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Sports and exercise medicine

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CONTENTS

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From the origin to the present: the history of sports and exercise medicine

Prof. Fabio PIGOZZI

The dawn of sports and exercise medicine (SEM) dates back more than one century, when the first medical investigations on trained or untrained individuals were collected in the Sports Laboratory in Dresden, Germany, managed by Arthur Mallwitz, during the 1st International Hygiene Exhibition, from May to October 1911. One year later the 1st Congress for the scientific investigation of Sports and Physical Exercises was held in Oberhof, Germany, with topics about the physical education, woman and physical fitness, cardiovascular adaptations to the training and doping. The first SEM Association was founded during this meeting and it was called the "German Committee for Scientific Investigation of Sports and Physical Exercises".

After the First World War, in 1928 the first "Association Internationale Médico-Sportive" (AIMS) was founded in St. Moritz, Switzerland, during the 2nd Winter Olympic Games. The purposes of the AIMS were to protect the athlete's health and to develop the sciences and the studies concerning sport and exercise. In 1934 the AIMS became "Fédération Internationale de Médecine Sportive" (FIMS) and, subsequently in 1998, "Fédération Internationale de Médecine du Sport" (Tittel and Wesseling, 2005).

In the last decade the network of FIMS has been considerably expanded: in the year 2016, 118 nations belonged to the International Federation of Sports Medicine (FIMS) and thanks to the realization of the FIMS Collaborating Centres of Sports Medicine (CCSM) project, 24 Centres have been already accredited worldwide functioning as local ambassadors of FIMS´ vision and mission, helping to achieve our shared objectives in all parts of the world. To this respect, one of the most important milestones has undoubtedly been the establishment of the FIMS Headquarters at the Maison du Sport Internationale in Lausanne, Switzerland - a return to the roots where FIMS was founded.

The aims of the International Federation of Sports Medicine can actually be summarized as follows:

Vision

- Caring for the athletes and sports communities.
- Leading education and science in sports medicine worldwide.
- Promote ethics in sports and medicine.

Mission

- Be the leader and prime reference in education, ethics and science for sports physicians at all levels worldwide.
- Protect the physical and mental health and ensure the wellbeing of all who are engaged in sports and exercise.
- Promote a healthy and active lifestyle.

In order to fulfil these goals, an important part of the cooperation with the National Sports Medical Associations is to spread and share information about the scientific, theoretical and practical aspects of SEM. What we need to find out is how SEM is currently considered and what future worldwide directions SEM could take.

In 1958, during the foundation of the Institute for Cardiology and Sports Medicine in Cologne, Germany, SEM was given this definition by Wildor Hollmann, former President of FIMS, and subsequently adopted by the FIMS in 1977: *"Sport and Exercise Medicine includes those theoretical and practical branches of medicine which investigate the influence of exercise, training and sport on healthy and ill people, as well as the effects of lack exercise, to produce useful results for prevention, therapy, rehabilitation, and the athlete"* (Hollmann, 1988).

SEM is nowadays an independent medical area dedicated to practice, study, teaching and research. It is, unfortunately, noticeable how SEM did not reach the same consideration and regard in all countries of the world, and since its first references in the early 20th century, all the purposes haven't been univocally achieved; I believe that the main objective of SEM

remains to date the promotion and safeguard of the athlete's state of health in a multidisciplinary program. The importance given to SEM in different countries brought the governments to emanate laws that approve a mandatory pre-participation screening for athletes practicing physical activity at competitive or non-competitive level. In Italy, for example, this law is in effect for over 30 years since 1982, thus consistently reducing the number of sport sudden deaths through the years (Corrado et al., 2006).

Physical inactivity has become the greatest public health problem of our time together with an increase of chronic diseases, either communicable or not. For this purpose, it is universally accepted that the diffusion of SEM should be promoted for two main reasons: to prevent sport-related diseases including sudden deaths (with the use of the pre-participation screening and other specific medical assessments), and to include SEM in a more focused program called "sport-therapy", promoting the use of physical activity in the management of patients with risk factors or chronic diseases. Healthcare networks should begin to sustain the idea to *"prescribe exercise as a drug to patients"* and important organizations such as the American College of Sports Medicine and the European Federation of Sports Medicine Associations promoted in recent years respectively "ACSM's Recommendations for Exercise Preparticipation Health Screening" (Riebe et al., 2015) and the "Exercise prescription for health" projects, making physical activity part of the disease treatment.

In conclusion, I really do hope that SEM will be officially recognized worldwide as a standard part also of the management and prevention of chronic diseases, in order to improve general health, quality of life and reducing public health costs.

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Running out of breath

Dr Danica BONELLO SPITERI

ABSTRACT

There is emerging evidence that the prevalence of exercise-induced bronchospasm (EIB) is significantly under-reported in many sports. Little is known about the potential performance improvement that may exist when sports players are detected and treated for EIB, but optimal airway health is crucial for anyone undertaking regular exercise at any level. Athletes may not be aware of an underlying diagnosis of EIB, as they may be asymptomatic, whilst other athletes may present with asthma-like symptoms but, upon testing, there is a negative test for EIB. The pathophysiology of bronchoconstriction that occurs in EIB differs from that which occurs in normal asthma, due to the large volumes of air that pass through the respiratory airways resulting in drying out of the aveolar fluid with resultant chemical release. A eucapnic voluntary hyperpnoea (EVH) challenge is the gold standard to detect underlying EIB when it results in a 10% drop from the baseline forced expiratory volume in one second (FEV_1) in comparison to the baseline spirometric FEV_1. When a negative EVH challenge results, alternative respiratory diagnoses must be sought and treated. Hence not all exercise related breathing disorders encountered in family practice should be labelled as exercise induced asthma and treated as such.

Key words / Phrases

Exercise induced asthma; eucapnic voluntary hyperpnoea; athlete; bronchoconstriction; exercise.

INTRODUCTION

Exercise induced asthma (EIA) is a condition that is overdiagnosed and underdiagnosed throughout the physically active population. Overdiagnosis occurs since most patients initially present to their family physician with various respiratory associated symptoms in relation to undertaking exercise. Through lack of understanding of what EIA constitutes and possible alternative diagnoses, most patients are labelled as 'exercise induced asthma' and started on the routine inhalers without any proper investigation or follow up. A better understanding of EIA would enable the family physician to better manage this condition as it has been noted that most patients still resort to their family physician rather that respiratory specialists in order to control their symptoms. Alternative diagnoses for exercise related breathing disorders may not be considered by family doctors, making the overdiagnosis problem larger. Underdiagnosis occurs since EIA can affect both the recreational and elite athlete, yet it is totally asymptomatic; hence it not easily picked up, either by the family doctor or by the patient, unless it is considered.

PREVALENCE

The sporting population is known to have a higher incidence of asthma than the general population. Athletes participating in summer sports have a lower prevalence of exercise-induced bronchospasm (EIB) than those practising winter sports, where in the latter the prevalence of EIB can range between 21-62% in different sports (Dickinson, McConnell and Whyte, 2011).

PATHOPHYSIOLOGY OF EIA

EIA occurs when a person undertakes exercise, resulting in a large amount of air exchange occurring throughout the bronchial and alveolar airways. Usually air is humidified through the nasal passages when inhaling, but at high levels of exercise these are bypassed, so the lower airways are responsible for humidifying the inhaled air. This increases the chance of the alveoli becoming dehydrated and the surface fluid will increase in osmolality. The bronchial epithelial cells respond by shrinking and releasing inflammatory mediators which results in bronchial constriction that limits airway flow, mainly in expiration (Anderson, et al., 1982). EIA is always reversible, either spontaneously upon cessation of

exercise or else following inhaled-agonists. This process is termed bronchoconstriction of the alveolar airways resulting in exercise induced asthma, or better termed, exercise induced bronchoconstriction.

SCREENING FOR EIB

As already outlined, there is often a potential for over or underdiagnosis of EIB, but the main worry concerns the risk of underdiagnosis. Overdiagnosis can occur when athletes are diagnosed with EIB on the basis of reporting symptoms (e.g. cough, wheeze, chest tightness, shortness of breath, sputum), where in reality, upon testing they would be negative for EIB (Ansley, et al., 2012). Underdiagnosis can occur when athletes who do not report any symptoms will test positive when tested for EIB.

Rundell, et al., (2001) found that when EIB is gauged in athletes depending on their symptoms, only 61% of athletes with EIB were detected. On the other hand, 45% of athletes with two or more symptoms related to asthma were not found to have EIB on testing. Thus, positive symptoms are insensitive to identifying EIB and a negative symptom is not specific. The main reason for screening for EIB is to prevent any detrimental effects on the athlete and the athlete's performance both during training and also during competition. The International Olympic Committee Medical Commission (IOC-MC) states that all safety measures should be taken to ensure that sports does not affect the health or welfare of athletes (Samaranch, 1998); thus athletes should be screened for EIB to ensure that there is optimum airway health. Asthma-related deaths in elite athletes often occur in conjunction with a sporting event (Becker, et al., 2004), and uncontrolled asthma itself plays a significant role in unexplained death.

There is increasing evidence that elite athletes fail to recognize and/or report symptoms that are related to EIB, as was described by Dickinson, McConnell and Whyte (2011) when 228 athletes from different sporting backgrounds underwent the eucapnic voluntary hyperpnoea (EVH) challenge to assess for EIB. In the UK, any athlete that competed at the 2008 and 2012 Olympics was screened for EIB; however non-Olympic athletes do not have any guidance as to who should and who should not be screened.

Athletes participating in sports where there is the presence of certain environmental pollutants are also at increased risk for EIB. Chlorine compounds in swimming pools and certain chemicals through car pollution pose an additional risk to athletes. These act as allergic triggers and may potentially exacerbate bronchospasm in athletes who already have increased susceptibility to EIB. Hence it makes it more essential to screen athletes for EIB. EIB varies in its manifestations from mild performance impairment to, rarely, severe bronchospasm with respiratory failure. Symptoms are often subtle, such as fatigue, or else may occur only in specific environments. Despite the fact that not all athletes are aware of ongoing EIB following exertion, they will recover spontaneously and airflow returns to baseline within 60 minutes, even in the absence of bronchodilator intervention.

The research by Dickinson, McConnell and Whyte (2011) verified that the presence of symptoms related to asthma was found both in athletes with and without EIB. Elite athletes may fail to associate any dyspnoea or other respiratory symptoms to EIB, but rather attribute this to physical exertion as part of their normal intense training or competition regime. Some athletes may also avoid reporting symptoms of EIB as they may be under the impression that it would signify a weakness on their behalf, or that they would risk not being chosen for the elite squad. Hence, routine screening for EIB implemented for all athletes would assist in reassuring both the coaches and athletes that EIB can be detected and treated accordingly with adequate medication. This would ensure that EIB athletes are not at a disadvantage in comparison to their non-EIB fellow athletes (Dickinson, et al., 2006).

EUCAPNIC VOLUNTARY HYPERPNOEA CHALLENGE

The EVH challenge is the most sensitive test to detect EIB as it detects a greater number of athletes that exhibit airway hyper-responsiveness than a sport specific or laboratory based exercise challenge (Dickinson, et al., 2006). This is because an athlete may undergo a laboratory or field test and not encounter the same conditions that initiate EIB. If there are high humidity levels, these may not trigger EIB, hence giving a false negative result. The EVH challenge is superior to other non pharmacological methods of testing since it has a tighter control over the main causes of airway hyper-responsiveness, mainly the inspired water content and the minute ventilation. EVH is also paradoxically more sensitive and specific for EIB than an exercise challenge performed either in the laboratory or in the field (Mannix, Manfredi and Farber, 1999).

The EVH challenge is a measure of prevalence of bronchial hyper-responsiveness in a group, such as that analysed by Holzer, Anderson and Douglass (2002),

where a prevalence of 50% was identified and 60% of these had reported asthma symptoms. This is in contrast to the methacholine challenge test, undertaken in the same study, which revealed a prevalence of only 18% with methacholine. In the latter group, all the subjects had reported asthma symptoms. This lends further to the evidence that EVH challenge is a more sensitive test for the diagnosis of bronchial hyper-responsiveness, than either asthma symptoms or methacholine challenge testing.

Initially a baseline spirometry is carried out to determine the forced expiratory volume in one second (FEV_1) and to calculate the target hyperventilation rate (30 x FEV_1). An EVH challenge is conducted in the laboratory which involves the athlete hyperventilating, whilst sitting down at rest, for 6 minutes (30 x baseline FEV_1) breathing in a gas mixture containing 5% carbon dioxide, 21% oxygen and 74% nitrogen. The inspired air temperature is 19.1ºC and the relative humidity is 2%. (Anderson, et al., 2001). After, the 6 minute test spirometry is carried out at 3, 5, 7, 10 and 15 minutes post test to monitor any change, especially any drop in the FEV_1.

A fall of ≥10% in FEV_1 following exercise or a stimulus is considered to be diagnostic of EIB according the European Respiratory Society (ERS) and American Thoracic Society (ATS) (Roca, et al., 1997). This was further widened to state that the fall should occur over two consecutive time points, based on the possibility that respiratory muscle fatigue can decrease the maximum effort needed to perform FEV_1 after exercise. This is to avoid a poor respiratory effort being misdiagnosed as EIB. The 10% value was chosen as this represents a basis for limiting exercise performance, and correlates with a 26% reduction in airway flow rates in flow volume loops (Custovic, et al., 1994).

Throughout pharmacological (methacholine or histamine) testing of EIB, a requirement of 20% drop in FEV_1 is commonly applied. However, if this drop is applied to an EVH challenge, it will be missing clear cases of asthma, yet such a threshold would be highly specific for EIB. A threshold of 10% drop in FEV_1 has a sensitivity of 63% and specificity of 90% (Hurwitz, et al., 1995), and this is the recommended level for general use, including athletes. In circumstances where avoidance of a false positive diagnosis is of utmost important, a threshold of 15% drop in FEV_1 can be employed, as this is highly specific for asthma.

FEV_1 was the spirometric parameter that is mostly altered following an EVH challenge. It is slightly more accurate overall than the forced expiratory flow at the 25% point to the 75% point of the forced vital capacity ($FEF_{25-75\%}$) in distinguishing asthmatics from non-asthmatics. If an individual is well motivated, peak expiratory flow rate can also be used instead of FEV_1, but this is more related to effort than the other parameters that can be obtained through spirometry. Hence it is less useful.

TREATMENT OF EIB

Once EIB has been diagnosed, through obtaining a positive test on the EVH challenge, proper management of EIB needs to be addressed. Athletes with a diagnosis of EIB should be treated according to the same British Thoracic Society (BTS) guidelines for asthma. The BTS guideline on the management of asthma (British Thoracic Society, 2016) advises a step-wise management plan according to severity of the disease, and moving up or down the ladder as needed, if control is good for more than 3 months.

Step 1:

Occasional short acting inhaled β_2-agonist (SABA) when required for symptomatic relief. If used more than once daily or having night time symptoms, go to step 2.

Step 2:

Add inhaled steroid (beclomethasone, budesonide or fluticasone) on a regular basis. Short acting β_2- agonists must not be used as maintenance.

Step 3:

Increase the dose of the inhaled steroid (beclomethasone, budesonide, fluticasone). Alternatively a long acting β_2-agonist (LABA), salmeterol, can be added onto the inhaled steroid regime. If there are problems with the high dose inhaled steroid, go to step 2, and add on either a long acting β_2-agonist or modified release oral theophylline.

Step 4:

Add on ≥1 of the following: inhaled long-acting β_2-agonist, modified release oral theophylline, inhaled ipratropium, modified release oral β_2-agonist, high dose inhaled bronchodilators, cromoglycate or nedocromil.

Step 5:

Add regular oral prednisolone as a one daily dose, preferably in the mornings.

It must not be forgotten that athletes are bound to the rules and regulations of the World Antidoping Association (WADA); hence they may require the use of a therapeutic use exemption (TUE) if the athlete requires any medication that is in the WADA prohibited substances list.

Most athletes with EIB are unable to control their symptoms with solely a SABA, thus a LABA is also taken in conjunction with a SABA. However, over time athletes with EIB are requiring additional doses of SABAs in order to control their EIB, or else the majority are also resorting to the use of inhaled corticosteroids.

A number of findings support this:

- a minority of athletes do not have adequate EIB prevention with β_2-agonists when inhaling the recommended dose.
- daily use of β_2-agonists increases the severity of EIB as well as decreasing the duration of protection against EIB.
- once an athlete is suffering from EIB, the recovery period after inhalation of a β_2-agonist is extended, the more a β_2-agonist is used on a daily basis, as well as requiring additional doses of LABA/SABA to achieve the same effect over time.
- bronchial hyper-responsiveness can be induced or increased by regular use of β_2-agonists.

The underlying concept is that there is desensitization or tolerance of the β_2-receptor as a result of daily drug usage (Bisgaard, 2000), Desensitisation is implicated to occur on the bronchial smooth muscle and/or the mast cell due to uncoupling of the receptors and internalization or sequestration of uncoupled receptors is followed by degradation, resulting in a net downregulation of receptors, since receptor resynthesis is not as fast.

There are also negative findings in relation to the regular, daily use of β_2-agonists as described by Anderson, Caillaud and Brannan (2006):

- There exists a minority of asthmatic athletes whose EIB does not respond to the clinically recommended dose of β_2-agonists. Anderson, Caillaud and Brannan (2006) detected unexpectedly high failure rates to control EIB after 4 weeks of regular treatment with a LABA (salmeterol), thus indicating that not all subjects have their asthma under control with a regular LABA, and thus may require the use of inhaled corticosteroids for improved control.
- Daily treatment of EIB with β_2-agonists can increase the severity of EIB (Anderson, Caillaud and Brannan, 2006). This is thought to be due to the enhanced release of a preformed mediator such as histamine.
- Daily inhalation of LABA decreases the length of time of protective effect against EIB. With SABA, protection against EIB was not evident 6.5 hours after the dose was administered. This was seen in 72% of subjects with EIB who were prescribed a SABA (Anderson, et al., 1991). In subjects who were given LABA, there is still a reduction in the duration of protection against EIB over time. This tolerance effect was not affected by changing to a once daily dose or by addition of a corticosteroid inhaler. The total time in hours of protection against EIB was significantly decreased after 4 weeks and after 8 weeks of treatment, in comparison to just 3 days of a LABA, namely salmeterol.
- The recovery of EIB from a standard dose of β_2-agonist is slower, when β_2-agonists are used on a daily basis (Storms, et al., 2004), thus requiring additional doses from a LABA or SABA.
- Bronchial hyper-responsiveness can be increased by the daily use of β_2-agonists.

MANAGEMENT OF A NEGATIVE EVH CHALLENGE

Some athletes may present with exercise related breathing difficulties, yet when an EVH challenge is performed, there is no drop in the FEV_1; hence this is a negative test result, and refutes the diagnosis of EIB. In such cases, disordered breathing patterns should be looked at and addressed, such as vocal cord dysfunction and exercise related laryngeal obstruction. In such cases, a good history is also indicative of the problem, where the athlete will, upon close questioning, admit to an inspiratory, rather than expiratory, difficulty with breathing. They will also report a 'wheeze', however this is often actually stridor, as it is often during the inspiratory aspect of respiration. It is often female endurance athletes, who have a tendency to anxiety and perfectionism as part of their personality, who have a higher tendency to present with this clinical picture, but it is not exclusive. In this scenario, various breathing rehabilitation techniques need to be implemented for the athlete to control the dysfunction and/or obstruction. This would involve learning how to perform diaphragmatic breathing in preference to apical lung breathing, which is often noted whilst performing the EVH challenge, or when asking the patient to inhale and exhale deeply a few times in clinic.

Repiratory muscle training, such as through the use of a 'powerbreathe' aid can help to strengthen respiratory

muscles, including the diaphragm, and allow the athlete to learn to 'relax' the vocal cords.

A psychologist's input may be considered for those who have a perfectionist or anxious personality or in the case of athletes feeling the 'pressure to perform', as this can be found even at young age groups.

Nevertheless, it is still worthwhile screening for EIB, as both conditions can co-exist and may need to be tackled synchronously.

CONCLUSION

Athletes have a higher prevalence of EIB than the general population, yet the main concern is that a number of these athletes do not realize they have EIB.

The family doctor is usually the first port of call for both elite as well as recreational athletes, hence the importance of a detailed history, which can possibly elicit the difference between underlying EIB or other respiratory issues.

A family doctor may initially opt to treat the athlete as EIB, and treat with appropriate inhalers, according to the BTS guidelines. However, follow up is important, as this is the main area where distinction can be made whether or not the athlete is well controlled with inhalers. If upon follow up, the athlete still reports a lack of control of his/her EIB symptoms, it may be worthwhile referring for EVH testing to determine whether or not EIB is present, or whether it is due to alternative breathing patterns that may be impairing normal respiration. In this case, inhalers are not recommended.

A history of inspiratory stridor, especially towards the end of competition or training helps the family doctor to suspect vocal cord dysfunction, rather than EIB, hence respiratory muscle training is more suitable in these cases, rather than inhaler based treatment.

The gold standard test to refute or accept whether EIB is present or not, still remains an EVH challenge, should there be any doubt about the exact diagnosis.

The International Olympic Committee medical commission aims to ensure that there is no long lasting harm or disease to sports participants. Therefore, athletes who demonstrate EIB through an EVH challenge should receive optimal treatment, both for prophylaxis and for symptomatic EIB.

Both winter and summer sports are likely to have a high prevalence of EIB. Hence this means that there are a large number of athletes who fail to recognise and report symptoms that may be related to EIB. This makes screening of athletes a valuable exercise to ensure optimal athlete health.

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Screening for heart disease in athletes

Dr Kirill MICALLEF STAFRACE, Prof. Joe CUMMISKEY

ABSTRACT

Physical activity, be it regular exercise or sports at whatever level, should be beneficial and not deleterious. Hence, it is important that the medical profession is aware that cardiovascular related deaths are the leading cause of mortality in athletes during sports. In 2009 the International Olympic Committee issued a consensus statement on the periodic health evaluation of elite athletes. This includes *'a comprehensive assessment of the athlete's current health status and risk of future injury or disease and, typically, is the entry point for medical care of the athlete*'. Although this consensus statement targeted elite athletes, the periodic health evaluation design is simple enough that it could easily be extrapolated for use for all physically active individuals. The periodic health evaluation's role is to screen for musculoskeletal or medical conditions that may place an athlete at risk for safe participation. Since this statement was issued, numerous international sport organisations have recommended a screening programme for individuals who partake in regular physical activity. Stress is made on the importance of a thorough health and family history with an emphasis on cardiovascular issues. There is no international consensus on the use of an electrocardiogram (ECG) as part of a screening programme; however most international sports federations and the European Cardiac and Sports Medicine societies strongly recommend it. What there is agreement on is that the doctor that reads an ECG should be knowledgeable of the physiological adaptations of the athletic heart that could lead to errant, yet perfectly safe, ECG traces.

Key words:
Athlete, medical, electrocardiogram, cardiac, screening

INTRODUCTION

The role regular physical activity has in the maintenance of a healthy lifestyle is well documented (The Lancet, 2012 and 2016). In fact the following quotes are often circulated to show the importance physicality has always held:

- Hippocrates, 5th century BC: "if one exercised they become more healthy, well-developed and age more slowly";
- Herodotus, 440 BC: "if we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health";
- Plato, 472 BC: "lack of activity destroys the good condition of every human being, while movement and methodical physical exercise correctly save it and preserve it".

However, physical activity, be it regular exercise or sports at whatever level, should be healthy and not deleterious. Hence it is important that the medical profession is aware that cardiovascular-related deaths are the leading cause of mortality in athletes during sports (Maron, et al., 2009; Harmon, et al., 2011). At the same time one must also not forget that musculoskeletal (MSK) issues go hand in hand with regular physical activity and even more so with contact sports (Ekstrand, Hägglund and Waldén, 2011). Although these are rarely fatal, they can have a significant effect on activities of daily living. Therefore, pre-participation screening is universally supported to identify athletes with pre-existing conditions that place them at risk of injury or an adverse cardiac event.

This paper shall focus primarily on what is recommended as a minimum requirement for the cardiovascular screening of an athlete, with MSK screening tackled in a future paper. It shall broach the subject by looking into the recommendations of the more established and recognised governing sporting authorities, namely the International Olympic Committee (IOC) and the Fédération Internationale de Football Association (FIFA), and the leading Sports and Exercise Medicine authorities in Europe and worldwide, specifically the European Federation of Sports and Exercise Medicine

(EFSMA), American College of Sports Medicine (ACSM) and the International Federation of Sports Medicine (FIMS). This paper shall not dwell on the myriads of documents that led to these recommendations, but rather view them in the local Maltese scenario.

INTERNATIONAL RECOMMENDATIONS

In 2009 the IOC issued a consensus statement on the periodic health evaluation (PHE) of elite athletes (Ljungqvist, et al., 2009). This includes *'a comprehensive assessment of the athlete's current health status and risk of future injury or disease and, typically, is the entry point for medical care of the athlete*'. Although this consensus statement targeted elite athletes, the PHE design is simple enough that it could easily be extrapolated for use for all physically active individuals. The PHE's role is to screen for MSK or medical conditions that may place an athlete at risk for safe participation. In fact the athlete may not even be aware that there is something wrong until this is revealed during a PHE. Alternatively, the athlete might have a current health problem and the PHE will serve to ensure that the medical ailment is being managed correctly and that the athlete is capable of safely undertaking physical activity at that particular moment. Amazingly, even athletes that have easy access to medical care sometimes choose to ignore, for whatever reasons, ailments that are causing significant symptoms. Other times, common asymptomatic conditions, such as a mild iron deficiency, may influence physical performance although the health of the athlete is not compromised. Ideally the PHE is undertaken early enough such that it allows sufficient time for the management of any injuries or medical problems that might be uncovered without affecting the athlete's season too much.

Periodic health evaluation requirements

According to the IOC, the general requirements of a PHE include:

- Based on sound scientific and medical criteria.
- Be performed in the primary interest of the athlete.
- Under the responsibility of a physician trained in sports medicine, preferably the physician responsible for providing ongoing medical care for the athlete, e.g. the team physician.
- The setting of the evaluation should be chosen to optimize the accuracy of the examination and respect the privacy of the athlete.
- Free and informed consent of the athlete and, if applicable, his/her legal guardian.

If the PHE provides evidence that an athlete is at serious medical risk, the physician must strongly discourage the athlete from continuing training or competing until the necessary medical measures have been taken. Based on such advice, it is the responsibility of the athlete to decide whether to continue training or competing.

If a physician is requested to issue a medical certificate, he or she must have explained in advance to the athlete the reason for the PHE and its outcome, as well as the nature of information provided to the third parties.

With the advent of many non-local athletes and the organisation of sports for all ages and physical capabilities, the PHE should be tailored to race, age, gender and be sport specific. Cultural sensitivities should also be considered. Once an injury or medical condition is identified, if deemed necessary, a referral should be organised to the appropriate specialist for further evaluation and management. The PHE is also an opportunity to assess any medications or nutritional products being used to determine if a Therapeutic Use Exemption (TUE) application to the World Anti Doping Association (WADA) is required.

Periodic health evaluation form

The PHE consists of a five-page document divided into two sections: the medical history section and the physical examination section (International Olympic Committee, 2009). The first section is thorough with an emphasis on elucidating any symptoms, signs or family history that could indicate an underlying cardiovascular issue. This cardiovascular focus is also seen in the physical examination section. This emphasis on cardiovascular evaluation of an athlete is stressed again since a 12 lead ECG is also required as part of a standard PHE. These all indicate how the prevention of sudden cardiac death in athletes remains a highly visible topic in sports and exercise medicine and cardiology.

When one is reviewing an ECG of an individual that regularly partakes in physical activity, one must note the cardiac adaptation and remodelling that regular physical training produces, which lead to common ECG alterations that could be mistaken as abnormal. Here the 'Seattle Criteria' document comes in handy as this is the outcome of the collaboration between a number of sports and exercise medicine organisations to tackle this ECG interpretation predicament (Drezner, et al., 2013). In fact, nowadays one can even acquire commercial ECG machines that have 'athlete specific' software based on

the Seattle Criteria to assist in the interpretation of the results. However, it is still highly recommended that physicians responsible for the medical care of athletes be guided by ECG interpretation standards that improve disease detection and limit false-positive results. Here one must stress again the recommendation by the IOC who encourages a referral to a specialist in the field, ideally a cardiologist attuned to the athletic heart, whenever there are any doubts.

To assist medical professionals that often have to deal with athletes, a number of free online courses have been created that tackle specifically ECG interpretation in athletes. Good examples are the British Medical Journal learning course: ECG interpretation in athletes (British Medical Journal, 2017) and the FEMEDE - La Sociedad Espanola de Medicina Del Deporte - course: Electrocardiography for sports medicine (FEMEDE, 2017).

The FIFA Pre-competition Medical Assessment (PCMA) (Dvorak, et al., 2009: Corrado, et al., 2010) follows the PHE of the IOC and involves a focused player medical history (PMH), family medical history (FMH) and cardiac specific physical medical examination. FIFA insists that a resting 12-lead ECG should be undertaken as part of the PCMA on all players at the beginning of their playing career and then once every year. (Dvorak et al 2013). However, different to the IOC PHE, the PCMA recommends that echocardiography be considered at least once in a player's early career to better detect structural disorders and should be undertaken by an experienced cardiologist and whenever abnormal results are found in the history, examination and/or ECG (Kramer, 2010). FIFA also recommends that an exercise test should be considered in athletes older than 35 years of age and when otherwise indicated. EFSMA issued a statement in 2015 indicating that without the ECG, athletic medical screening has low sensitivity and will also likely have a very low specificity (Löllgen, et al., 2015). This statement has recently been supported by a meta-analysis (fifteen papers) showing that ECG in athletes " is 5 times more sensitive than history, 10 times more sensitive than physical exam, has higher positive" and "lower negative likelihood ratio" with a "lower false positive rate" (Harmon, Zigman and Drezner, 2015).

LOCAL SCENARIO

In Malta the two larger non-governmental sports organisations, namely the Malta Football Association and the Maltese Olympic Committee, follow the lead of their parent organisations (FIFA and IOC), and require that athletes participating in their tournaments or games have a 12 lead ECG as part of their medical screening and that the physicians that conduct the medical screening have a sound knowledge of Sports and Exercise Medicine and ECG interpretation.

However, here one must note that not all Sports and Exercise Medicine organisations believe in the need of the ECG and the Joint Consensus Statement between the American College of Sports Medicine (ACSM) and the International Federation of Sports Medicine (FIMS) 'Advancing the Preparticipation Physical Evaluation (PPE)' is an example of this (Roberts, Löllgen and Matheson, 2014). The ACSM and FIMS did not reach a consensus on ECG screening as a routine part of PPE, but agreed that a history and physical examination focusing on cardiac risk is essential, and an ECG should be used where risk is increased.

CONCLUSION

A thorough medical evaluation is a must prior to commencing any form of regular physical activity, be the athlete a weekend warrior, a walker or a professional athlete. The minimum requirements for recreational athletes are a detailed history and physical examination focusing on cardiac risk; an ECG should be used when the perceived risk is increased. For competitive athletes, a 12 lead ECG is not only recommended but might even be an essential sport federation requirement for participation. Ideally the physician undertaking the medical screening is familiar with the sport concerned and with its specific physical requirements. Maltese general practitioners that work with athletes can avail themselves of the aforementioned online ECG courses and have in place an appropriate referral procedure for any queries that might. The goal is that, one day, Malta will have the same legal requirement that is found in other countries, such as Italy, where all individuals that undertake physical activity in an organised fashion, be it as a member of a fitness club, a sport club or participation in sporting events, such as road races, must undertake a pre-participation health evaluation that will include an ECG and ideally this is undertaken with physicians that have undergone the appropriate training.

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Prescribing medication for athletes: guidelines for general practitioners

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ABSTRACT

The number of persons taking part in organized sports in our islands is increasing every year. Many of these athletes and the events that they participate in are subject to doping control tests by the National Anti-Doping Organisation (NADO) or the national federation or association of their particular sport. A small number of these tests record a prohibited substance present in the athlete's sample, which may have serious consequences on the sporting career of the athlete. Many athletes consult their general practitioner (GP) or team doctor regularly for advice when they develop a medical condition. This article is intended to provide the GP with background information regarding drugs that may be used safely and without consequences for the athlete, the procedure to follow when the athlete needs to be treated with drugs which are prohibited to athletes, and the pitfalls of accidental doping.

Key words

Doping, sports, athlete, supplements, prohibited list

INTRODUCTION

The sanctioning of star tennis player Maria Sharapova in 2016, following alleged medical use of the drug meldonium, resulted in a spate of media activity which brought to the attention of the world the possibility of athletes being sanctioned when using drugs prescribed legitimately. The drug was declared a prohibited drug on 1st January 2016 and resulted in a total of 283 positive tests worldwide during that year. It is prudent to bring the issue of safe prescribing to athletes to the attention of the family doctor / general practitioner (GP), and provide the necessary tools to make an informed decision when treating athletes. Contrary to normal patients, athletes are not allowed to use certain medications as this may result in a positive doping control test, which could lead to a sanction.

The World Anti-Doping Agency (WADA) was established in 1999 as an international, independent agency composed and funded equally by the sport movement and governments of the world. Its key activities include scientific research, education, development of anti-doping capacities, and monitoring of the World Anti-Doping Code (WADC/Code) – the document harmonizing anti-doping policies in all sports and all countries. The first Code was drawn up in 2004 and revised in 2015.

Malta ratified the Anti-Doping Convention of the Council of Europe and the UNESCO Convention against Doping in Sport in 2011. The first Anti-Doping Regulations were passed in 2011 (LN 281 of 2011) and the Maltese National Anti-Doping Organisation (NADO) started operation in February 2012 in line with the WADC. Since then the Anti-Doping regulations were changed in 2015 (LN 17 of 2015) to be in line with the new WADC, which, in a nutshell, lays down the rules on what constitutes an Anti-Doping Rule Violation (ADRV) and how the NADO should conduct its operation (Anti-Doping Regulations of Malta, 2015). This involves testing, results management and sanctioning. Since its inception, Maltese NADO has carried out 441 doping control tests and sanctioned 18 athletes.

There are 10 ADRVs in our law and the WADC. These are summarised in Table 1. The most common ADRV by far is finding the presence of a prohibited substance or its metabolites in an athlete's sample. This is what constitutes a positive doping control test.

THE PROHIBITED LIST

The WADA Prohibited List (List) is the comprehensive document serving as the international standard in identifying substances and methods prohibited in all sports (World Anti-Doping Agency, 2017). The List is revised every year after months of review by experts and stakeholders and comes into force on 1st January of every year. The Maltese Anti-Doping Regulations refer to this

Table 1: Antidoping rule violations

1	The presence of a prohibited substance or its metabolites or markers in the athlete's sample.
2	The use or attempted use of a prohibited substance or prohibited method.
3	Evading sample collection or refusing or failing to submit to sample collection.
4	Any combination of three missed tests or filing failures in one calendar year.
5	Tampering or attempted tampering with the doping control process.
6	Possession by an athlete support personnel of any prohibited substance or method in and out of competition.
7	Trafficking or attempted trafficking of a prohibited substance or method.
8	Administration or attempted administration to an athlete of any prohibited substance or method.
9	Assisting, encouraging, aiding, abetting, conspiring, covering up involving an ADRV.
10	Prohibited association.

document and a copy is published in the Government Gazette in January of every year and it is also available online. It is very important that athletes and their medical providers are aware that changes may occur from year to year according to new evidence which would have emerged regarding performance enhancing drugs.

A substance or method is considered by WADA for inclusion in the prohibited list if it meets two of the following three criteria:

- Medical or scientific evidence, pharmacological effect, or experience that it has the potential to enhance or enhances sport performance.
- Medical or scientific evidence, pharmacological effect, or experience that the substance represents an actual or potential health risk to the athlete.
- Use of the substance is considered to violate the spirit of sport.

All athletes participating in organized sports are subject to doping control testing at all times. The definition of athlete in the Maltese legislation is as follows: *"athlete" means any person who competes in sport at the international level as defined by each international federation or at the national level as defined by each national anti-doping organisation."* This means that any person registered with a local sporting association or federation, or who participates in a competition organized by the same, is bound to abide by the anti-doping regulations. These athletes may be tested not only during a competition but also at other times (out of competition).

The Maltese Anti-Doping Regulations and the WADC stipulate athlete 'strict liability'. This principle is applied in situations where urine or blood samples collected from an athlete have produced adverse analytical results, and means that the athlete is held responsible for the substances found in his or her bodily specimen. An anti-doping rule violation occurs whenever a prohibited substance (or its metabolites or markers) is found in the specimen, whether or not the athlete intentionally or unintentionally used a prohibited substance (even if it was legitimately prescribed by a doctor) or was negligent or otherwise at fault. This means that the athlete is solely responsible for any prohibited substance found in his sample and needs to be very vigilant about which medications or substances he or she might be consuming at all times, not just around the time of competition.

The substances and methods included in the List are divided into 4 sections as follows:

- Substances prohibited at all times (Table 2). These drugs cannot be used by athletes in and out of competition. This section includes anabolic steroids, beta 2 agonists, diuretics and growth hormone among others.
- Substances prohibited in-competition only (Table 3). This section includes stimulants, narcotics, glucocorticoids and cannabinoids. The athlete must pay attention to stop any medication containing any of these drugs early enough for the all of the drug to be metabolized and cleared by the

Table 2: Substances prohibited at all times

Class			Examples of substances
S0. Non approved substances	Any pharmacological substance not addressed by the other subsections and not approved for human therapeutic use	Drugs under clinical or pre-clinical development or discontinued, designer drugs, drugs approved only for veterinary use	GW501516
S1. Anabolic agents	1. Anabolic androgenic steroids (AAS)	Exogenous AAS	Bodenone, nandrolone, stanazolol
		Endogenous AAS, when administered exogenously	Testosterone, DHEA, androsterone, epitestoterone
	2. Other anabolic agents		Clenbuterol, selective androgen receptor modulators (SARM's), tibolone, zilpaterol
S2. Peptide hormones, growth factors, related substances and mimetics	1. Erythropoetin-receptor agonists	1.1 Erythropoesis stimulating agents (ESA's)	EPO, dEPO, CERA
		1.2 Non erythropoetic EPO-receptor agonists	ARA-290, asialo EPO, carbamylated EPO
	2. Hypoxia inducible factor (HIF)	HIF stabilisers	HIF stabilisers e.g. cobalt, HIF activators e.g. argon, xenon
	3. Chorionic gonadotrophin (CG) & luteinsing hormone (LH) & their releasing factors in MALES		• Buserelin, • gonadorelin, • leuprorelin
	4. Corticotrophins and their releasing factors		• Corticorelin
	5. Growth hormone (GH) and its releasing factors	Growth hormone releasing hormone (GHRH) and its analogues, secretagogues (GHS) and releasing peptides (GHRP's)	• CJC-1295, sermorelin, ghrelin, GHRP-6, hexarelin

Class			Examples of substances
	Additional prohibited growth factors		• IGF-1, FGF. HGF, VGEF, PDGF
S3. Beta2 agonists	All beta2 agonists including optical isomers EXCEPT INHALED salbutamol, salmeterol, formoterol in therapeutic doses		Terbutaline, albuterol
S.4 Hormone and metabolic modulators	1. Aromatase inhibitors		Aminoglutethimide, anastrolzole, formestane
	2. Selective estrogen receptors modulators (SERM's)		Tamoxifen, raloxifen, toremifen
	3. Other anti-estrogenic substances		Clomiphene, cyclofenil, fluvestrant
	4. Agents modifying myostatin function		Myostatin inhibitors
	5. Metabolic modulators		Meldonium, insulin and insulin-mimetics, trimetazine
S.5 Diuretics and masking agents	All diuretics & masking agents	EXCEPT drosperinone, pamabrom, ophthalmic use of carbonic anhydrase inhibitors, local use of fenylpressin in dental anasethesia	Probenicid, acetazolamide, bumetanide, furosemide, indapamide, thiazides, spironolactone

body in time for competition. Different substances have got different rates for elimination and this also varies from person to person.

- Substances which are prohibited in particular sports only (Table 4). This section includes alcohol, and beta blockers, which are prohibited in certain sports.
- Prohibited methods (Table 5). Examples of this category include blood transfusions, intravenous infusions and genetic manipulation.

The List provides a long list of examples of drugs in each category. However it needs to be emphasized that all drugs belonging to the particular categories are prohibited even if they are not mentioned in the List.

THERAPEUTIC USE EXEMPTIONS (TUE'S)

When an athlete has a health condition, which demands treatment or medication, it is extremely important for the athlete and/or the doctor to check the status of the substance or method to be used with the Prohibited

List. If the substance or treatment method is prohibited, the athlete must apply for and obtain a Therapeutic use Exemption (TUE) from the NADO (available from http://nadomalta.org/tue-form), and treatment must not start until this confirmation is received. Only in acute medical emergencies is an athlete allowed to start treatment before the TUE is approved. There is no guarantee that, in every case, an approval will be granted retrospectively. Although the doctor completes much of the TUE application form for the athlete, it remains the athlete's responsibility to ensure that they have a valid TUE when they are taking, or have taken, a prohibited substance, or used a prohibited method.

The evaluation of TUEs by the NADO is governed by a mandatory International Standard for Therapeutic Use Exemptions (ISTUE). This standard first came into effect in January 2005 with several revisions since then, the latest one came into effect on 1 January 2016.

According to the ISTUE, an athlete may be granted a TUE if, (and only if), he/she can show, by a balance of probability, that each of the following conditions is met:

1. The prohibited substance or prohibited method in question is needed to treat an acute or chronic medical condition, such that the athlete would experience a *significant* impairment to health if the prohibited substance or prohibited method were to be withheld.
2. The therapeutic use of the prohibited substance or prohibited method is highly unlikely to produce any additional enhancement of performance beyond what might be anticipated by a return to the athlete's normal state of health following the treatment of the acute or chronic medical condition.
3. There is no reasonable therapeutic alternative to the use of the prohibited substance or prohibited method.
4. The necessity for the use of the prohibited substance or prohibited method is not a consequence, wholly or in part, of the prior use (without a TUE) of a substance or method which was prohibited at the time of such use.

Table 3: Substances prohibited in competition: all substances prohibited out of competition and the following

Class			Examples of substances
S.6 Stimulants	a. Non-specified		Amphetamine, bromantan, cocaine, fenfluramine, mesocarb
	b. Specified	Note: cathine, ephedrine, pseudoephedrine subject to urinary levels.	Cathine, ephedrine, adrenalin, seleginine, pseudoephedrine, methylhexanamine, dimethylbutylamine
S.7 Narcotics			Morphine, pethidine, fentanyl, mathadone
S.8 Cannabinoiods	a. Natural		Marijuana, hashish, cannabis, THC
	b. Cannabimimetics		"Spice", JWH-018, JWH-073, HU-210
S.8 Glucocorticoids	All prohibited when administered by oral, intra-muscular, intra-venous, rectal route	Allowed when administered by inhalation, nasal, dermal, ophthalmological applications	

Table 4: Substances prohibited in particular sports

Class	Comments	Sports	Examples of substances
P.1 Alcohol (ethanol)	Blood concentration threshold of 0.10 g/L	Air sports, archery, automobile, powerboating	
P.2 Beta-blockers	Prohibited in competition	Archery, automobile, billiards, darts, golf, shooting, skiing, snowboarding, ski jumping, underwater sports	Atenolol, carvedilol, labetalol, propranolol, sotalol, timolol etc.
	Prohibited in-competition and out-of-competition	Archery, shooting	

Table 5: Prohibited methods

Class	Comments
M1. Manipulation of blood and blood components	1. Administration or reintroduction of any quantity of autologous, allogenic (homologous) or heterologous blood or red blood cell products of any origin into the circulatory system. 2. Artificially enhancing the uptake, transport or delivery of oxygen. Including, but not limited to: perfluorochemicals, efaproxiral (RSR13) and modified haemoglobin products e.g. haemoglobin-based blood substitutes and microencapsulated haemoglobin products, excluding supplemental oxygen. 3. Any form of intravascular manipulation of the blood or blood components by physical or chemical means.
M2. Chemical and physical manipulations	1. Tampering, or attempting to tamper, to alter the integrity and validity of samples collected during doping control, including but not limited to: urine substitution and/or adulteration, e.g. proteases. 2. Intravenous infusions and/or injections of more than 50 mL per 6 hour period except for those legitimately received in the course of hospital admissions, surgical procedures or clinical investigations.
M3. Gene doping	1. The transfer of polymers of nucleic acids or nucleic acids analogies. 2. The use of normal or genetically modified cells.

One of the basic principles for treating athletes is to prescribe medication or treatments that are not prohibited. For example a hypertensive athlete who needs treatment can be prescribed several classes of allowed drugs, but not diuretics and beta-blockers (the latter in certain sports only, Table 4). The only situation where these drugs may be considered for a TUE is when the athlete can provide sound medical evidence that all allowed drugs were not effective in controlling his blood pressure and he responds only to the prohibited ones. The TUE application needs to be accompanied by medical evidence to prove this.

There is a belief among the local sports community that as long as a TUE application form is filled in and

submitted, it will be accepted automatically and TUE granted. This is not the case. The TUE Committee needs to be convinced that the condition that requires the prohibited drug exists and there is no other alternative treatment. Comprehensive medical evidence needs to accompany the application. This includes a detailed medical report, any laboratory and test results and imaging studies. The TUE panel takes all the evidence into consideration and reaches a decision whether to grant or refuse the TUE. This decision has to be in line with ISTUE standards. There have been instances where doctors have insisted on their right to decide how and when to treat patients. This can be understandable for the non-athletic population. However, with regards to athletes that have to abide by the WADA code, prescription must be guided by the relevant anti-doping regulations.

RETROACTIVE TUE's

There are infrequent situations for which TUE's may be granted retroactively. These cases are evaluated in the same way as standard TUE applications i.e. the TUE Committee evaluates the application and issues its decision. The ISTUE stipulates which situations may result in the granting of a retroactive TUE, as follows:

1. Emergency treatment or treatment of an acute medical condition was necessary (a medical emergency or acute medical situation is one which justifies immediate administration of a prohibited substance or method and failure to treat immediately could significantly put the athlete's health at risk). It is always preferable to address a TUE application prospectively rather than retrospectively; or
2. Due to other exceptional circumstances, there was insufficient time or opportunity for the athlete to submit, or the TUEC to consider, an application for the TUE prior to sample collection; or
3. Applicable rules for the particular sport required the athlete or permitted the athlete to apply for a retroactive TUE.
4. It is agreed, by WADA and by the NADO to whom the application for a retroactive TUE is or would be made, that fairness requires the grant of a retroactive TUE.

Once a TUE is granted, this would be for a specific method or substance, with a defined dosage and route of administration. It would also be for a specific period of time and would, therefore, have an expiry date. The TUE approval certificate should, ideally, be presented to doping control officials at the time of any eventual doping controls. When the doping control authority receives a report of an adverse analytical finding from the laboratory, an initial evaluation will take place to verify that the TUE is still in effect and that the results of the analysis are consistent with the TUE granted (nature of substance, route of administration, dose, time frame of administration, etc.). If the review is satisfactory, the result of the test will be recorded as negative. It is important to note that rejected TUE's can be appealed to WADA under the rules of International Federations and NADOs. However, one may always reapply to the NADO to have a new TUE application considered, especially if new compelling medical information is presented.

PITFALLS FOR THE ATHLETE AND THE GP

As explained above, the athlete is always responsible for what goes into his body. Therefore he needs to discuss both the need and the choice of medication with the doctor, pointing out that he may be subject to doping control. There are online applications that may be accessed to check whether medications are prohibited or not. A useful one is a website maintained by the United Kingdom, Canadian, Japanese, Swiss, Australian and Unites States authorities called Global DRO which can be accessed at http://www.globaldro.com/UK/search.

The commonest situations where accidental doping may occur are when using:

1. 'Cold & flu' and cough preparations. Many times these contain drugs from the stimulant class, which would help to relieve the nasal congestion e.g. ephedrine, pseudo-ephedrine. Both these drugs are prohibited in-competition up to a certain urine concentration. The athlete and doctor must make sure that they are not consumed within a week of competition to allow time for the drug and its metabolites to be cleared from the body. A better solution would be to avoid these preparations altogether and use alternative medications like intranasal decongestants, e.g. xylometazoline, which are allowed.
2. Supplements. The majority of athletes make use of different kinds of dietary supplements to enhance their nutrition and optimise performance. The most widely used are protein, creatine, amino acids and various combinations of vitamins. Several studies have reported that prohibited substances

were found in a number of supplements on the market varying from 3-19% of the total number of supplements tested (Geyer et al., 2014; Judkins, Hall and Hoffman, 2007; Judkins, 2008; Kamber et al., 2001). These drugs would not be declared on the list of ingredients and athletes would think that the supplements are safe to consume. Classes of drugs most commonly found in these studies were anabolic steroids and stimulants. Contamination of these supplements may occur either as a deliberate, undeclared inclusion by the manufacturer to increase the effect of the supplement, or cross contamination during manufacture from poorly maintained machinery. In 2013, Jamaican athletes Asafa Powell and Sharon Simpson tested positive after making use of a supplement called Epiphany D3 which was spiked with an undeclared stimulant oxilofrine. (Drayton, 2014), and were eventually sanctioned.

3. Herbal medication or supplements. Such products are usually labeled as "natural", and athletes mistakenly believe that they are safe. Plants may contain metabolically active substances which are prohibited. For example, the Chinese herb ma huang is the equivalent of ephedra and contains ephedrine. 'Geranium oil' product labeling is often associated with the banned stimulant methylhexaneamine (DMAA). In actual fact geranium oils do not contain methylhexaneamine but these herbal supplements are spiked with the synthetic drug. (Lisi et al, 2011).

WADA and the International Olympic Committee advise athletes not to make use of dietary supplements as that is the only way to make sure that no prohibited substances are consumed inadvertently. Otherwise athletes need to scrutinize in detail the contents of supplements and only consume those which have been batch tested by the manufacturer. There are several websites which list supplements that are batch tested, and therefore safer for consumption by athletes than those which are not. The following are the most useful lists:

1. http://www.informed-sport.com/certified-product-brands
2. http://www.koelnerliste.com/en/product-database.html
3. http://www.nsf.org
4. http://info.nsf.org/Certified/Dietary/

CONCLUSION

Athletes need to be vigilant about what they are consuming. Their health care providers must be aware that certain drugs may not be used by athletes as they may result in serious consequences for the athletes and their sporting careers. TUE requests must be filled in correctly and comprehensively and always backed by sound medical evidence. There are several online tools to help both athlete and doctor to arrive at an informed decision. It is also important to keep in mind that the Prohibited List is subject to change every year from the 1st of January.

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The role of sports and exercise medicine in the military

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ABSTRACT

Background

Military training is notorious for being physically intensive interspersed by limited recovery periods, culminating in a high frequency of training-related injuries. Confusion may arise when military personnel are compared to athletes in other sporting disciplines in view of different training regimes employed by the military according to the set standard of the respective army. Hence, in line with other sporting disciplines having a designated medical team of sports and exercise professionals that is experienced in that particular field, this article discusses the importance of having such a team in the military.

Objective

The benefits of having a designated sports and exercise medicine set-up are discussed vis-à-vis the military.

Methods

A literature review of injuries related to military training comparing different armies is presented. Audit work attained from a military sports and exercise clinic is presented, listing injury type (acute or overuse) as well as the anatomical areas involved to highlight the specifics of injury outcomes in this population.

Results

A total of 72% of injuries listed were overuse in nature with a high propensity of injuries recorded in the lower limbs, in keeping with the methods of training employed by armies worldwide.

Conclusion

The availability of a designated sports and exercise clinic in a military setting can serve various purposes, not only through the provision of a service that is specific to military personnel and which therefore complements the ongoing training structures, but also through the provision of guidance in the planning of training regimes as well as in pre-training medical screening.

Key words

Military, sports and exercise, injury, screening, training.

INTRODUCTION

Over the past years, sports and exercise medicine has gained recognition as a separate medical speciality which has grown and evolved in parallel with the demands of professional and recreational athletes. Military personnel are likewise faced with increasing physical demands on a regular basis to enable them to carry out their duties effectively. Although certain military operations may be pre-planned and therefore operation-specific training can be undertaken prior to start of a specific operation, the respective army may be faced with emergencies necessitating the deployment of military personnel for local or offshore operations with little preparatory training. Hence there is a need of continual training to ensure high levels of physical and mental preparedness amongst all personnel. The undertaking of such training may be facilitated by access to a designated team of professionals specialised in sports and exercise medicine who can manage injured soldiers from diagnosis till return to full and unrestricted duties.

Military recruits consist of a separate group of army personnel representing the transition of civilians with different levels of physical endurance into military personnel. Basic military training (BMT) is essentially a transition undertaken by recruits involving high loads of physical, theoretical, military conduct and drill training over a predefined time period with limited rest interludes. The end result is that a high number of injuries are observed that are compounded further by the limited time available to military medical personnel to fully treat and rehabilitate injured recruits. Whilst injuries in active servicemen result in time off from military duties, delays

in recognising injuries and commencing treatment in military recruits may lead to premature discharge and therefore loss of eventual manpower. The assistance provided by a designated multidisciplinary sports clinic with access to a number of therapeutic and diagnostic modalities would therefore span both regular active servicemen and military recruits. This study presents a review of a designated sports clinic in the Maltese armed forces that assessed both recruits and active servicemen over a 14-week period, including details of the anatomical regions mostly afflicted in military personnel.

BACKGROUND

From a body-conditioning perspective and in line with other endurance sporting disciplines, military training results in improvements in aerobic fitness as well as fat free mass (Williams, 2005). Malavolti et al. (2008) noted that although military training resulted in body fat reductions and improvement in cardiovascular performance (as measured by VO_2 scores, where VO_2 represents the volume of oxygen per body weight utilised per minute), improvement in strength scores amongst recruits only followed an augmentation of the training programme by additional strength training (Santtila, et al., 2008). Intense military training remains generally associated with an increase in fat free mass and decrease in fat mass (Malavolti, et al., 2008); however the same has not been described in post-deployment studies. In fact, body composition studies of military personnel deployed to Iraq (Lester, et al., 2010) and Afghanistan (Sharp, et al., 2008) identified increments in body fat percentages. Furthermore, this was associated with declines in aerobic capacity, further suggesting that pre-deployment training is not continued during the actual deployment, resulting in loss of aerobic gains.

In audit work of injuries in military personnel, in a population cohort of 10,692 personnel of varying military backgrounds, up to 52% had sustained at least one exercise and sports related injury (Hauret, et al., 2015). When one takes into consideration that running forms the bulk of endurance training in the military, it is no surprise that running constituted up to 45% of overuse exercise related injuries with acute sprains and strains representing another 40% of the reported injuries. In a prospective study of BMT in military police recruits, 34.2% of men and 66.7% of women sustained at least one training related injury (Knapik, et al., 2013). Jones and Knapik (1999) identified a similar gender difference in earlier audit work investigating BMT in the United States Army, where a cumulative incidence of injury of 25% for men and 50% for women was demonstrated. The authors also described a number of potentially modifiable risk factors that may alter injury risk in this specific population, further enhancing the requirement that military personnel should be managed and assessed in a different manner than sport-specific athletes, to better reflect their differing physical demands (Jones and Knapik, 1999).

With reference to the Maltese military, limited data is available. From unpublished audit work carried out in 2012, up to 40% of actively serving military personnel who had been excused from the regular line of duty for 30 days or more claimed musculoskeletal ailments as a cause of their exemption. This work served as the foundation for a prospective study investigating risk factors for lower leg, ankle and foot injuries in Maltese recruits undertaking BMT (Psaila and Ranson, 2016). A number of risk factors were investigated with only decreased pre-recruitment fitness scores being significantly associated with an increased injury risk. This is concordant with the findings of a number of studies (Knapik, et al., 2001; Knapik, et al., 2006).

Shortly after the start of 2016, a joint sports clinic was set up in the Maltese army medical centre between a military medical officer and a sports and exercise medicine consultant. Clinics were organised on a weekly basis and were of three hours' duration during which all serving personnel could attend for assessment of their sports injuries. Likewise, military medical officers could refer soldiers directly to this clinic for further assessment and investigation. Allied health professionals did not form part of this clinic directly although a number of referrals from this clinic were made to physiotherapists for treatment and podiatrists for treatment and detailed biomechanical assessments.

MILITARY SPORTS CLINIC

From a review of the first three months of the above-mentioned sports clinic, a total of 115 actively-serving men and women as well as recruits attended the sports clinic, with 32 ailments being acute and 83 representing chronic or overuse injuries. Only new cases were recorded and follow-up visits for the same ailment were not included in this total. Over 14 weeks, attendance to this clinic averaged 8.2 patients per clinic session. This allowed bridging the gap between the Maltese army medical centre and the Maltese general hospital, expediting in the process access to investigative and

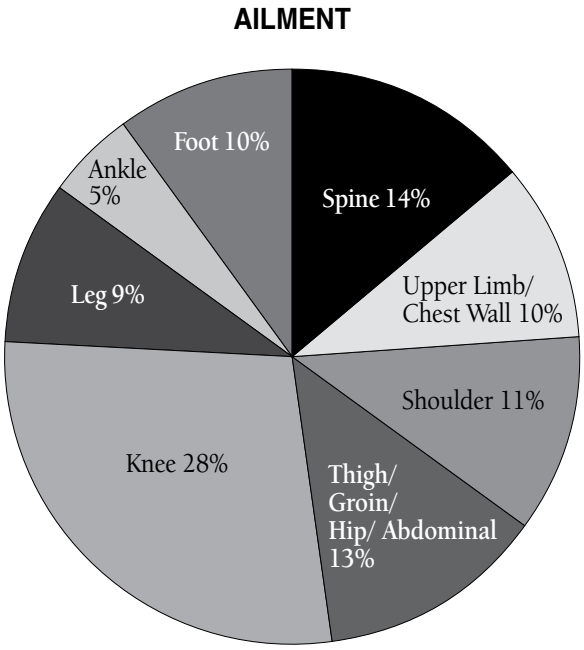

Figure 1. Ailment distribution according to anatomical region.

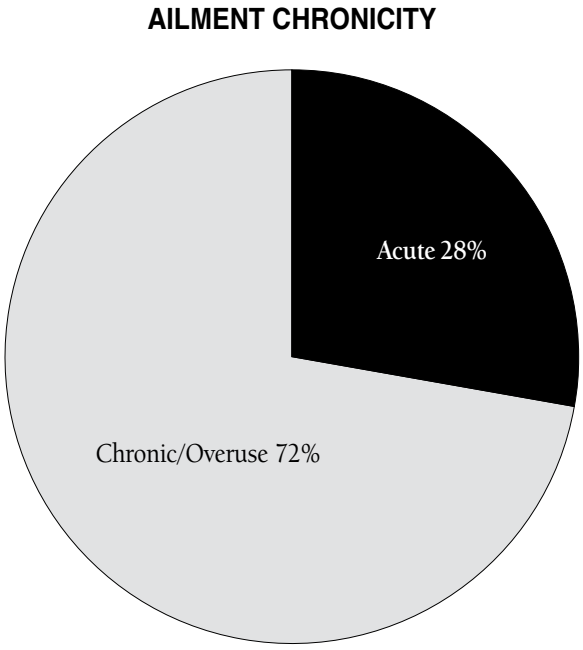

Figure 2. Ailment type represented according to chronicity.

therapeutic modalities. The pie chart depicted in Figure 1 highlights the distribution of ailments according to anatomical region. Figure 2 depicts the ailment according to chronicity. Of note is the relative majority of lower limb regions, again a reflection of the endurance training employed by the military which many times involves lower limb loading through running and marching. Nonetheless, upper body conditioning forms an important part of soldier training reflecting itself in shoulder and upper limb injuries which represented 21% of all ailments seen at the sports clinic.

With regards to injury type, as identified in similar studies on foreign military recruits (Kaufman, Brodine and Shaffer, 2000; Schwartz, et al., 2014), the most prevalent injury type were overuse injuries, with medial tibial stress syndrome being the commonest overuse injury identified. This is similar to the conclusion of Psaila in his unpublished review of risk factors for lower limb injuries. This highlights the importance of further studies investigating overuse injuries in the military population as well as the need to train military physical instructors towards using training patterns that help reduce the risks of such injuries. Such modifications might include gradual running distance increments and night rest to reduce injury risk (Wyss, et al., 2014). Studies on the local military population would further help to expand the limited data available.

CONCLUSION

From this review article, the role of a designated military based sports clinic can be appreciated. The term military is used to reflect the specialised role of such a team which is experienced both in the screening of military personnel as well as identifying and treating injuries that are commoner in this specific population. Such a sports and exercise multidisciplinary team can assist military physical instructors in planning their military training, routine physical training as well as specialised pre-deployment training, in an attempt to help reduce injury risk. This should augment the number of servicemen available for duty to respond to their day-to-day tasks as well as emergencies and deployments as required by their respective army. With regards to the professionals forming part of the sports clinic, in view of the number of referrals to allied health professionals for treatment and further assessment, it would be advisable that this study is repeated in the future with the inclusion of both a physiotherapist and a podiatrist.

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COMMEMORATION

Ten years of specialist training in family medicine in Malta 2007-17

Dr Mario R SAMMUT

On the 9th July 2007, specialist training in family medicine was launched in Malta under the auspices of the government's Primary Health Care Department, with the Malta College of Family Doctors (MCFD) responsible for ensuring the quality of academic training and assessment. This came about after Malta's accession to the European Union in 2004, following which family medicine was accepted as a specialty and a 'Specialist Training Programme in Family Medicine – Malta' was drawn up by the MCFD in 2005 and approved by the Ministry of Health's Specialist Accreditation Committee in 2006. The training programme is accredited for international membership of the UK's Royal College of General Practitioners.

Figure 1. The 2007-intake GP trainees and their coordinator, 19th October 2007. Front row, from left: Elaine Desira Lauria, Dorothy Zammit, Myriam Camilleri, Pamela Seychell, Arlene Bonello, Marie-Claire Formosa; back row, from left: Robert V Gauci, Mark Camilleri, Mario R Sammut (coordinator), Kenneth Vassallo, Daryl Xuereb, Mark L Grech.

The first cohort of eleven trainees (see Figure 1) who completed training in 2010 have been followed by another fifty-nine doctors, bringing the total of MMCFD and MRCGP[INT] graduates so far to seventy. Another twenty-one doctors are currently in training, with eighteen more due to join the programme in October 2017, under the coordination of the postgraduate training coordinators in family medicine Dr Mario R Sammut and Dr Gunther Abela.

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The prevention of fractures in adults

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ABSTRACT

Background

General practitioners (GPs) encounter patients who have suffered a fracture or are at an increased risk. Fragility fractures cost Europe 32 billion Euros per year. Recognizing this challenge and understanding its management allows GPs to engage in primary and secondary prevention of fragility fractures.

Aim

To illustrate lifestyle and pharmacological management options offered by a general practitioner to an adult at increased risk of fractures or low bone mineral density (BMD). The National Osteoporosis Guideline Group (NOGG, 2016), World Health Organisation (WHO), International Osteoporosis Foundation (IOF, 2012), Kidney Disease Improving Global Outcomes (KDIGO, 2009), Scottish Intercollegiate Guidelines Network (SIGN) and National Institute for Health and Care Excellence (NICE) management guidelines are discussed in this regard.

Objectives

- To provide key definitions in the management of osteoporosis.
- To identify groups at risk of developing low BMD, vitamin D deficiency and fragility fractures.
- To illustrate the current management options for an adult at increased risk of fractures or low bone mass by a general practitioner.
- To discuss current methods of investigation and measurement of low BMD, fracture risk assessment and vitamin D deficiency.
- To address dietary requirements of calcium and vitamin D and local formulations available.

Method

A literature search was conducted using Pubmed and Google search engines. Keywords included: osteoporosis; low bone mineral density; vitamin D; fragility fracture; postmenopausal. The NOGG (2016), WHO, IOF (2012), KDIGO (2009), SIGN and NICE management guidelines were included directly. Treatments ranging from fall prevention, dietary modification, anti-resorptive therapy and tailoring in subgroups were reviewed.

Conclusion

Guidelines can close the gap between physicians in primary and secondary care, institutions and private practice providing a multifaceted approach for the proper identification, prevention and management of fragility fractures.

Key words

Osteoporosis, risk assessment, bone density conservation agents.

INTRODUCTION

General practitioners (GPs) encounter patients who have suffered a fracture or are at an increased risk. Post-fracture management models of care (IOF, 2012) have been developed to better identify those at risk. Nine million fragility fractures occur annually globally. Thirty-two billion Euros per year are spent in Europe. Recognising this challenge and understanding its management allows GPs to engage patients at primary and secondary prevention before a fracture career sets in.

Aim

To illustrate the management options that could be offered by a general practitioner for an adult at increased risk of fractures or low bone mineral density. The NOGG - National Osteoporosis Guideline Group (2016), WHO – World Health Organisation, IOF - International Osteoporosis Foundation (2012), KDIGO - Kidney Disease Improving Global Outcomes (2009), SIGN - Scottish Intercollegiate Guidelines Network, and NICE - National Institute for Health and Care

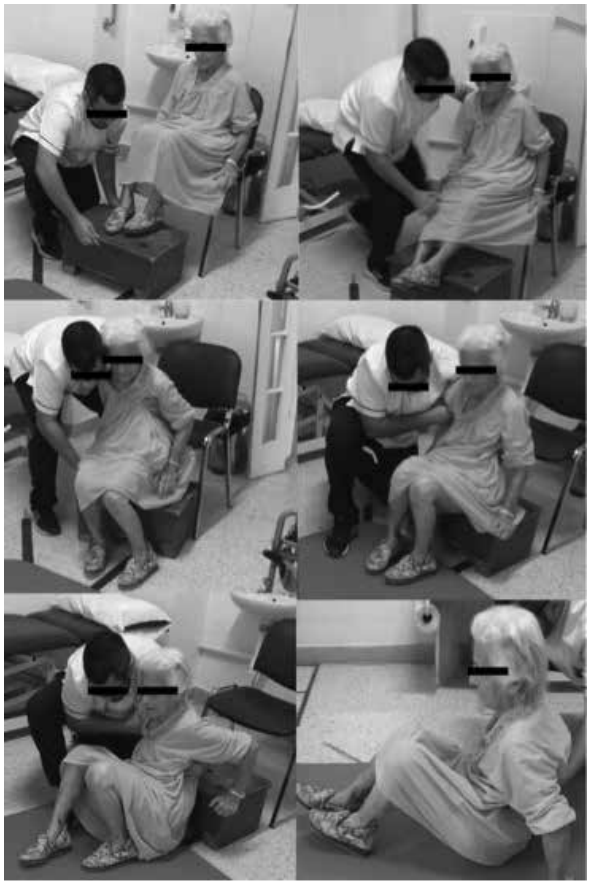

Figure 1: Fall management exercise.

Excellence management guidelines are discussed in this regard. Treatments ranging from fall prevention, dietary modification, anti-resorptive therapy and tailoring of treatment in subgroups were reviewed.

Objectives

- To provide key definitions in the management of osteoporosis, fracture prevention and vitamin D physiology.
- To identify those at risk of developing osteoporosis and vitamin D deficiency.
- To discuss methods of measurement and investigation of low bone mineral density (BMD), fracture risk assessment and vitamin D deficiency.
- To address the dietary requirements of calcium and vitamin D and local formulations available.
- To discuss the recommended treatments for low bone mass, osteoporosis and persons at high risk of fragility fractures.

METHOD

A literature search was conducted using Pubmed and Google search engines. Keywords in searches included: osteoporosis; low bone mass; vitamin D; fragility fracture; postmenopausal. Sources directly included were the Kidney Disease Improving Global Outcomes (KDIGO, 2009), International Osteoporosis Foundation (IOF, 2012), National Osteoporosis Society (England) (NOS, 2013), International Society for Clinical Densitometry (ISCD, 2015), the National Osteoporosis Guideline Group (UK) (NOGG, 2016), the Scottish Intercollegiate Guidelines Network (SIGN), the National Institute for Health and Care Excellence (NICE, UK) and the 71st edition of the British National Formulary.

Ethical aspects

Photos included in this article of patients at Karen Grech Hospital were attained after permission was granted by the hospital's data protection officer and chief executive officer, and written informed consent was obtained from the patients.

RESULTS

Definition and diagnosis of osteoporosis

In 1994 the World Health Organization (cited by NOGG, 2016) described osteoporosis as a 'progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture'. 'Osteoporosis' is defined operationally as a value for BMD that is 2.5 standard deviations (SD) or less below the young adult mean value (T-score ≤ –2.5 SD). Lorentzon and Cummings (2015) however concluded that no perfect definition yet exists that can ascribe to the properties of fragile bone measured in terms of bone strength, risk factors and prior fractures. 'Severe osteoporosis' refers to the above and an additional

Figure 2: Lower limb proprioception exercise.

Figure 3: Stepping exercise.

documented fragility fracture. A higher threshold describes 'low bone mass' as a T-score that lies between –1 and –2.5 SD (NOGG, 2016).

Assessment of fracture risk

The NOGG (2016) and ISCD (2015) recommend the use of FRAX® as the preferred fracture risk score assessment tool in calculating the 10-year probability of major osteoporotic and hip fractures. FRAX® was modelled on population-based cohorts where the femoral neck BMD was used. The latter is therefore preferred when calculating risk, especially in the elderly where arthrosis and arthritis are established in the spine (University of Sheffield, 2011). Outcomes and follow up of treatment favour scores of the lumbar spine. The lower of the two T-scores should be used in diagnosing osteoporosis. Z-scores should be used in adults under 50 years of age with values < -2 being below the expected range (ISCD, 2015).

Strategies in the prevention of osteoporosis

The NOGG (2016) endorses a group of strategies in high-risk groups to prevent fragility fractures globally. The main message is that of increasing mobility and calcium intake, stopping smoking, reducing alcohol consumption (less than 3 units a day), undertaking fall prevention programmes, weight bearing and balance exercises (Figures 1-5). Other indirect interventions, such as the correction of visual acuity and the adjustment of medication that could affect alertness, have also been promoted.

Vitamin D

A serum level of 25-hydroxyvitamin D (25-(OH)D) (calcifediol) below 25nmol/L (i.e. <10ng/mL) is considered as 'vitamin D deficiency' and may lead to mineralization defects. 'Vitamin D insufficiency' occurs between 25nmol/L and 50nmol/L (i.e. <20ng/mL) and can lead to increased bone turnover and parathyroid hormone anomalies. The NOS (2013) states that half the patients with levels of vitamin D between 20-30nmol/L are vitamin D sufficient but all those above 50nmol/L are practically sufficient. The sufficiency of vitamin D on individuals varies according to the response on parathyroid hormone. Adverse effects may occur with levels above 125nmol/L and annual high dose vitamin D (500,000 IU) is associated with greater incidences of falls and fractures (NOGG, 2016). On the other hand Rizzoli et al. (2013) as part of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal diseases and the NOS (2013) recommend vitamin D levels to be at least above 60nmol/L in the general population and ideally 75nmol/L in frail elderly patients who are at risk of falls or fracture for skeletal and extra-skeletal benefits.

Ross et al. (2013) recommend an intake of 800IU of vitamin D daily. Simple deficiency can be treated by administering 400 units (10ug) of ergocalciferol or colecalciferol twice daily. In those with little exposure to sunlight or have a limited diet, 800 units is recommended. Higher doses of 40,000 units (1mg) daily are appropriate in intestinal malabsorption and chronic liver disease states. Severe deficiency (<8ng/ml) may even require 50,000 units daily for one to three weeks (JFC, 2016). In cases of mild to severe deficiency (8-25ng/ml) 50,000 IU weekly for 8 weeks can be offered, followed by a maintenance dose of 800-2000 IU vitamin D orally daily for one month (NOS, 2013; Płudowski, et al., 2013). Serum calcium must be checked one month after the last loading dose to unmask hyperparathyroid states, and vitamin D measured 3-6 months after treatment has been terminated as levels reach a steady state after this period (NOS, 2013). Routine monitoring is not recommended but may be appropriate in patients with malabsorption syndromes and poor compliance (Kennel, Drake and Hurley, 2010; Ross, et al., 2011).

NICE (2016) determined that persons at risk of vitamin D deficiency include:

- infants and children aged under 5 years;
- pregnant and breastfeeding women, particularly teenagers and young women;
- people over 65 of age;
- persons with little or no exposure to the sun, for example persons who remain indoors for long periods or have a large surface of their body covered due to cultural reasons;
- people with darker skin.

Vitamin D in Chronic Kidney Disease

As Figure 6 demonstrates, renal function plays a part in the conversion of 25-(OH)D to the active form 1,25-$(OH)_2$D. This ability diminishes at an estimated glomerular filtration rate (eGFR) <30ml/min/1.73m^2 and leads to impaired hydroxylation of vitamin D. Secondary effects include: raised parathyroid hormone (PTH) levels, reduced intestinal calcium absorption, reduced phosphaturia, and reduced calcium urinary reabsorption. PTH, calcium and phosphate should be measured to reflect this deficiency. The cardiovascular, biochemical, endocrine and bone mineral disorders that develop secondary to renal impairment were coined 'Chronic Kidney Disease-Mineral and Bone Disorder'. 'Renal osteodystrophy' is restricted to describing an alteration of bone morphology which is confirmed by bone biopsy in those with chronic kidney disease (KDIGO, 2009a). Alfacalcidol, a hydroxylated form of vitamin D, can be used as an alternative. It will not influence 25-(OH)D plasma concentrations and cannot be directly measured. Alfacalcidol can be prescribed at 1ug daily in adults and 0.5ug daily in the elderly. Calcium and phosphate levels serve as rough indicators to whether one is overtreating (JFC, 2016).

Figure 4: Parallel bars for walking and gait training.

Table 1: Local preparations of combined calcium and vitamin D

Formulation	Calcium salt per single unit	Percentage of elemental calcium per salt	Elemental calcium per tablet	Cholecalciferol	Comments
Tablet	1250mg calcium carbonate	40%	500mg	400IU	
Tablet	Not available.		400mg	400IU	Magnesium, zinc, copper, manganese, selenium and boron included
Effervescent tablet	Not available.		400mg	100IU	
Syrup	Not available.		600mg per 20ml	300IU per 20ml	
Tablet	300mg calcium lactate	13%	39mg		25 tablets daily would be recommended for adequate elemental calcium intake.
Tablet	600mg calcium hydrogen phosphate	23%	138mg	500IU	4-5 tablets needed to attain the recommended dose of elemental calcium; however the intake of vitamin D would be high.

Sources: Globalrph, 1993; Ross, et al., 2011.

Calcium

The Institute of Medicine (IOM, US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium recommends 1gr. of elemental calcium per day after meals (IOM, 2011). The low pH improves absorption and halving the dose into a twice daily regimen prevents saturation of the gastrointestinal tract. Thiazide diurectics, lithium and low sodium diets will enhance renal excretion of calcium and losses (WHO, 2004; Kennel, Drake and Hurley, 2010; SIGN, 2015).

Calcium supplements contain different amounts of elemental calcium. The supplements facts panel of a product can be used to calculate the amount of elemental calcium available. There are online calculators that can determine this (Institute of Genetics and Molecular Medicine, 2016). Table 1 presents local combined preparations of calcium and vitamin D and the percentage of elemental calcium per salt.

Identifying cases of osteoporosis and low bone mineral density

A study by Gourlay et al. (2012) followed the time needed to reach a T-score of -2.5 on BMD in almost 6,000 predominantly white women over 65 years of age, who were ambulatory and did not suffer a prior hip or vertebral fracture. The study included co-variates for age, smoking, glucocorticoid use, oestrogen use and self-reported rheumatoid arthritis. The outcomes for recommended follow up DXA scanning for osteopenia was shown to depend on the severity as illustrated in Table 2. The global risk still needs to be considered when following up patients, as well as the onset of new diseases such as diabetes, immobility, etc. This study was criticized on these grounds as risk for fracture is not attributable to T-scores alone. Apart from this a clinically significant change in BMD was appreciable after a minimum of 2 years according to the National Clinical Guideline Centre (2012). Women were not given lifestyle advice or started on supplementation in the study, which could influence the rate of deterioration in BMD.

Figure 5: Training stairs used for lower body co-ordination and balance.

NOGG (2016) identifies the secondary causes of osteoporosis as:

- chronic obstructive pulmonary disease,
- rheumatoid arthritis,
- untreated hypogonadism in men and women,
- prolonged immobility,
- organ transplantation,
- type I diabetes,
- hyperthyroidism,
- gastrointestinal disease,
- chronic liver disease.

Investigations to exclude secondary sources may be indicated were appropriate. Serum total calcium, total protein and albumin for a corrected calcium level (or ionized calcium), phosphate, alkaline phosphatase levels for Paget's disease, creatinine for eGFR and PTH are to be assessed if calcium levels are deranged. A full blood panel and erythrocyte sedimentation rate would screen for inflammatory processes while serum protein electrophoresis would assess for free light chains indicative of multiple myeloma. Thyroid function tests are advised in suspected thyrotoxicosis, serum testosterone for hypogonadism, coeliac serology for related malabsorption and an overnight dexamethasone suppression test to exclude Cushing's disease (Lee and Vasikaran, 2012).

Types of fractures

The NOGG (2016) defines the different types of clinically relevant fractures. A major osteoporotic fracture is a clinical spine, hip, forearm or humerus fracture; however multiple major fractures carry a higher risk than the adding up of each individual risk. Vertebral fractures carry a two-fold higher risk than other types of fractures. A fragility fracture follows a fall from standing height or less. Fragility fractures may be consequential to osteoporosis or other more serious conditions affecting bone such as metastatic bone cancer or myeloma.

Pharmacological interventions in osteoporosis

There are conflicting recommendations when it comes to starting treatments. The NOGG (2016) deemed treatment be considered in those above the intervention threshold

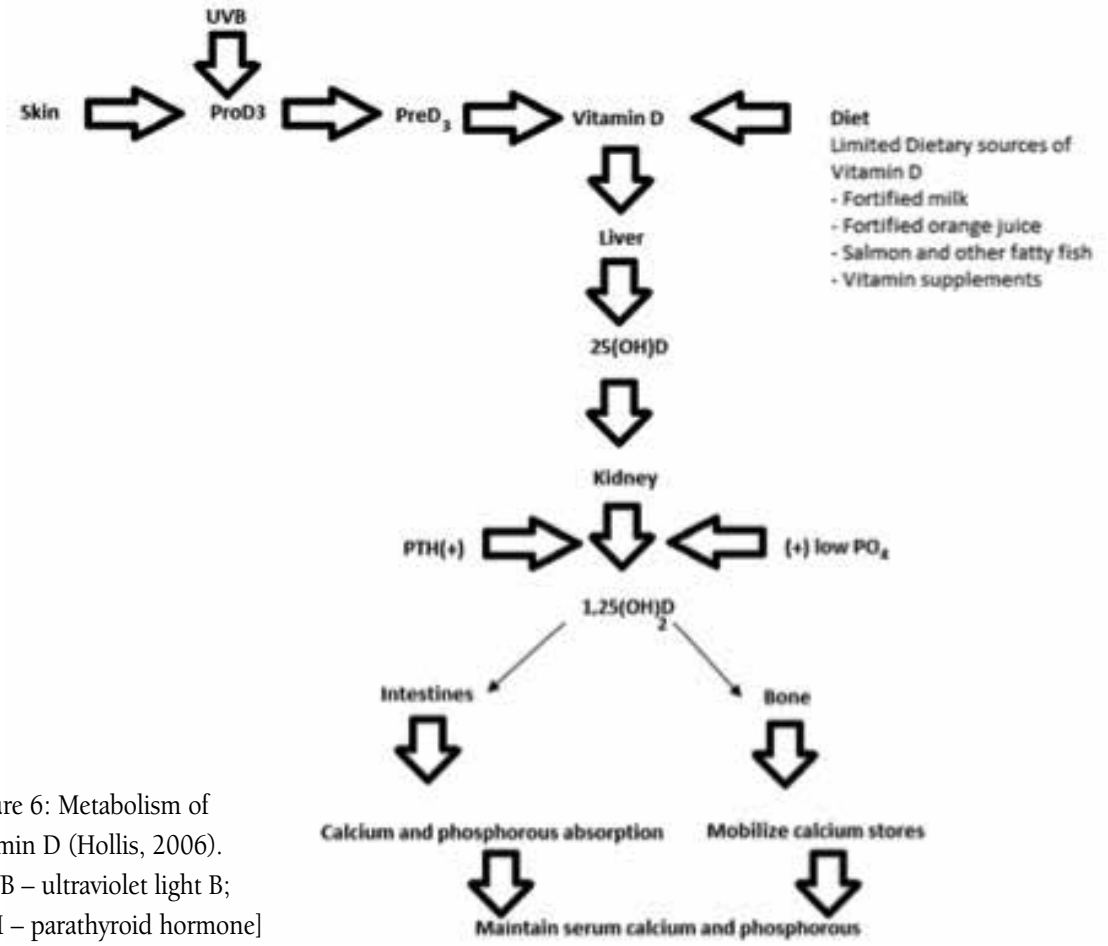

Figure 6: Metabolism of vitamin D (Hollis, 2006). [UVB – ultraviolet light B; PTH – parathyroid hormone]

calculated by FRAX® and started without prior BMD in:

- postmenopausal (PMP) women who have had a previous fragility fracture,
- people over 70 years of age who are taking large doses of oral corticosteroids,
- PMP women and men under 50 years of age who have had an osteoporotic fracture (specialist management is recommended in this group).

SIGN (2015) is more cautious and recommends measurements of BMD by DXA in those above the intervention threshold, with pharmacotherapy started in those with T-scores < -2.5. The group goes on to comment that therapy can be commenced in patients with prevalent vertebral fractures without undertaking BMD measurements if these are felt to be inappropriate or impractical, implying that skeletal imaging be performed as part of screening in certain cases. NICE does not comment with regards to the grey area incorporating those who are above the intervention threshold but have a femoral neck T-score > -2.5. Perhaps the intervention here lies in the global initiatives recommended by NOGG (2016) as the effect of alendronic acid, studied by Cummings et al. (1998) in the FITS trial, showed only a statistically-significant reduction in clinical fractures in women with a femoral neck T-score < - 2.5 after 4 years. Women treated with higher T-scores did not show an improvement in fracture rates.

Patients treated with anti-resorptive therapy will have a demonstrable improvement in BMD after three years of treatment and for this reason guidelines recommend repeat BMD testing after this period and not sooner as the within-person variations differ widely with DXA measurement after just one year of treatment (Sharma and Stevermer, 2009; Ott, 2013; Doshi, et al., 2016).

The preferred first line treatments offered by NICE are bisphosphonates. They act by inhibiting bone resorption by binding to hydroxyapetite crystals. Indications such as glucocorticoid induced osteoporosis or vertebral fractures make certain interventions more appealing than others (Table 3). To postmenopausal women who are unable to comply with the special instructions, have a contraindication or are intolerant to certain treatments, NICE gives the variables (e.g. BMD thresholds) and clinical scenarios against which other treatment options can be weighed.

Denosumab is a monoclonal antibody that inhibits osteoclast formation, function and survival. Its use is

recommended with caution in those with an eGFR < 30ml/min/1.73m^2 (NOGG, 2016) and is second-line to cases where there was an insufficient response, along with zoledronic acid. Strontium ranelate works by stimulating bone formation and reducing resorption. Raloxifene acts as a selective oestrogen receptor modulator that inhibits bone resorption and is only indicated in the secondary prevention of osteoporosis (JFC, 2016) (Table 3).

After three to five years of treatment, NOGG (2016) asks physicians to review BMD measurements and to offer patients to stop treatment if acceptable T-scores have been reached and no fractures have occurred. Follow up DXA scanning should take place after two years (three years in the case of zoledronic acid) and after a new fracture regardless of when this occurs.

Interventions in chronic kidney disease

Chronic kidney disease (CKD) stages 1-2 and stage 3 with a normal PTH range are recommended management as for the general population for osteoporosis and/or high risk of fracture. With abnormal biochemical markers at CKD stage 3 one should consider the degree and reversibility of the biochemical anomalies and a bone biopsy. In CKD stages 4-5D having biochemical anomalies of chronic kidney disease -mineral and bone disorder (CKD-MDB), low BMD or fragility fractures, a bone biopsy is suggested prior to therapy with anti-resorptive agents (KDIGO, 2009b). Table 4 illustrates the frequency of measurements of bone turnover markers.

Treatment issues and counselling

Patients should be counselled about the following issues before and during anti-resorptive treatment:

- dental checkups should take place prior to treatment and on a regular basis. Invasive dental procedures should be avoided. Gum swelling and hypermobility of the teeth should be immediately reported.
- bisphosphonate tablets are to be swallowed whole with plenty of plain water only. Their use is cautioned or contraindicated in patients with gastric or duodenal ulcers, bedridden patients and those with eGFR<35ml/min/1.73m^2 (NOGG, 2016).
- calcium supplements are to be taken at least two hours before or after a bisphosphonate and should be taken during anti-resorptive treatment along with vitamin D.
- the length of time one should avoid food before and after taking a bisphosphonate should be consulted for every product according to the dose. Aldendronic acid should be taken 30 minutes before breakfast on an empty stomach. Thirty minutes must elapse before eating or taking other medications and lying down after taking alendronic acid.
- atypical fractures of subtrochanteric and diaphyseal regions of the femoral shaft should be reported to the prescriber.
- it is important to check serum calcium one week before and two weeks after administration of denosumab and monitor for the presence of hypocalcaemia.
- patients taking raloxifene should be counselled that discontinuation should take place at least 72 hours prior to and during prolonged immobilization as it confers a greater risk of stroke and venous thromboembolic events. It also confers a reduction in risk of breast cancer but can also procure hot flushes (JFC, 2016).

Bisphosphonates could be continued indefinitely in high-risk individuals who (NOGG, 2016):

- are aged 75 years or more;
- have sustained a hip or vertebral fracture;
- are taking continuous oral glucocorticoids at a dose of ≥ 7.5 mg/day prednisolone or equivalent;
- sustain a low trauma fracture during treatment, after exclusion of poor adherence to treatment (<80% of treatment) and causes of secondary osteoporosis have been excluded (in such cases treatment should be re-evaluated);
- have a total hip or femoral neck BMD T-score ≤ -2.5 SD.

Table 2: Time to develop osteoporosis in low bone mass in white women over 65 years of age, who were ambulatory and did not suffer a prior hip or vertebral fracture

Severity	T-Score Ranges	Time (years)
Mild	-1.00 to -1.49	15
Moderate	-1.5 to -2	5
Severe	-2 to -2.49	1

Source: Gourlay et al. (2012).

Table 3: Recommended anti-resorptive treatments

Choice	Drug	Indication			Duration	Frequency	Dose
		PMP Women	Gluco-corticoid induced	Men			
First	Alendronate	Yes	Yes	Yes	5-10 years	daily	10mg
						weekly	70mg
	Risedronate	Yes[1]	Yes	Yes	5-7 years	daily	5mg
						weekly	35mg
First / Second	Zoledronic acid	Yes[2]	Yes	Yes	3 years	yearly	5mg
Second	Denosumab	Yes[3]			5 years	six months	60mg
	Teriparatide	Yes[4]			24 months	daily	20ug
Third	Strontium ranelate	Yes[5,6]		Yes	10 years	daily	2g
	Ibandronate	Yes			5 years	monthly	150mg
	Raloxifene	Yes			Until 50 years of age	daily	60mg

Source: NICE, 2008a; NICE, 2008b; JFC, 2016; NOGG, 2016; SIGN, 2015.

(1) Risedronate is recommended as second line in the primary and secondary prevention of osteoporotic risk fractures in patients unable to tolerate alendronate against the variables provided by NICE (2008a; 2008b).

(2) Zoledronic acid was shown to improve survival in hip fracture patients unable to tolerate oral osteoporosis treatment and is recommended as second line in such cases (SIGN, 2015) or if inadequate response to initial agents.

(3) Denosumab is recommended as third line treatment in the primary and secondary prevention of osteoporotic fractures if alendronate and either risedronate or etidronate are not tolerated and against the variables recommended by NICE (2010) or if inadequate response to initial agents.

(4) Teriparatide is indicated in severe spinal osteoporosis as second line to alendronate or risedronate.

(5) NICE recommends that raloxifene and strontium ranelate are recommended as alternative treatment options for the secondary prevention of osteoporotic fragility fractures in PMP women who are unable to comply with the special instructions for the administration of alendronate and either risedronate or etidronate, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate against the variables recommended by NICE (2008a; 2008b).

(6) Strontium ranelate is recommended as third line to alendronic acid, etidronate and risedronate when it comes to the prevention of osteoporotic fragility fractures in PMP women (NICE, 2008a; NICE, 2008b). Strontium ranelate is recommended in severe PMP osteoporosis to reduce the risk of vertebral and non-vertebral fractures in women without established cardiovascular disease when other treatments are contraindicated (SIGN, 2015).

Table 4: Frequency of measurement per respective bone turnover marker in chronic kidney disease

Stage	eGFR (ml/min/1.73m^2)	Frequency of measurement (months)		
		Calcium and phosphate	Parathyroid hormone	Alkaline phosphatase
3	30-59	6-12	According to disease progression	
4	15-29	3-6	6-12	12[1]
5	<15	1-3	3-6	

1. Stages 4–5D alkaline phosphatase activity measurement: every 12 months, or more frequently in the presence of elevated PTH.
Source: KDIGO, 2009a.

Glucocorticoid-induced osteoporosis

Steroid doses greater than an equivalent of 7.5mg prednisolone daily for more than three months are considered significant. Daily doses of prednisolone higher or equal to 15mg however should need a higher adjustment of fracture probability (NOGG, 2016). Treatment should be started at the beginning of steroid therapy in patients considered at risk of fracture (JFC, 2016).

Osteoporosis in men and women

Secondary causes are commoner amongst men and will need investigation (NOGG, 2016). Hormone replacement therapy (HRT) should be offered to women who have experienced premature menopause (before 45 years of age) to reduce the risk of fragility fractures and for the relief of menopausal symptoms. If the main concern is increased fracture risk, bisphosphonate therapy should be offered first line. HRT was shown to decrease fracture risk but benefits were lost shortly after stopping therapy. HRT should be continued up until 50 years of age and then stopped and the need for continuing treatment with an alternative drug considered (JFC, 2016).

DISCUSSION

The different levels of Vitamin D for different ages is still a subject of debate. Ultimately the pathophysiology behind low bone mineral density reflects our investigation and management.

Secondary causes and risk factors should be looked out for pending a mandatory dental review along with proper counselling if bisphosphonates are considered. T-scores measured after a minimum 2 years of treatment with anti-resorptive agents accompanied by calcium and vitamin D supplementation should then be followed up. Earlier measurements can deceive GPs into perceiving that no improvement BMD deterioration has occurred as within-person variation confounds measurements. Those with an eGFR $<30 min/1.73m^2$ should have bisphosphonate therapy stopped and be switched to alfacaldidol or another suitable vitamin D alternative. For those with BMD > -2.5 bisphosphonates will not decrease fracture rates and prevention lies in managing other risk factors. Patients after a minimum three year period with an adequate BMD (T-score > -2.5) should be counselled about stopping antiresorptive therapy and considered for follow up after 2 years. At the end of the spectrum recognising fragility fractures allows us to treat them as such, irrespective of the sex of the patient. Major osteoporotic fractures, especially spinal fractures, increase one's fracture probability further and should be accounted for when using prediction tools.

The authors look forward to the identification of other risk factors that could have a role in osteoporosis. Anti-resorptive treatments are currently limited by gastric side-effects and renal impairment. Safer alternatives are still needed in these groups.

Limitations

This review does not include the management of secondary causes of osteoporosis and younger age groups.

CONCLUSION

Guidelines can close the gap between physicians in primary and secondary care, institutions and private practice by providing a multifaceted approach for the proper identification, prevention and management of fragility fractures.

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