate more time with them, but given the nature of my work, sometimes it's not possible.

An activity which I enjoy is running, and although I don't run very often, I try to run a half-marathon at least once a week, usually early on a Sunday. I think it's a very important part of my routine, as I believe that as doctors we need to keep healthy. It's a little difficult to give advice to someone about their health, when you're living an unhealthy lifestyle.

TS: WHAT DO YOU THINK ABOUT THE SYNAPSE?

I think The Synapse has become an institution in Malta. Every doctor knows The Synapse and the huge efforts made towards creating its content; The Synapse was very helpful to us to develop e-learning modules for the Foundation Programme. It is unique in that it has Dr Wilfred Galea who is full of energy and enthusiasm, with a lot of new ideas. So I believe it's good that first of all, people in the profession make use of the resources offered by The Synapse and secondly, that as Maltese professionals we should appreciate the importance of having a resource that is *local* and addresses *local* issues.

HAVING TO BORROW THE ULTRASOUND MACHINES FROM THE X-RAY DEPARTMENT AT ST LUKE'S TO CONDUCT MY WORK AFTER HOURS

ULTRASOUND IMAGING
ADENOMYOSIS

PIERRE VASSALLO

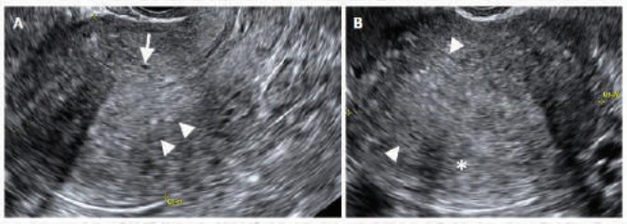

Figure 1: Longitudinal (A) and transverse (B) scan of the uterus showing an ill-defined endometrial-myometrial border (arrowheads) and thickening of the inner myometrial layer, myometrial heterogeneity (*) and cysts (arrow).

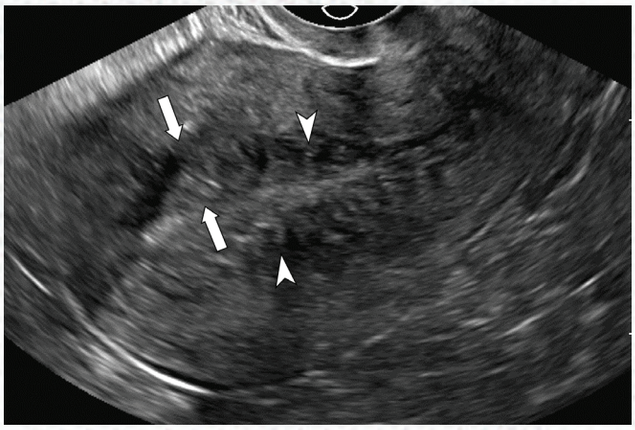

Figure 2: Sagittal US scan of the uterus showing a thickened inner myometrium (arrows) and myometrial striations (arrowheads).

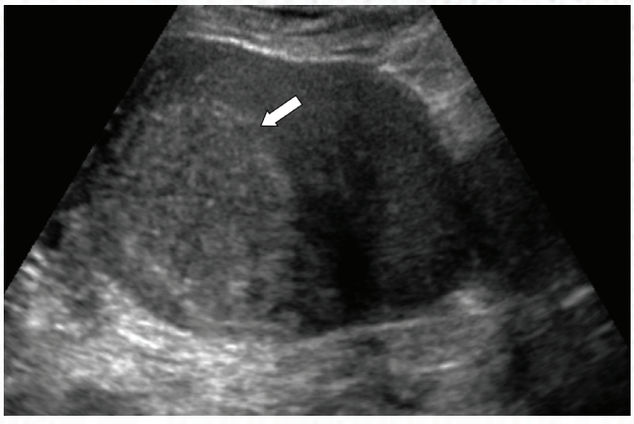

Figure 3: Sagittal US scan of the uterus showing focal adenomyosis (arrow). Note how the lesion extends on both sides of the endometrial cavity and is indistinct from it: these features are not seen with fibroids.

INTRODUCTION

Adenomyosis is a common condition in which tissues of the endometrial lining (endometrial glands and stroma) migrate into the myometrium. These ectopic endometrial tissues incite uterine enlargement through myometrial hyperplasia and hypertrophy. They also cause increased myometrial vascularity.

INCIDENCE

Adenomyosis has been reported to occur in around 20-30% of women.[1] In the past, this disease was thought to occur mainly at around 40-50 years of age because it was most frequently diagnosed on hysterectomy specimens. However, with the advent of MRI and more recently, high resolution endovaginal ultrasound, this disease is now frequently diagnosed in 20-40-year-olds and in post-menopausal women.[2]

CAUSES

The cause for the migration of endometrial tissues into the myometrium is unknown. Proposed mechanisms include endometrial invagination, migration of endometrial tissues along myometrial lymphatics and embryologically displaced Mullerian remnants.

While there has been a clear association between adenomyosis and multiparity, patients with traits towards high oestrogen exposure such as early menarche and short menstrual cycles, and individuals with a high body-mass-index also show an increased risk.[2]

While the association with multiparity may be explained through high oestrogen exposure, migration of endometrial tissues may also result from trophoblastic penetration that occurs during placental growth.[2]

PATHOPHYSIOLOGY

The pathological findings seen in adenomyosis can be categorised into three components: the "adeno" component involves migration of endometrial tissues into the myometrium, the "myosis" component is the reaction of the adjacent myometrium that includes myometrial hyperplasia and hypertrophy, while the third component consists of increased myometrial vascularity.

SIGNS AND SYMPTOMS

Approximately a third of adenomyosis cases are asymptomatic, being diagnosed only on endovaginal ultrasound. The most common symptom is menorrhagia (heavy periods), which is thought to result because of the increased number of endometrial glands and increased myometrial vascularity. The second most common symptom of adenomyosis is dysmenorrhoea (painful periods) that likely occurs because of intramyometrial bleeding and increased prostaglandin levels, which lead to myometrial contraction and vasoconstriction. Other symptoms of adenomyosis include pelvic pain, metrorrhagia (irregular uterine bleeding most notably between menstrual periods) and dyspareunia (painful intercourse).

The association with infertility is thought to result from changes in the junctional zone of the endometrium that interfere with implantation. An increased rate of spontaneous abortion

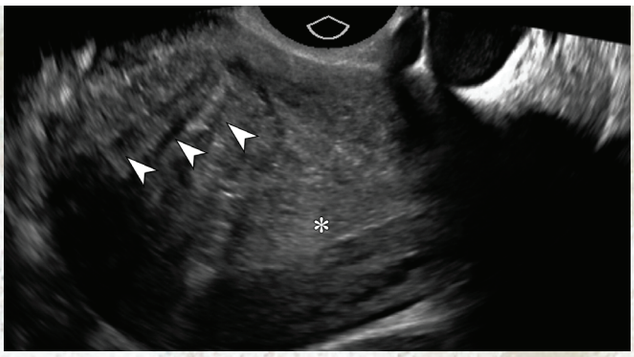

Figure 4: Longitudinal scan of the uterus showing loss of the endometrial/myometrial interface (*) and anterior focal myometrial heterogeneity and venetian blind shadowing (arrowheads).

seen in patients with adenomyosis is likely due to increased uterine contractions, endometrial inflammation and an altered hormonal environment.

Signs of adenomyosis are non-specific including pelvic tenderness and uterine enlargement, which are also seen with uterine fibroids and endometriosis.

ULTRASOUND (US) FINDINGS

US findings may be classified based on the three pathological mechanisms described above.

A. The US findings related *to migration of the endometrial glands* include a loss of definition of the endometrial/myometrial interface, a thickened inner myometrial layer, myometrial heterogeneity and myometrial cysts (Fig 1). These cysts are typically 1-5mm in diameter and are usually anechoic. However, since they contain endometrial glands, they may contain echogenic material representing blood degeneration products. Occasionally a cyst may connect to the endometrium through a long duct ("lollipop diverticulum").

B. Since migrated endometrial glands are hormonally active, they induce a local reaction (*myosis*) in adjacent myometrium. This is seen as thickening of the inner myometrium on US, which may sometimes demonstrate myometrial striations (Fig 2). Focal myometrial thickening (Fig 3) may resemble a fibroid, however the latter usually has more distinct margins. Diffuse uterine enlargement may also occur. The portion of the myometrium affected by adenomyosis shows a course heterogeneous texture with thin vertical shadows that has been termed a venetian blind appearance (Fig 4).

C. *Increased vascularity* of the myometrium at the site of adenomyosis can be readily seen on colour Doppler US imaging (Fig 5). The increased vascularity is reactive to muscle hyperplasia and hypertrophy. Vascularity tends to be central in adenomyosis and peripheral in a fibroid (Fig 6).

The best way to visualise the above findings are with high frequency endovaginal probes. However, with a large uterus, the settings may need to be adjusted to lower frequencies to penetrate to the posterior myometrium. Occasionally, transabdominal pelvic US may be required for very large uteruses.

Using 3D US to generate reconstructions of the uterus in any plane has also been suggested by some authors, with limited degrees of success.

Saline-infusion sono-hysterography (SIS) is a technique whereby saline is injected into the endometrial cavity during US examination to better assess the endometrial lining. It is the US equivalent of X-ray hysterosalpingography, which avoids ionizing radiation. SIS may be beneficial in equivocal cases of adenomyosis as it clearly demonstrates the endometrium and may show filling of the endometrial glands with saline (Fig 7).

In short, adenomyosis is a common cause of dysmenorrhoea, menorrhagia and metrorrhagia. It may also cause infertility. High-frequency endovaginal ultrasound provides efficient confirmation of this condition and should be the first test if the condition is suspected. This imaging technique readily detects the disease and serves to distinguish other gynaecological causes of pelvic pain such as adnexal cysts, ectopic gestation and pelvic inflammatory disease.

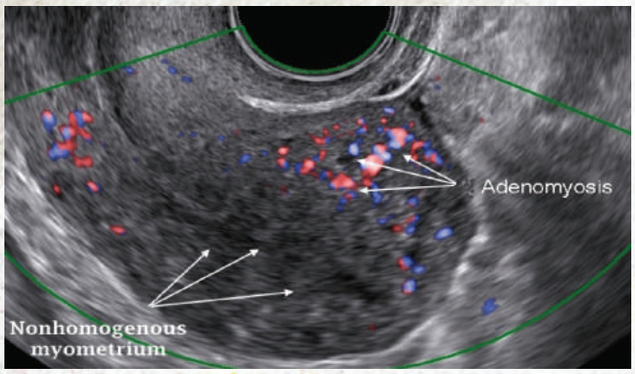

Figure 5: Sagittal US scan of the uterus showing increased colour flow at the site of adenomyosis and a non-homogeneous myometrium surrounding the endometrial cavity.

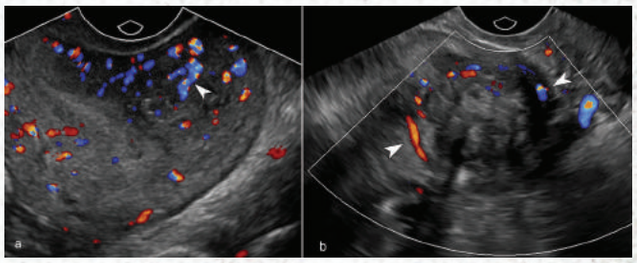

Figure 6: (a) shows a focus of adenomyosis with torturous wide vessels (arrowhead). (b) shows a fibroid (arrowheads) with peripheral vessels.

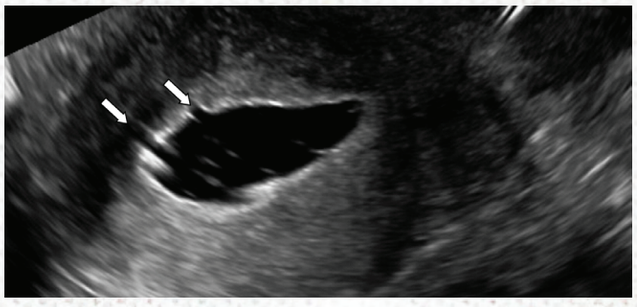

Figure 7: Sagittal US scan of the uterus following intrauterine injection of saline (SIS) showing fluid-filling of the endometrial glands (arrows).

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