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A novel Maltese medical journal

Victor Grech, Pierre Ellul

PubMed is a leading and free database of references and abstracts published in academic journals pertaining to the life sciences and biomedical topics. The database is maintained by the United States government via the National Library of Medicine at the National Institute of Health and there are millions of articles indexed in this repository. Well over 5000 journals are represented and the decision as to whether or not to index a journal is based on considerations of both scientific policy and scientific quality. A journal applying for inclusion and indexing in PubMed must have ample scope and coverage, along with adequate technical merit in the papers represented. The journal must also demonstrate suitably high levels of objectivity, credibility and quality.

A journal with sufficiently high standards may also be indexed in PubMed if it is accepted for inclusion in PubMed Central (PMC), an even larger and free open-access repository that archives publicly accessible full-text papers within the biomedical and life sciences literature. One of the preconditions for consideration for indexing is that the papers included must be made completely available, for free: text, tables and graphics. This repository now houses millions of papers.

Images in Paediatric Cardiology was the first Maltese journal to be indexed in PMC, and this journal has been active since 1999. It was created by one of the authors of this editorial (VG) in conjunction with a prestigious international Editorial Board. The journal has always been open-access, and is published quarterly.

The previous Editorial Board of the Malta Medical Journal attempted to include the MMJ in PubMed but did not meet with success as the journal was deemed to have too low a circulation. The current Editorial Board applied for the MMJ to be included in PMC (not PubMed) in 2013. A negative decision was communicated to the MMJ Editorial Board this year, phrased thusly:

I regret to inform you that Malta Medical Journal has not passed the first stage of acceptance to PMC. NLM has determined that the journal does not meet PMC's Scientific Quality standard. The application to PMC will not be accepted at this time. Malta Medical Journal is eligible to reapply in 24 months from today. NLM would like to see an overall improvement in the quality of science.

After deliberation both within the Editorial Board and within the Faculty Board of Medicine, it was decided to revamp the MMJ and create a new in-house, peer-reviewed journal in the hope that eventual reapplication for MMJ inclusion in PMC would be successful.

The MMJ will henceforth only review papers that are:
1. Research articles of sufficient scientific quality.
2. Potential international interest.
3. This does not exclude the review of sufficiently rare/ unusual case reports or images.

The new journal will be launched in 2017 and will be called the Mater Dei Hospital Gazette. This will only review papers that are of:
1. Sufficient scientific quality. Audits will be reviewed but must have completed the audit cycle and include outcome implementation.
2. Potentially only of local interest.
3. This includes the review of rare/unusual case reports or images.

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Editorial

The Editorial Board of both journals will be led by the authors of this editorial and will include the editors of the MMJ. Submissions to both journals will continue as previously and should adhere to the instructions to the authors on the MMJ website. A website for the Mater Dei Hospital Gazette will also be created and its instructions pertaining to papers submitted to this journal must also be adhered to.

It is hoped that this new, peer-reviewed journal will serve as an outlet for the publication of high-quality material that is of only local interest.

Cover Picture:
‘Memento Vivere’
Watercolours
By Christian Camilleri

Christian Camilleri Christian Camilleri is an anaesthesia trainee who began painting in childhood. His preferred medium and subject consist of watercolour figures, portraits and battle scenes. He derives inspiration from both Baroque and early 20th Century sources.

Corinthia Group Prize in Paediatrics, 2016

Only once before, since its inception in 1999, has the Corinthia Group Prize in Paediatrics been shared by two doctors. However, in 2016, the prize was yet again awarded jointly to Dr Sarah Micallef and Dr Samuel Zahra, who both obtained the highest aggregate mark over the combined examinations in Paediatrics in the fourth and final year of the undergraduate course. Whilst offering our congratulations to both Drs Micallef and Zahra, we would also like to congratulate all those who performed admirably during the undergraduate course in Paediatrics. In the accompanying photograph, Dr Sarah Micallef and Dr Samuel Zahra are seen receiving their prizes from Professor Simon Attard Montalto, Head of Paediatrics, in the Boardroom of the Medical School. Finally, the Academic Department of Paediatrics and Medical School remain indebted and are extremely grateful to the Corinthia Group for their ongoing support.

Professor Simon Attard Montalto
Surgical Antibiotic Prophylaxis: Adherence to hospital’s guidelines

Daniela Bonello, Yanika Stafrace

Abstract
Aim: This study was designed to assess the compliance to local hospital guidelines for antimicrobial prophylaxis in general surgery in terms of the appropriateness of prophylactic antibiotic indication, the choice of antibiotic, the dose administered, the time of administration and the duration of prophylaxis.

Method: Data regarding antibiotic prophylaxis was collected from the patients’ records and compared to the local guidelines. The overall percentage adherence was then calculated, as well as the percentage of correct antibiotic, dose, administration and duration.

Findings: A total of 110 cases, which included patients undergoing general surgery procedures, were assessed from 6 surgical wards. From the total, only 9.3% were found to be completely adherent to local guidelines. In 24.4% of the cases, correct use of antibiotics, dose and route of administration was observed, while correct duration of prophylaxis was recorded in 9.3% of the cases.

Conclusion: Antibiotic prophylaxis is an effective and cost-efficient way of avoiding surgical skin infections; hence hospitals should ensure appropriate use of antibiotic prophylaxis.

Keywords
antibiotic prophylaxis; general surgery; guideline adherence

Introduction
Antibiotic prophylaxis refers to the administration of a brief course of antimicrobial therapy to prevent infection complications following surgery. The incidence of surgical wound infection is reduced when antibiotic prophylaxis is administered appropriately. Prophylaxis is normally recommended for all clean-contaminated, contaminated and dirty procedures. For clean procedures, it may be considered for certain patients and surgeries that meet specific risk criteria.1

The European Centre for disease prevention and control (ECDC), in a paper entitled ‘Systemic review and evidence-based guidance on peri-operative antibiotic prophylaxis’, identifies 5 key Perioperative Antibiotic Prophylaxis (PAP) modalities. These refer to effective measures to improve the compliance of healthcare professionals with appropriate administration, timing, dosage and duration of PAP, preventing surgical skin infections (SSIs), and include:

1. Establishing a multidisciplinary anti-microbial team to develop and implement protocol of appropriate PAP.
2. To ensure appropriate timing, the anaesthesiologist should be responsible of PAP.
3. Efficacy is greatly affected by the timing of antibiotic administration. Ideally, the first dose should be administered less than 60 minutes before surgical incision (usually in anaesthetic room at induction of anaesthesia).
4. If the duration of the procedure exceeds one to two half-lives of the antibiotic or there is extensive blood loss intra-operatively, re-administration is recommended.
5. Generally, post-operative administration is not indicated.2

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The antibiotic chosen should be a narrow-spectrum agent(s) that targets the organism(s) most commonly causing wound infection in the concerned procedure. If two drugs are of otherwise equal spectrum, efficacy and toxicity, the less expensive drug should be chosen. Drugs that are likely to be used in the treatment of severe sepsis should be avoided to prevent development of resistance.

The general indication for surgical prophylaxis is a single dose, except in cases involving potentially high contamination such as large bowel intervention and the insertion of prostheses. The duration of PAP should not exceed 24 hours after the end of surgery.

Surgical skin infections not only have an enormous impact on the patients’ quality of life but also on the financial cost of patient care.

Method

The audit was conducted over a period of 4 weeks from 17th August 2015 – 14th September 2015, and looked at elective and emergency General Surgery procedures carried out in the principal General Hospital of Malta – Mater Dei Hospital.

The audit reviewed medical, anaesthetic and nursing records, as well as medication charts, and antibiotic prescriptions were then compared with the local hospital guidelines on antibiotic choice, duration of prophylaxis, dose, dosing interval and timing of the first dose. The latter local guidelines for antimicrobial surgical prophylaxis, were approved and issued by the Infection Control Committee, at Mater Dei Hospital.

Data was obtained from the general surgical wards (S1, S2, S4, S5, SAU) and Day Care Unit. At the outset, the outline of the study and protocol was first shown to and accepted by the Nursing Officer in charge of each ward. A list of post-operative patients was obtained and data obtained from these patients’ files.

Outcome measures:
- The appropriateness of prophylactic antibiotic indication
- Choice of antibiotic
- Dose administered
- Time of administration
- Duration of prophylaxis

Audit Measurement tool

The data was recorded under three headings as shown in table 1.

Method of Analysis

The collected data was analysed using the flow chart in figure 1.

All the patients who were already on antibiotic treatment prior to surgery were excluded. The remaining patients where then subdivided into two groups, according to whether antibiotic prophylaxis was recommended or not and, if not, whether antibiotics were administered anyway.

Where recommended, patients were subdivided according to whether antibiotics were given or not, and subsequently on the appropriateness of choice, dose, route of administration, timing and duration of prophylaxis.

The data was then inputted in a database, where surgeons were given a code (1-14) in order to ensure anonymity. Codes were also used for the wound classes (see table 1 above) (1-4) and for the rest of the variables, 1 was taken to indicate yes and 0 indicated no.

The percentage of patients in each category was calculated using the following formula:

\[
\text{Percentage} = \frac{\text{Number of patients in (X) category}}{\text{Total number of patients}} \times 100 = \% 
\]

Results

A total of 110 patients were collected from a total of six surgical wards. A list of the procedures carried out is shown in table 2.

13 patients were excluded from this audit as they were on antibiotic treatment prior to surgery. The remaining cases were divided into two categories, namely ‘prophylaxis recommended’ and ‘not recommended’. The results are depicted in figure 2.

Out of the 88 cases in which antibiotic prophylaxis was recommended, 2 cases were excluded from table 3, as antibiotics were not given.

Assessment of individual parameters:

Indication

In concordance with the local guidelines, antibiotic prophylaxis was indicated in 88 cases but was given in 86 cases (97.7%).
Table 1: Data recorded

<table>
<thead>
<tr>
<th>Patient specific details:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name and Surname</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>ID number</td>
</tr>
<tr>
<td>Date of admission</td>
</tr>
<tr>
<td>Admitting consultant</td>
</tr>
<tr>
<td>Admission ward and bed number</td>
</tr>
<tr>
<td>Patient coming from: Home/ Institution/ Unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Information:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure carried out</td>
</tr>
<tr>
<td>Date of operation</td>
</tr>
<tr>
<td>Surgeon carrying out procedure</td>
</tr>
<tr>
<td>Wound class (clean, 1; clean-contaminated, 2; contaminated, 3; dirty, 4)</td>
</tr>
<tr>
<td>Status of surgery (elective or emergency)</td>
</tr>
<tr>
<td>Previous history of MRSA or CRE (carbapenem-resistant enterobacteriaceae)</td>
</tr>
<tr>
<td>Co-morbidities (diabetes, COPD, CHF, corticosteroid use, blood transfusions, drains)</td>
</tr>
<tr>
<td>ASA class</td>
</tr>
<tr>
<td>Smoker</td>
</tr>
<tr>
<td>Any surgical complications</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedure specific prophylaxis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic name</td>
</tr>
<tr>
<td>Administered dose</td>
</tr>
<tr>
<td>Route of administration</td>
</tr>
<tr>
<td>Time of administration</td>
</tr>
<tr>
<td>Duration of antibiotic prophylaxis</td>
</tr>
<tr>
<td>Time the agent was discontinued</td>
</tr>
<tr>
<td>Appropriateness of prophylaxis</td>
</tr>
</tbody>
</table>
**Figure 1:** The flow chart used as method of analysis

**Table 2:** Types of procedures studied

<table>
<thead>
<tr>
<th>Type of procedure</th>
<th>ICD-9 codes</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal surgery (non-gastrointestinal)</td>
<td>41.5, 52.0, 52.1, 53.0, 53.1, 53.29, 53.51, 53.69, 54.11, 54.19, 54.3</td>
<td>31</td>
</tr>
<tr>
<td>Upper gastrointestinal surgery (oesophageal, stomach, duodenal, small intestine)</td>
<td>42.40, 43.5, 44.39, 44.41, 45.6, 45.62, 46.01, 46.42, 46.51</td>
<td>19</td>
</tr>
<tr>
<td>Hepatobiliary surgery</td>
<td>41.5, 51.22, 51.23, 51.24, 52.6</td>
<td>6</td>
</tr>
<tr>
<td>Lower gastrointestinal surgery (appendicectomy and colorectal)</td>
<td>17.35, 17.36, 17.39, 45.73, 45.81, 47.0, 47.01, 48.52, 48.62, 48.69, 49.0</td>
<td>44</td>
</tr>
<tr>
<td>Skin and other clean procedures (breast and endocrine)</td>
<td>06.4, 07.3, 85.45, 86.01, 86.04, 86.11</td>
<td>11</td>
</tr>
</tbody>
</table>
Figure 2: Recommended cases of perioperative antibiotic prophylaxis

Table 3: Number of patients and percentage adherent to each individual parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of patients</th>
<th>% Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct antibiotic</td>
<td>21</td>
<td>24.4%</td>
</tr>
<tr>
<td>Correct dose</td>
<td>21</td>
<td>24.4%</td>
</tr>
<tr>
<td>Correct administration (route)</td>
<td>21</td>
<td>24.4%</td>
</tr>
<tr>
<td>Correct duration(&lt;24 hours)</td>
<td>8</td>
<td>09.3%</td>
</tr>
</tbody>
</table>

Antibiotic choice
The correct choice of antibiotic was given in 24.4% of cases (n=22). In the majority of cases where the choice was incorrect, it was due to an inappropriate combination of antibiotics. The most common example of this was the use of metronidazole and ciprofloxacin instead of metronidazole and gentamicin in gastrointestinal surgery. Also, discordance was noted in cases of appendicectomy where, in the majority, co-amoxiclav was prescribed instead of metronidazole and gentamicin.

Table 4 shows the combination of antibiotics used.

Duration of antibiotics
Perioperative antibiotic prophylaxis is generally indicated for less than 24 hours and in cases where antibiotics were given for more than 24 hours, the duration was considered inappropriate.

The duration was appropriate in 9.3% of cases studied.

Timing
The percentage of correct timing of PAP could not be calculated accurately, as the exact timing was not documented in case files.

Adherence to the local guidelines including the correct bundle of antibiotic choice, dose, administration, timing and duration was observed in a total number of only 8 cases out of 86 (9.3%). This is shown in figure 3.
**Table 4:** Combinations of antibiotics used and their frequency of use

<table>
<thead>
<tr>
<th>Combinations</th>
<th>Frequency used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-amoxiclav</td>
<td>24</td>
</tr>
<tr>
<td>Metronidazole + Gentamicin</td>
<td>18</td>
</tr>
<tr>
<td>Ciprofloxacin + Metronidazole</td>
<td>16</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>7</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>7</td>
</tr>
<tr>
<td>Piperacillin/ Tazobactam</td>
<td>6</td>
</tr>
<tr>
<td>Metronidazole + Cefuroxime</td>
<td>4</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>2</td>
</tr>
<tr>
<td>Ciprofloxacin + Co-amoxiclav</td>
<td>1</td>
</tr>
<tr>
<td>Ciprofloxacin + Gentamicin + Metronidazole</td>
<td>1</td>
</tr>
<tr>
<td>Ciprofloxacin + Metronidazole + Co-amoxiclav</td>
<td>1</td>
</tr>
<tr>
<td>Co-amoxiclav + Gentamicin + Metronidazole</td>
<td>1</td>
</tr>
<tr>
<td>Gentamicin + Flucloxacillin</td>
<td>1</td>
</tr>
<tr>
<td>Gentamicin + Teicoplanin</td>
<td>1</td>
</tr>
<tr>
<td>Metronidazole + Piperacillin/ Tazobactam</td>
<td>1</td>
</tr>
<tr>
<td>Piperacillin/ Tazobactam + Phenoxy methylpenicillin</td>
<td>1</td>
</tr>
</tbody>
</table>

**Figure 3:** Percentage adherence with local guidelines

- Adherent to local guidelines 9.3%
- Non-adherent to local guidelines 90.7%
Discussion

Comparison of this study with international studies on antibiotic prophylaxis

Numerous studies from other countries have shown a wide variation of adherence to antibiotic prophylaxis. The overall compliance in the majority of these studies was less than 50%. In a multicentre audit in 13 Dutch hospitals, 1763 procedures were considered, out of which 28% (n=493) had full adherence to the local guidelines. In this study the parameters that needed most improvement were the dose interval (57%; n=457) and timing (50%; n=810). On the other hand, antibiotic choice was correct in 92% (n=1621) of cases in contrast to 24.4% (n=22) achieved in our audit. This Dutch study by van Kasteren et al was more comprehensive, as multiple hospitals were included, a large number of procedures were studied and local guidelines were used as a point of reference as opposed to the majority of other studies that used international guidelines. However, this study is not the ideal comparison with our audit as it included other procedures apart from General Surgery.

Obstacles that prevent the implementation of adequate PAP

The main barriers to adherence with recommended guidelines include lack of awareness of the latest version of the guidelines and lack of consensus or disagreement with the guidelines. Also there is a misconception amongst surgeons that multiple antibiotics or prolonged therapy are more effective in the prevention of surgical wound infections.

Lack of communication between different staff members, inappropriate hand-over from the theatre to the wards regarding the duration of PAP, illegible handwriting and inappropriate documentation in the patient’s notes are also major barriers to adherence with guidelines.

Improvements

There are various ways to improve on the poor compliance observed in this study. Enforcing checklists prior to the operation will ensure optimal timing of antibiotic prophylaxis. Theatre nurses can be assigned this task before the start of the surgery.

Personalised surgical antibiotic kits can be prepared by the hospital’s pharmacy to be used for elective surgeries. These should include the appropriate combination and dose of antibiotics depending on the surgery. However, this would not apply in emergency situations or where there are contraindications such as allergies to the antibiotics. The PAP protocol should take into account individual patient factors like BMI, underlying diseases or colonisation with resistant pathogens.

Lack of awareness can be improved by offering continuous training and education to surgeons, anaesthesiologists and nursing staff to familiarise themselves with updated guidelines. Also guidelines should be made easily accessible both electronically and in theatres as notices. Time should be given to the health care professionals to adapt to newly updated versions of the guidelines. It is important to test the feasibility and acceptance of clinical guidelines among the target group before implementation, in order to avoid lack of consensus and disagreement.

Clear instructions regarding the duration (i.e. number of doses) of PAP should be included in the operation report sheet, as well as the treatment chart. Also standardised pre-printed order forms can be implemented to guarantee appropriate PAP administration.

Guidelines should be set up by a multidisciplinary team including a medical officer, clinical microbiologist and a clinical pharmacist. This team should be available for consultation when required by the surgeons. This would be particularly effective as surveys show that the majority of surgeons base their decisions on discussions with colleagues more than other sources of information.

The advantage of using local over international guidelines is that these take into account local resistant bacterial strains and thus are more effective in preventing infection and complications. Studies have also shown that there is a higher rate of adherence to local guidelines as opposed to international ones.

Limitations of this audit

The results presented in this study may not be indicative of surgeons’ compliance to the local guidelines as a limited number of cases were collected over a short time period (one month). The timing of the administration of antibiotic prophylaxis was assumed to be at the induction of anaesthesia as recorded in the Anaesthesia Record Sheet, but this could not be verified.
Some information regarding the antibiotic prophylaxis given and the procedure details were missing from the patients’ files.

Conclusion

Peri-operative antibiotic prophylaxis (PAP) is considered one of the most effective measures for preventing surgical site infections (SSI). Barriers to appropriate administration of PAP include lack of education and awareness of guidelines, hierarchal problems, disagreement with guidelines, poor communication and feedback problems. Such obstacles can be overcome by the improvements mentioned in this paper.

References

Abstract
The promotion of safe cycling is a way to address physical inactivity, one of the risk factors for non-communicable diseases (NCDs). In the report Road safety in the European Union: Trends, statistics and main challenges (March 2015), 8% of all fatalities are cyclists.

Bicycle helmets can reduce the risk of head and brain injuries and death. Most EU Member states have no requirement in legislation for bicycle helmets. Consequences of mandatory helmet legislation include decreases in head injuries and death, decreases cycling as a mode of transport, and increases helmet use. Other considerations, which influence bicycle accidents, need to be considered.

In Malta there were three deaths due to cycling between 2006 and 2015. The number of Accident & Emergency (A&E) attendances with cycling related injuries increased between 2009 and 2015. The number of A&E attendances in the 0-19 age group decreased whereas the 20-39 and 40-59 year age groups increased. In 2013, there were 173 registered injuries in cyclists, with head, upper extremity and lower extremity involvement in 28%, 40% and 21% respectively.

Recommendations include improving data collection, education campaigns, strong recommendation for helmet use in adults, to consider the introduction of mandatory helmet legislation in children and implementation of infrastructure measures to make roads more cycling friendly.

Key words
Head injuries, bicycle helmet and legislation.

Introduction
The promotion of safe cycling is a way to address physical inactivity, which is one of the common risk factors for non-communicable diseases (NCDs). NCDs are responsible for a large part of the disease burden in Europe. The World Health Organisations’ (WHO) “Global Report on Diabetes” claims that “the physical or built environment plays an important role in facilitating physical activity for many people” and that “urban planning and active transport policies can ensure that walking, cycling and other forms of non-motorized transport are accessible and safe for all”. However cyclists fall under the category of “vulnerable road users” together with pedestrians, as they are less protected in traffic from a collision than car drivers or passengers and are at a greater risk of injury or fatalities.

In the report “Road safety in the European Union: Trends, statistics and main challenges”, 8% of all fatalities are cyclists. Whilst there has been a low decrease of fatalities over time, there are big differences between countries. Serious head and neck injuries were the most common. The DaCoTA research project (Road safety Data Collection, Transfer and Analysis) found that bicycle helmets can reduce the risk of head and brain injuries between 63% and 88% in the case of a serious crash.

The main legislation regulating cycling in Malta is Subsidiary Legislation 26 of Chapter 65, which is a set of regulations that is known as “Low-Powered Vehicles and Pedal Cycles Regulations”. A “pedal cycle” is defined as “a two or three-wheeled vehicle that is propelled solely by human power by means of pedals”. The use of helmets is not required for pedal cyclists. However, children under ten travelling on someone else’s pedal cycle or power assisted pedal cycle, which was adapted to do so, shall be seated in a safety seat and shall wear a bicycle helmet. Best practice guidelines in Part 3 article 55 of The Highway Code states that cyclists
should wear a cycle helmet, which conforms to current regulations. However, this is not supported by the law.

In the European Union, there is no universal mandate on the use of bicycle helmets. Whilst some countries have partial rules, others have none. Bicycle helmet laws vary across the world. Only Australia and New Zealand currently require and enforce universal use of helmets by cyclists.5-6

Background

Demographics
In a recent systematic review, there were more male cyclists and they had a higher incidence rate (IR) of bicycle accidents than women. The IR increased with age especially in single bicycle accidents. The fatality rates and hospital admissions per million hours of cycling was higher for male cyclists younger than 17 and older than 50, with an incremental increase for those over 70 years of age. Female cyclists had lower fatality and hospital admission rates per million hours of cycling in all ages except between 17 and 20 years.7

The evidence for the protective effects of bicycle helmets

Empirical evidence
A retrospective case-control study showed that helmeted cyclists were less likely to have a skull fracture (p=0.01) and a scalp laceration (p=0.01) when compared to non-helmeted riders. However there was no difference between the two groups for the development of intracranial haemorrhage (p=0.1).8 However a retrospective case-control study showed that non-helmeted cyclists were more likely to have severe traumatic brain injury on computed tomography scan (p=0.004), longer length of stays in an intensive care unit (p=0.001) and more neurosurgical interventions (p=0.04).9 Helmeted cyclists injured in collisions with motor vehicles have a 72-74% reduced risk of head injuries.10-11 Helmeted cyclists had a 44% reduced odds of mortality (p = <0.01) and a reduced odds of facial fractures by 31% (p= <0.001).12 In summary, bicycle helmets reduced the risk of head and brain injuries; this is in keeping with previous case-control studies.13-16

Systematic reviews and meta-analysis
The largest and most recent systematic review and meta-analysis to date concluded that for cyclists involved in a crash or fall, helmet use was associated with an odds reduction (OR) for head (OR=0.49, 95% confidence interval (CI) 0.42-0.57), serious head (OR=0.31, 95% CI 0.25-0.37), face (OR=0.67, 95% CI 0.56-0.81), and fatal head injury (OR=0.35, 95% CI 0.14-0.88). Neck injury was rare and not associated with helmet use (OR=0.96, 95% CI 0.74-1.12).13 This is keeping with an older meta-analysis which was later reviewed, which found that bicycle helmets reduce the risk of head injury (OR=0.51, 95% CI 0.47-0.56) and offer slight protection against facial injury (OR=0.74, 95% CI 0.67-0.81).18

Consequences of mandatory helmet legislation

Effects on head injuries or deaths among cyclists
A systematic review demonstrated that mandatory helmet legislation (MHL) resulted in a decrease in head injury rates in the populations for which it was implemented.19 Following the introduction of MHL in Alberta, Canada there were significant declines in the proportion of child cyclists under 13 years of age to the Emergency Department with head injuries.20 Similar results were seen in New South Wales, Australia where there was a 46% drop in head injuries compared to arm injuries up to 2006 and a 51% drop by 2010 following MHL in 1991.21-22

In Ontario, Canada deaths decreased for children under 16 years by 52% (mortality rate per 100 000 person years decreased by 55%) with time series analysis indicating significant reductions following the introduction of MHL.23

Effects on the amount of cycling
In Australia, the decline in cycling varied between 20 and 40% across States following the introduction of MHL.24 Usage rates for bike sharing schemes in Brisbane and Melbourne were reported to be abysmal with only 5-10% of what was expected.25 Melbourne Bike Share survey results showed that helmet use was cited as the most common reason for not using the bike sharing scheme with 36% saying it was hard to find a helmet and 25% not wanting to wear a helmet (see Figure 1).
Other considerations

Factors influencing bicycle accidents and collisions are key to development and implementation of policy measures to improve safety in cyclists. According to a recent systematic review, there are four factors which influence bicycle accidents:

1. Demographic parameters
2. Built environment
3. Weather
4. Behaviour

Demographic parameters were described previously.

Built environment:
- Johnson et al. (2010) reported that cyclists generally have high situational awareness on the roads whereas drivers of collisions were not aware of the cyclists travelling alongside or behind them.
- Hoffman et al. (2010) reported that a dedicated infrastructure for cyclists was important.
- de Geus et al. (2012) reported that the safety of cyclists was not ensured by solely ensuring a good bicycle infrastructure especially if it was not well kept.

Weather:
- There is an increased incidence of bicycle accidents when the roads were snowy or icy and in the months of December and January.

Behaviour:
- Wearing visible clothing, having greater bicycling experience or helmet use were not shown to reduce the relative risk of being involved in an accident.
- Protective clothing reduces accident severity (described previously).

Local Data

Data from the National Mortality Register showed that fatalities from cycling are rare occurrences with three deaths due to cycling between 2006 and 2015 (Table 1).

Cycling-related morbidity statistics in terms of Accident & Emergency (A&E) attendances and Discharges from Mater Dei Hospital (MDH) was obtained from the Clinical Performance Unit of MDH. Permission to use the data was obtained from the Clinical Chairperson of A&E and the Data Protection Officer of MDH.

A textual search of the registration notes and triage notes of A&E attendances in the Clinical Patient Administration System (CPAS) including “bicycle” and “bike” (motorbike and quadbike excluded) was performed. The number of A&E attendances at MDH with bicycle related accidents has steadily increased between 2009 and 2015.
(Figure 2). The age group with the most A&E attendances at MDH was 10-14 years (Figure 3). This was closely followed by the 15-19 year age group. However time trend analysis shows that the number of A&E attendances in the 0-19 age group is decreasing over time in contrast to the 20-39 and 40-59 year age groups (Figure 4).

Discharge data was obtained from the Hospital Activity Analysis using ICD-10 code V19 as well as using a textual search. The number of discharges from MDH with bicycle related accidents varied between 2009 and 2015. The three-year moving average for the total number and the number of males discharged from MDH appears to be decreasing, whereas the three-year moving average for the number of female discharges appears to be increasing (Figure 5).

The age group with the most discharges from MDH was 10-14 years (Figure 6). This was closely followed by the 15-19 year age group. This mirrors the distribution evident in the number people attending A&E. Other studies noted a similar age distribution.\textsuperscript{7,20} Time trend analysis for discharges was not performed in view of the small numbers.

Registered injuries in cyclists in 2013 from the Malta Injury Database showed that two in five registered injuries occurred in children 15 years of age or less (Table 2). Overall, just over one in four registered injuries involved the head (Table 3).

Table 1: Deaths due to cycling over the past 10 years in residents and tourists dying in Malta

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>pedal cyclist (V10-V19)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 2: Number of cyclists attending A&E for males, females and total between 2009 and 2015
Figure 3: Number of cyclists attending A&E in 2009 and 2015 by age groups

Figure 4: Number of cyclists attending A&E between 2009 and 2015 by broad age groups
Figure 5: Number of patients discharged from MDH following cycling related injuries for males, females and total between 2009 and 2015.

Figure 6: Number of patients discharged from MDH following cycling related injuries in 2009 and 2015 by age groups.
Table 2: Registered injuries in cyclists by age and sex in 2013 in Malta

<table>
<thead>
<tr>
<th>Injuries registered</th>
<th>&lt;15</th>
<th>16-25</th>
<th>26-34</th>
<th>35-44</th>
<th>45-54</th>
<th>55-64</th>
<th>&gt;65</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>58</td>
<td>20</td>
<td>19</td>
<td>18</td>
<td>13</td>
<td>9</td>
<td>6</td>
<td>143</td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>72</td>
<td>24</td>
<td>24</td>
<td>21</td>
<td>16</td>
<td>9</td>
<td>7</td>
<td>173</td>
</tr>
</tbody>
</table>

Table 3: Registered injuries in cyclists by injury type and site in 2013 in Malta

<table>
<thead>
<tr>
<th>Injury type registered</th>
<th>Head</th>
<th>Neck, throat</th>
<th>Trunk</th>
<th>Upper extremities</th>
<th>Lower extremities</th>
<th>Multiple body parts</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contusion, bruise</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Abrasion</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>Open wound</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>28</td>
</tr>
<tr>
<td>Fracture</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>4</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Luxation, dislocation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Distorsion, sprain</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Crushing injury</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Concussion</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Injury to blood vessels</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other specified type of injury</td>
<td>8</td>
<td>1</td>
<td>8</td>
<td>44</td>
<td>14</td>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td>Unspecified type of injury</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>1</td>
<td>12</td>
<td>70</td>
<td>37</td>
<td>4</td>
<td>173</td>
</tr>
</tbody>
</table>

Discussion
Following the literature review and a look at the local data a number of recommendations can be made:

1. **Improve the data collection**: Data from the National Injuries Database collects data on all accidents and injuries attended to at the A&E Department of Mater Dei Hospital and Gozo General Hospital. However it does not capture data from health centres or the private primary or secondary care and thus it may both underestimate and misrepresent the results. The introduction of an emergency medical text classifier of A&E records with triage notes could help to capture more accurate and complete data of A&E attendances. Helmet use was not recorded in either the National Mortality Register or
Injuries Database. Also geographical, temporal and situational data of the fatalities and injuries were not recorded. The chapter on Road Transport published by the National Statistics Office in the annual Transport Statistics report does not include any information on cyclists involved in road traffic accidents. Also exposure data for cyclists is unknown. To be able to measure risk exposure and compare rates over time and between countries, it is important to know how many deaths and injuries there were and the distance-time exposure. Otherwise a decrease in the total number of fatalities and injuries could be due to a decrease in bicycle use. A survey is recommended.

2. **Education campaigns:** for safe cycling including training for cyclists, educating motorists to be have greater situational awareness, and instill road safety skills and habits in children. This is in keeping with the Road Safety Strategy Malta 2014 – 2024.

3. **Strong recommendation for helmet use in adults:** The protective effect of bicycle helmet use is clear. Bicycle helmet use saves lives. However mandatory helmet legislation may deter adults from cycling altogether forgoing beneficial personal health gains.

4. **Consider the introduction of mandatory helmet legislation (MHL) in children:** The introduction of MHL in children is already in effect in seven European Union Member States. Children are more likely to attend A&E and be admitted to hospital with bicycle-related injuries than adults. This may be due to a higher use of bicycles and less bicycling experience when compared to adults. Also children who grow up cycling with a helmet are probably likely to becomes adults who spontaneously use bicycle helmets.

5. **Implement infrastructure measures:** to separate cyclists and motor vehicles, including cycling lanes, where it is possible. New road design needs to be cycling friendly. This is in keeping with the Road Safety Strategy Malta 2014 – 2024.

**References**


2. Road safety in the European Union. 2015.


Robinson DL. Public health Do enforced bicycle helmet laws improve public health? No clear evidence from countries that have enforced the wearing of helmets. 2006;332(March):722–5.


Abstract
In Malta phenylketonuria (PKU) is mostly due to dihydropteridine reductase (DHPR) deficiency rather than phenylalanine hydroxylase deficiency (classical PKU), and is associated with long term neurodisability in all affected patients. The absence of newborn screening for PKU in Malta results in a later diagnosis and an increased burden on families and affected individuals. This burden is further compounded by problems in adherence to strict low-phenylalanine diets, in part due to problems dispensing appropriate amounts of low-phenylalanine products and, in those with DHPR, the regular provision of neurotransmitter and cofactor supplementation. Over a 6.5-year review, complete provisions were dispensed in 68% of all prescriptions for L-dopa, 67% for 5-hydroxytryptophan, 63% for low protein food, 61% for folinic acid and just 30% for low protein drinks. The problems encountered in the management of PKU highlight similar problems facing those with other rare, metabolic or ‘orphaned’ diseases. Yet some of these problems, particularly with regard to the dispensing of medicines and special food products can be reduced or eliminated. This would require a radical and comprehensive overhaul of the funding, procurement, stocking and dispensing of all pharmaceutical provisions in order to achieve stable phenylalanine levels throughout childhood and through to later life.

Keywords
phenylketonuria, suboptimal provision, Malta

Introduction
Phenylketonuria (PKU) is a rare condition affecting approximately 1 per 10-19,000 of most populations studied, and several subtypes exist.1,2 The more uncommon atypical form resulting from dihydropteridine reductase (DHPR) deficiency2 appears to be most prevalent in Malta, and it has been estimated that up to 3.3% of the population may carry the abnormal gene mutation for this condition.3 Despite this high carriage rate, phenylketonuria is not yet screened for at birth and presents late, although the case for routine newborn screening for PKU at a national level was made as early as 2005.4 The burden of PKU in childhood in Malta has been recently reviewed by Attard and Attard Montalto.5 The spectrum of PKU-related medical complications including significant neurodisability in all affected individuals, the daily requirements of medication and food alternatives, complex management and the psychosocial, educational and financial burden of PKU on patients, their families and Health services has been described in detail.5

Five of the six children diagnosed with PKU in Malta since 1996 suffer with DHPR deficiency and, for them, dietary manipulation is insufficient and they require daily medication with dopamine-pathway analogues and cofactors including L-dopamine, 5-hydroxytryptophan, folinic acid as well as low protein food products and low or phenylalanine-free drinks/milk.6-7 The short half-life of these medications necessitate dosing four to five times daily and delays in treatment of just a few hours is rapidly followed by neurological symptoms such as dystonia, irritability and behavioural changes.7 The requirement for regular and timely medication to sustain steady-state conditions is paramount and poses yet another challenge to the day-to-day burden of PKU.8 Ideal medical control can only be achieved by patient and
parent cooperation together with an efficient provision of all therapeutic requirements. The latter cannot be under-estimated and this study, a qualitative phenomenological case-based review of patient experiences, was designed to review this crucial aspect in the management of these children.

Methods

All children below the age of 16 years with any form of PKU were identified over a twenty-year period, from 1996-2015. For those still resident in Malta in 2015, their official ‘yellow’ pharmacy-issued and updated cards were analysed for the preceding six and a half-year period, when Paediatric Services migrated to the new national hospital. All PKU-related prescriptions including medicines, food products and special milks/drinks, were identified and assessed for quantity dispensed. Routinely, and in accordance with the prevailing hospital policy at the time, these medications and provisions were supplied and dispensed for a two-month period. Hence, any dispensed medication that provided adequate provisions for the next two months was taken to represent 100% for that individual prescription. Anything less (or more) was calculated as a percentage of the ‘standard’ two-month allowance, and this exercise was performed for all PKU prescriptions over the 6.5-year period, January 2009 - June 2015.

Results

Over a twenty-year period from 1996-2015, five patients with PKU due to DHPR and one patient with classical PKU due to phenylalanine hydroxylase deficiency were diagnosed in Maltese children. Of these, three siblings with DHPR deficiency emigrated and prescriptions were analysed for the remaining three patients. Two boys with DHPR deficiency required regular medication with L-dopamine, 5-hydroxytryptophan and folinic acid, whilst both patients required low protein food and low/free phenylalanine milk/protein drink substitutes. The third patient with classical PKU was diagnosed midway through the study period and required low protein food and low/free phenylalanine milk but no dopamine pathway analogues. This study showed that, over a 6.5-year period, 456 prescriptions were issued for PKU-related products. Of those, 412 were for the two patients with DHPR deficiency, with just 9.5% for milk and food products for the girl with classical PKU. If all prescriptions that were issued covered 100% of the patients’ requirements in all cases, there should have been approximately 430 item-prescriptions for these three patients in the same time period, averaging 30 each per annum (p.a.) for those with DHPR, and 12 p.a. for classical PKU. In practice, DHPR patients were issued with 31.7 prescriptions p.a. (median 31, SD±5.1), and one patient with classical PKU received 12.3 prescriptions p.a. (median 12, SD±0.5). Table 1 shows the breakdown of the individual prescriptions, and confirms that the main contributor to the 5.8% ‘above estimate’ prescriptions arose due to repeat/extra prescriptions for low protein drinks.

Table 1: Prescriptions according to pharmaceutical item over 6.5 years

<table>
<thead>
<tr>
<th>Prescribed item</th>
<th>Estimated number of prescriptions</th>
<th>Actual number of prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-dopamine</td>
<td>78</td>
<td>56</td>
</tr>
<tr>
<td>5-hydroxytryptophan</td>
<td>78</td>
<td>80</td>
</tr>
<tr>
<td>folinic acid</td>
<td>78</td>
<td>70</td>
</tr>
<tr>
<td>Low protein food</td>
<td>78</td>
<td>84</td>
</tr>
<tr>
<td>Low protein drinks*</td>
<td>98</td>
<td>130</td>
</tr>
<tr>
<td>Phe-free protein milk**</td>
<td>20</td>
<td>36</td>
</tr>
</tbody>
</table>

*Required for all patients; ** only for young girl with classical PKU, diagnosed half way through study period.

The child with classical PKU did not require medication, was diagnosed more than half way during the study period and, for this patient, data was incomplete and was not included in subsequent analyses. For the two boys with DHPR, further breakdown of the actual amounts dispensed compared with what was prescribed for a two-month period, showed that all PKU medications were intermittently or frequently supplied in inadequate amounts. As shown in Figure 1, L-Dopa was insufficiently dispensed in 32% of prescriptions, 5-hydroxytryptophan 33%, folinic acid in 39%, low protein food in 37% and PKU cooler (low protein drink) in 70% of all prescriptions. Figures 2A-E show the spread of prescriptions for each individual item over a 6.5-year period, and highlight the frequency of incomplete amounts dispensed relative to the prescribed two-monthly supply. Suboptimal
dispensing averaged approximately one third of all prescriptions for most items, with low protein drinks being consistently unavailable in sufficient quantities and, therefore, not dispensed ‘in full’ for more than two thirds of the time.

**Figure 1:** Frequency (as %) of complete PKU items dispensed over 6.5 years

**Figure 2A:** L-dopa
**Figure 2B: 5HT**

**Figure 2C: Folinic acid**
Legend to Figures 2A-E: Prescriptions are denoted as a percentage of the amount ordered where 100% equals stock dispensed for a two month period. Amounts issued as a % of the totals ordered are shown for 5 items over 6.5 years, 2009-15. All items are frequently supplied in insufficient quantities: L-dopa 68%; 5HT 67%; low protein food (e.g. bread, pasta) 63%; folinic acid 61%, and low protein drinks (PKU cooler) being the most affected, averaging just 30% of the requested stock being dispensed.
Discussion

Phenylketonuria (PKU) in Malta is mostly due to dihydropteridine reductase (DHPR) deficiency, is not screened for at birth and presents late, invariably with developmental delay and neurodisability.\(^5\) The management of this condition is complex and patients/their families face many challenges on a daily basis.\(^5\)\(^-\)\(^8\) This study has shown that the burden of PKU in Malta is further compounded by non-adherence to PKU diets, in part, due to irregular provision of neurotransmitter and cofactor supplementation, as well as PKU-specific food items. Collectively, these children only consume small amounts of specific food items that change from time to time, and are not widely available, thereby discouraging local pharmaceutical agents to maintain stocks. Limited stocks lead to under-dispensing that, at best, is as much as 32% for some less problematic medications like L-dopa but may be as high as 70% of what is required for other items like low protein drinks (e.g. PKU Cooler). In practice, patients with PKU are issued with close-to-the-expected number of prescriptions per year with the exception of low protein drinks. For the latter, many more prescriptions are issued, presumably to ‘make up’ repeated deficits in the incomplete amounts dispensed. However, chronic under-dispensing was observed for all drugs and food items for PKU-related prescriptions, a situation that resulted in frequent hospital attendances to collect the shortfall. These extra hospital trips for repeat ‘top-ups’ are inconvenient but, more significantly, any delays in treatment are associated with increased symptoms as doses are missed and compliance with PKU-diet is suboptimal.

These shortfalls are the result of several factors including, at times, poor supply by the importing agents, compounded by the short half-life of some of these products especially the food products, milk and low protein drinks, and is not helped by the relatively costly and small quantities required. An inefficient procurement process with cumbersome tendering, little in-built flexibility and perpetual budgetary limitations often results in frequent ‘out of stock’ events, with subsequent incomplete/delayed prescriptions necessitating urgent and costly top-ups. In addition, food items frequently surpass their sell-by-date when collected by patients who, in turn, shun these items that are then discarded. Wastage begets ever more barriers to future orders, incurs greater delays and creates a vicious cycle of negative supply.

Although this study is based on a qualitative review of a small number of patients, and carried out by the same patients’ potentially biased caring physicians who may be equally frustrated with chronic under-dispensing for their patients, it nevertheless highlights a chronic problem for these patients and a significant lacuna in the service. This study would suggest that a comprehensive overhaul of the pharmaceutical provision for children with PKU with effective dietary and medicinal provision is essential. A serious exercise to address all of these issues is required, but one option whereby families are given a carefully monitored budget to procure and manage their own supplies is one model that can be applied for PKU and similar rare disorders that require multiple, ‘special’, hard-to-obtain, expensive items with a short half-life.\(^9\)\(^-\)\(^10\)

This would have to be combined with greater efficiency at the point of delivery by importing agents as it would otherwise simply transfer an added burden from the hospital pharmacy to the patient. In line with ‘best practice’, all these patients are managed in conjunction with a tertiary centre\(^1\) and, alternatively, supplies could be obtained directly from the shared care tertiary centre in the UK, again with due monitoring from both health services. This set-up may also prove to be more cost-effective as it would eliminate wastage relating to expired/unused/surplus items. In tandem, a dedicated section/sub-department within the hospital service could be responsible for all aspects of supplies for PKU and related disorders, and would be expected to work closely with a local dedicated dietetic service that can closely monitor food items, ‘sell by dates’, stocks and supply, as well as liaise regularly with the tertiary metabolic centre.

Conclusion

A small number of children with PKU require low phenylalanine food products with or without additional medications, and they should receive the required products at the right quantity and at the right time. Failure to do so results in neurological and behavioural symptoms in the short term and may compound neurodisability long term. This is an important issue that has ethical as well as potentially serious medico-legal implications. Despite strenuous efforts by all concerned, the
current system has repeatedly failed to provide adequate stocks, ensure in-date medications and avoid delays in the dispensing of PKU-related items. A comprehensive review of all aspects of the present set-up is required with urgency.

References
The use of Botulinum Toxin for focal hyperhidrosis – life changing and not only cosmetic

Leonard Callus, Philip Sciortino, Jessica Schembri Higgans

Abstract
Focal hyperhidrosis is the excessive sweating from one part of the body most often the axillae, palms, soles and face. This condition is known to carry a high social and psychological burden with studies showing that patients with this condition end up avoiding leisure and social activities with sometimes even affects on their occupation. The aim of this literature review is to evaluate the different types of focal hyperhidrosis and how they can be treated. It seeks to compare Botulinum toxin treatment to other treatment options available for focal hyperhidrosis in terms of cost, efficacy and side effects. Research on Botulinum toxin and available serotypes are being done to help improve hyperhidrosis treatment by reducing side effects and improving efficacy. It also focuses on the effects of this condition on the patient’s lifestyle and how debilitating this condition can be. This kind of treatment is sometimes regarded as a cosmetic procedure since medical professionals consider hyperhidrosis as benign. However, research has shown that effective treatment of hyperhidrosis with botulinum toxin improves patient’s quality of life (QoL) significantly.

MeSH Terms
botulinum toxin, quality of life, hyperhidrosis, cost benefit, efficacy treatment, botulinum toxin type a, botulinum toxin type b.

Introduction
Focal hyperhidrosis was found to affect 3% of the population in the United States suffer from hyperhidrosis most of which suffer from axillary hyperhidrosis. It affects mostly people between age 25 and 34 and affects more females and males. Due to this significant prevalence, recent developments in treatment especially with Botulinum toxin and lack of research and studies on focal hyperhidrosis here in Malta, it was important to review available literature on focal hyperhidrosis.¹

Hyperhidrosis on the other hand is defined as a disorder of excessive sweating beyond what is necessary for thermoregulation. Eccrine glands are those responsible mainly for hyperhidrosis and they are densely found at the soles of the feet, forehead, palms and cheeks thus leading to focal hyperhidrosis. Apocrine glands which are mainly focused at the axillary and urogenital regions are regulated by a hormonal process and are thus not usually responsible for hyperhidrosis. However it is difficult to quantify excessive sweating and usually diagnosis is based on dysfunctional sweating, that is, how much the condition affects the patient’s quality of life (QoL).² In order to establish a standard with regards to the extent that hyperhidrosis is affecting a particular patient, a scale known as Hyperhidrosis Disease Severity Scale (HDSS) can be used. In this scale, the doctor scores the patient according to how much the disease is affecting the patient with a score of 1 showing least impact and 4 showing the worst.³ This same scale was used in studies done in the United States which showed that the majority of those with axillary hyperhidrosis had a score of 3 or 4 in the HDSS scale. At least 1.3 million

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individuals in the United States have severe focal hyperhidrosis that might require management with Botox to control. Table 1 shows the HDSS scoring sheet used to grade the severity of hyperhidrosis.1,4,5

**Table 1: Hyperhidrosis Disease Severity Scale (HDSS)**

<table>
<thead>
<tr>
<th>“How would you rate the severity of your Hyperhidrosis?”</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>My sweating is never noticeable and never interferes with my daily activities</td>
<td>Score 1</td>
</tr>
<tr>
<td>My sweating is tolerable but sometimes interferes with my daily activities</td>
<td>Score 2</td>
</tr>
<tr>
<td>My sweating is barely tolerable and frequently interferes with my daily activities</td>
<td>Score 3</td>
</tr>
<tr>
<td>My sweating is intolerable and always interferes with my daily activities</td>
<td>Score 4</td>
</tr>
</tbody>
</table>

Apart from the HDSS score, there are also diagnostic criteria that help to diagnose focal idiopathic hyperhidrosis. These criteria state that there needs to be focal, visible, excessive sweating for a period of at least 6 months without apparent reason and with at least two of the following characteristics:

1. Bilateral and relatively symmetrical sweating
2. Frequency of at least 1 episode per week
3. Impairment of daily activities
4. Age of onset less than 25 years
5. Positive family history
6. Cessation of sweating during sleep.

Hyperhidrosis is mainly subdivided into two, generalized and focal hyperhidrosis, with the former one affecting the sweat glands of the entire skin surface area while the latter affecting certain areas. Generalized hyperhidrosis is usually secondary to drugs, such as, anti-depressants but can also be caused by endocrine conditions, such as, hyperthyroidism, chronic infections and neoplastic conditions, for example, Hodgkin’s Lymphoma.6

The focus of this review is on focal hyperhidrosis since it is the one that can be treated with BTX.

Focal hyperhidrosis is further sub-divided in three other groups, primary idiopathic, gustatory sweating and neurological. Table 2 shows the different types of focal hyperhidrosis sub divided into these categories. Axillary hyperhidrosis is the most common type of focal hyperhidrosis. In a national survey done in the United States of people having focal hyperhidrosis, half of them had axillary hyperhidrosis. This is followed by focal hyperhidrosis in the soles and in the palms.1

**Table 2: Types of focal hyperhidrosis**

<table>
<thead>
<tr>
<th>Primary Idiopathic</th>
<th>Axillary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmar</td>
<td>Plantar</td>
</tr>
<tr>
<td>Craniofacial</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gustatory sweating</th>
<th>Frey’s syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain foods such as, citric acid, coffee, chocolate, peanut butter and spicy food</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurological</th>
<th>Neuropathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Injury or disease</td>
<td></td>
</tr>
</tbody>
</table>

**Method**

We performed a search using PubMed and Google Scholar to find studies or systematic reviews relevant to focal hyperhidrosis especially if including treatment with Botulinum toxin. Search terms and phrases used were the various combinations of botulinum toxin, quality of life, focal hyperhidrosis, cost benefit and efficacy, treatments for hyperhidrosis, botulinum toxin type a, botulinum toxin type b and guidelines for focal hyperhidrosis. The search was conducted between August and September 2016. We made sure that the majority of the studies considered were recent (ideally after 2008) and that non-original articles were excluded. Preferred studies used in this review compared Botulinum toxin to other treatments and/or included patient’s quality of life before and after treatment with Botulinum toxin.

**Results**

Research has shown that Botulinum toxin (BTX) works by targeting the presynaptic cholinergic neuromuscular junctions that innervate the eccrine glands in that area, hindering the release of acetylcholine thus inhibiting contraction and release of sweat from the sweat secreting cells in the eccrine sweat gland. Figure 1 shows the target site of BTX to stop sweat production compared to other treatments for focal hyperhidrosis. BTX usually takes around 1-14 days to work. After around 4 to 17 months, new neuromuscular junctions form and the patient might need another
injection of BTX to avoid developing the symptoms again.\textsuperscript{8-9} BTX injection for hyperhidrosis also has its own side effects. A common side effect is myalgia at the site of injection. This may cause the patient to refuse more BTX injections to avoid such pain. However, in a study done in 2007, it was found that this side effect can be avoided by injecting Botox constituted with lidocaine. This double blind study showed that the use of lidocaine with BTX-A reduces pain at the injection site without affecting its effectiveness.\textsuperscript{10} Botulinum toxin treatment for palmar hyperhidrosis is also known to cause reversible minor weakness of palmar muscles with reduced handgrip.\textsuperscript{11} Other side effects include myalgia, itching and increased compensatory sweating of the face.\textsuperscript{9,10} BTX therapy is contraindicated for patients who are pregnant or lactating, suffering from neuromuscular disorders, have an organic cause of hyperhidrosis or are taking medications that are known to interfere with neuromuscular transmission. BTX must only be administered by a specialized physician trained in the administration of Botulinum toxin.\textsuperscript{5}

**Treatment of focal hyperhidrosis with Botulinum toxin compared to other treatments available – costs and benefits.**

BTX treatment is to be discussed in the context of the other available therapies. **Aluminium chloride hexahydrate** applied topically to the affected area is currently the first line treatment for most forms of focal hyperhidrosis. This chemical works by blocking the epidermal duct of the eccrine sweat glands. It is thought that this causes direct damage to the eccrine sweat gland, specifically to the glandular secretory cells causing them to atrophy. Their effect extends also to the epidermal cells of the duct which undergo necrosis. This therapy is known to cause skin irritation in about 50% of patients thought to be caused by the formation of hydrochloric acid when this topical treatment makes contact with water. New formulations with aluminium chlorohydroxide in purified water try to avoid this side effect. Alternatively, local hydrocortisone 1% is applied with this topical treatment to relieve this burning and painful sensation. However the main disadvantage of this treatment is the short duration of effect. Within 48 hours, its effectiveness diminishes and within one week, the patient’s condition goes back to how it was before treatment started, making BTX treatment a better option for those who want a more long term solution. However unlike BTX, this treatment is low cost and convenient so it is for this reason that aluminium chloride salts are chosen as first line treatment especially for mild cases of hyperhidrosis.\textsuperscript{9,12} The cost of a single injection of BTX A 50 Units which is used per axilla range from €81 to €87 (powder only) compared to an average of €3.50 for the liquid form of aluminium chloride hexahydrate or €8 for the more convenient spray form.\textsuperscript{13}

Another treatment which is available for focal hyperhidrosis is **tap water iontophoresis.** In this treatment, the patient has to put the affected areas with focal hyperhidrosis, usually the palms of the hand or the soles of the foot, in small containers with tap water and a pulsed direct current with a high frequency of 5-10 kHz is passed through the water. The treatment usually takes around half an hour and needs to be repeated three to four times a week or until adequate results are achieved. This treatment is only possible for flat surfaces affected by focal hyperhidrosis, namely the soles and palms. However it can be considered as a cheap and effective treatment for highly motivated patients. It is usually considered for palmar and plantar hyperhidrosis when topical treatment with aluminium chloride hexahydrate fails. Side effects of iontophoresis range from burning discomfort and skin irritation to burns and cutaneous necrosis if not used properly.\textsuperscript{14} Costs for tap water iontophoresis are fairly reasonable. In the UK according to NHS, iontophoresis kits that one can use at home cost between €280 and €560.\textsuperscript{15} In some studies, **addition of BTX-A to iontophoresis** was attempted and it was found that focal hyperhidrosis improved drastically without any pain which is usually reported with BTX injections. Compensatory hyperhidrosis was also reported in one study post-treatment with tap water iontophoresis which wasn’t the case for BTX-A iontophoresis done in the same study.\textsuperscript{16} However, in a recent study published about 2 years ago, injection administration provided more long term reduction in sweat production than when it was administered with iontophoresis. In this randomized, controlled trial, it was found that after 6 months, 50% of patients treated with Botulinum injections still had significant reduction in focal hyperhidrosis compared to 32% with BTX iontophoresis.\textsuperscript{17}

**Systemic anticholinergics,** such as,
oxybutynin or glycopyrrolate are also sometimes considered for focal hyperhidrosis since these inhibit sweating through competitive blocking of muscarinic receptors. However, these have a lot of systemic side effects with the most common one being dry mouth. In a study done by V. Bajaj and J. Langtry, it was found that although 75% of patients reported improvement with glycopyrronium bromide for hyperhidrosis (9 generalized and 15 focal hyperhidrosis), 79% of them reported dry mouth and 50% dropped out from the study. Given the side effects, this type of treatment can be therefore considered if topical treatment fails and Botulinum treatment is either not available or cannot be afforded by the patient. In other studies showed that decreased sweating at high environmental temperatures may cause fever and heat stroke. Diarrhoea may herald incomplete intestinal obstruction. Other adverse effects include blurred vision, urinary retention, dry mouth, vomiting, drowsiness and palpitations. Glycopyrronium bromide tablets are contraindicated in medical conditions that preclude antimuscarinic therapy (NICE 2013). Just like with BTX, glycopyrronium bromide can be administered to the affected area via iontophoresis and in a recent study, it was found that 81.8% patients treated with this method had a significant improvement in their condition. However, glycopyrronium bromide used for iontophoresis is quite expensive. Robinul powder for solution for iontophoresis costs €298 compared to €144 for 100 units of BTX used for iontophoresis. Topical anticholinergics can also be used for the treatment of focal hyperhidrosis. It was found that daily topical application of 0.5% glycopyrrolate is effective in controlling craniofacial hyperhidrosis. However, symptoms tend to recur after two days without treating.

Different surgical treatments for axillary and palmar hyperhidrosis exist and these usually offer a more permanent solution to focal hyperhidrosis. Local surgery includes subcutaneous curettage to excise sweat glands and this kind of operation is usually reserved for severe axillary hyperhidrosis unresponsive to topical and BTX treatments. This surgery is known to have high complication rates and morbidity with reduced arm movement, scars, infections and haematomas. Suction curettage is another type of local surgery to control hyperhidrosis. In suction curettage the surgeon places a cannula between the dermis and the hypodermis of the affected area to destroy sweat glands in this area through liposuction. This offers much less side effects than local direct excision; particularly less scars. However, this also carries its own side effects, such as bleeding, infection and even damage to the brachial plexus when used to treat axillary hyperhidrosis. The most invasive surgeries available for focal hyperhidrosis are those that cause sympathetic denervation – sympathectomy or ganglionectomy and sympathectomy. In sympathectomy or ganglionectomy, the sympathetic chain is transected endoscopically at a level above or below T2 ganglion or the ganglion itself is destroyed while in sympathectomy, the rami connecting to T2 ganglion are transected. Cost of such surgeries are considerably higher than Botox treatment. In a study it was shown that while the baseline cost of BTX treatment for focal hyperhidrosis is €389 with an annual cost of around €853, that of an uncomplicated endoscopic thoracic sympathectomy is €9389 with costs going up to €11390 if complications occur. These kinds of operations often carry the risk of side effects, mainly sexual dysfunction and sometimes even compensatory sweating with the incidence of such complications varying from 14% to 90%. Other major complications associated with such operations include vascular injury and pneumothorax. They are therefore not common and usually reserved for patients who didn’t respond to topical, BTX treatments and even oral anticholinergics.

A study done by I. Hoorens and K. Ongenae which prepared guidelines for the different types of focal hyperhidrosis listed BTX therapy as second line treatment for most focal hyperhidrosis. It can also be used as first line for moderate to severe conditions in which the patients’ lifestyle is severely affected or their lifestyle doesn’t allow them to continuously use aluminium chloride hexahydrate sprays or iontophoresis. Unlike most treatments, BTX injections usually only need to be applied once and take months before the patient goes back to pre-treatment stage. It helps to treat the condition locally without having to resort to systemic drugs, such as, anticholinergics or surgery that carry major side effects, with the risk of compensatory sweating. BTX injections are also considered first line in gustatory sweating usually caused by Frey’s Syndrome. This syndrome
occurs in different extents in patients who undergo parotidectomy due to aberrant regeneration of transected parasympathetic fibers between the otic ganglion and subcutaneous vessels. An intracutaneous injection of BTX-A helps to effectively control this condition with long lasting results.\textsuperscript{27} The same can be said for forehead hyperhidrosis with studies showing BTX-A to be the most effective treatment for this kind of hyperhidrosis with a reduction in sweating of approximately 75\% for a period of around 5 months.\textsuperscript{28} Figure 1 shows the target site of action for each treatment mentioned in this section.

\textbf{Table 3} summarises the treatment of the common forms of focal hyperhidrosis organised as step-by-step approach and evidence obtained mainly using randomised trials, case control studies and non-randomized controlled cohorts. It shows that BTX-A treatment can be considered even first line in severe cases of focal hyperhidrosis while second or third line in mild presentations after topical treatment fails.

Laser treatment and Miradry are new treatments for focal hyperhidrosis that are currently being researched but still not widely available. \textbf{Laser treatment} enables physicians to target specific body structures accurately, limiting damage to surrounding tissue. Added advantages include decreased risk of infection and reduced bleeding. These procedures are relatively quick; they take less than an hour, and can be done on an outpatient basis. Studies have shown that underarm sweating is reduced significantly; by approximately 78\% at six months' time. Another advantage is that treatment is permanent as the sweat glands do not regenerate. Side effects include bruising, swelling and numbness, which take approximately one to two weeks to resolve.\textsuperscript{30} \textbf{Miradry} is a new microwave therapy developed as a non-surgical treatment for hyperhidrosis. Microwaves are absorbed more in high-water-content tissue, and thus heating is localised. The target is the skin-adipose interface, because most of the eccrine glands in the skin are found there with a focal energy zone created at this interface. In a study done to show the efficacy of this treatment reported an average sweat reduction of 82\% and patient satisfaction were high when assessed using HDSS scoring before and after the treatment. Advantages of this treatment are that it is permanent, safe and effective. Discomfort and oedema in the underarm area are expected within the three day period following the microwave therapy and this may take several days to resolve. Other adverse effects include altered sensation in the treatment area and partial loss of underarm hair, temporary lumpiness and bumps in the axilla, bruising at the injection sites due to local anaesthetic and redness from device suction.\textsuperscript{31}
### Table 3: Step by step treatment (medical and surgical) for the four most common types of focal hyperhidrosis divided according to severity; HDSS <2 as mild and HDSS 3-4 as severe. ACH = Aluminium chloride hexahydrate, BTX-A = Botulinum Toxin A treatment.\(^9,29\)

| Axillary Hyperhidrosis | | | | | |
|------------------------|--|------------------|--|------------------|--|------------------|--|------------------|--|------------------|--|------------------|--|
| HDSS Score <2 | Topical ACH | Topical ACH | Systemic anticholinergics | Suction Curettage or excision of sweat glands. Repeat if failed | Reconsider suction curettage. Sympathetic Denervation |
| HDSS Score 3-4 | Topical ACH | Systemic anticholinergics | Suction Curettage or excision of sweat glands. Repeat if failed | Sympathetic Denervation |

| Palmar Hyperhidrosis | | | | | |
|----------------------|--|------------------|--|------------------|--|------------------|--|------------------|--|------------------|--|------------------|--|
| HDSS Score <2 | Topical ACH | BTX-A 100-150U per palm. OR Topical ACH OR Iontophoresis | BTX-A 100-150U per palm. OR Topical ACH OR Iontophoresis | Systemic anticholinergics OR Topical together with BTX-A or Iontophoresis | Sympathetic Denervation |
| HDSS Score 3-4 | Topical ACH | Iontophoresis either by tap water, anticholinergics or BTX-A | Iontophoresis either by tap water, anticholinergics or BTX-A | Systemic anticholinergics | Sympathetic Denervation |

| Plantar Hyperhidrosis | | | | | |
|-----------------------|--|------------------|--|------------------|--|------------------|--|------------------|--|------------------|--|------------------|--|
| HDSS Score <2 | Topical ACH | Iontophoresis either by tap water, anticholinergics or BTX-A | Iontophoresis either by tap water, anticholinergics or BTX-A | Topical together with BTX-A or Iontophoresis | Systemic anticholinergics |
| HDSS Score 3-4 | Topical ACH | Systemic anticholinergics | Systemic anticholinergics | |

| Craniofacial hyperhidrosis | | | | | |
|-----------------------------|--|------------------|--|------------------|--|------------------|--|------------------|--|------------------|--|------------------|--|
| HDSS Score <2 | BTX-A up to 100U - First line for Frey’s Syndrome. Consider topical AC. | Systemic anticholinergics |
| HDSS Score 3-4 | BTX-A up to 100U - First line for Frey’s Syndrome. Consider topical AC. | Systemic anticholinergics | Sympathetic Denervation |
Effects of treatment with Botulinum Toxin on the patient’s quality of life

Medical professionals sometimes underestimate the morbidity of this condition failing to recognize the impact of this disease on patient’s QoL. The condition itself causes a lot of anxiety together with physical discomfort, functional impairment and psychosocial issues. In survey done in the U.S. about the impact of axillary hyperhidrosis, almost half of the participants complained that they find it difficult to meet new people especially due to the fact that they continuously soil clothing, paperwork and shoes and avoid handshakes as their palms are always wet and cold. Some even complain finding it difficult to engage into intimate situations and romance. More than a quarter of the participants had to change or even stop sports and some even reporting spending less time working due to their condition. However the most worrying facts that came out of this study were that more than half of the participants reported feeling less confident than they would like due to their condition and 35.7% reported feeling depressed. The latter showed the most impairment (score of 3 or 4) according to the HDSS score. 38% of the participants decided to seek out help from a medical professional with regards to this issue and the rest failed to recognise this as a medical problem and blamed themselves instead. Excessive focal sweating is also sometimes responsible for secondary medical conditions, mainly bacterial and fungal overgrowth and eczematous dermatitis, adding insult to injury already caused by this condition.1

Different studies on the BTX treatment and QoL after treatment have been done, most of these show positive results. In a recent study done in Sweden, a cohort of 84 patients suffering with focal hyperhidrosis were treated with BTX injections – Xeomin®, which is BTX-A and a more novel Neurobloc® which is a BTX-B . Fifty-eight of these patients were suffering from axillary hyperhidrosis, and were treated with Xeomin®, while the rest suffered from palmar hyperhidrosis, and were treated with Xeomin® and Neurobloc®. After a 3 week follow up, all patient treated for axillary hyperhidrosis were satisfied and reported an improvement in QoL which was evaluated by a Dermatology Life Quality Index (DLQI). With regards to palmar hyperhidrosis patients, all except for 1 reported satisfactory results and improvement in QoL, with the unsatisfied patient complaining of muscle weakness.32 A very recent study used HDSS as well as and Hospital Anxiety and Depression Scale (HADS) to assess both QoL and mental health related to primary hyperhidrosis. This study also showed significant improvement in both scales 2 weeks after treatment.33 Another study delved into the social and occupational aspects of focal hyperhidrosis and how they improved after BTX therapy. It was found that 68% of patients found it difficult to meet people before they were treated and 58% of patients felt that their condition was limiting their performance at their job. Other complaints, such as having to shower twice or more daily, feeling less confident and changing leisure activities were reported. All of these were significantly reduced after treatment, with results observed within 1 week of treatment. 34

In other studies, QoL after BTX treatment was compared to that after other treatments for focal hyperhidrosis. In a study aimed to compare QoL and cost effectiveness of BTX treatment and endoscopic thoracic sympathectomy, QoL was also accessed using DLQI questionnaires. Patients were asked to fill the questionnaire before treatment and 4-6 weeks following treatment. This study showed that BTX treatment not only improved the patient’s quality of life but also proved to be a much more cost effective treatment than surgery. Study also showed that cost-equivalence is reached after about 13 years and considering Botulinum toxin treatment carries less risk, such treatment is more suitable than surgery.25 In another study, patients who were unresponsive to topical treatment with aluminium chloride for axillary hyperhidrosis were treated using Botulinum injections and followed up. After 14 weeks, it was found that 81.4% rated the treatment as excellent with a significant improvement in QoL. Most patients were satisfied and only a few (around 1.4%) chose to rate the procedure as fair, would not recommend it or didn’t respond to the questionnaire given.35

Discussion

BTX treatment has been shown to be one of the most cost effective and safe treatments for focal hyperhidrosis and has proven to improve quality of life significantly.9 It also provides long term treatment and can prove to be an ideal treatment for patients who do not wish to use anti-perspirants, oral treatments or tap water iontophoresis
repeatedly or their lifestyle doesn’t allow them to treat themselves repeatedly every day. In this review, current treatments have been analysed and compared to BTX treatment. It was shown that BTX can be used as a second line treatment for most types of focal hyperhidrosis after cheaper topical treatments have failed, without having to resort immediately to surgery or systemic drugs. It can also be used as first line for certain focal hyperhidrosis mainly Frey’s syndrome and frontal hyperhidrosis. As discussed above BTX treatment is not only cosmetic, as it also significantly improves the patient’s QoL. This highlights the importance of its availability and should therefore be offered even by governmental secondary care hospitals.

Botulinum toxin treatment is still being improved and researched. In recent studies, new serotypes of Botulinum toxin are being used and sometimes combined with the more commonly used BTX-A. A combination of Xeomin® (BTX-A) and Neurobloc® (BTX-B) used for palmar hyperhidrosis has shown that sweating reduced significantly and only one patient complained of reversible muscular weakness. This study not only showed that QoL can be improved with BTX therapy, but also that a combination of both Xeomin® and Neurobloc® can help lower the risk of muscular side-effects that occurs more often when BTX-A is used on its own. Similar results was obtained in another study in which only 12.5% had mild side effects from such treatment and significant reduction in hyperhidrosis was noted from 4 weeks post treatment.

References


The main aim of this study was to define the contemporary dietary habits of both patients with Type 2 diabetes mellitus (T2DM) and nondiabetes in Malta and to compare the results with the findings of a similar study performed in 1983 by Katona et al. The study was a cross sectional study of representative subsets of the Maltese population. A questionnaire was used to collect the data and record baseline characteristics, information about diet and exercise levels. Results showed that there were no statistically significant differences between the diets of the T2DM and nondiabetic cohorts. Compared to the 1983 data, the Maltese are eating more carbohydrates, less fat and fibre. Diabetics appear not to be changing their lifestyle habits once they are given their diagnosis. The results suggest that continuous education is needed on all aspects of a healthy lifestyle including dietary advice and should include both diabetics and non-diabetics.

Introduction

Changes in the nutritional habits of the Maltese population have increased the incidence of obesity and of chronic diseases such as T2DM. The prevalence of diabetes in Malta is about 9.9% and 26.6% of the population are obese. Over the past centuries there was a change in the type of food eaten by the Maltese. Before the nineteenth century, the Maltese had a lower standard of living. Their diet consisted of ‘barley bread, cheese, olives, garlic, dried fruit, salt-fish, oil and similar foods.’ They ate in abundance whatever was in season and ‘they drank moderate amount of wine’. Eventually, with a general improvement in standard of living the Maltese diet started to include bread, pasta and meat which previously were almost non-existent in the Maltese diet. The Maltese diet nowadays has more red meat, fried foods, refined sugars, fats and carbohydrates. Recent data from the European Health Interview Survey (EHIS) showed that 74% of the respondents consumed fruit at least once a day and 51% consumed vegetables at least once a day.

In 1981, WHO commissioned a study named National Diabetes Programme in Malta. The aim of this study was to investigate the prevalence of diabetes and diabetic complications. They included a dietary history from which the percentage contributions of different nutrients to the total calorie intake were calculated. From this study it was shown that the Maltese, particularly those working, usually had a one main meal and minor snacks during the day. Diets were rich in fat, low in fibre. Over the following thirty years there were major lifestyle changes including dietary changes,
heavy use of private cars and low amounts of physical activity.  

Aims of this study
The aim of this study was to investigate the nutritional habits of both diabetic patients and non-diabetics in Malta and to compare the findings with the findings of Katona et al in 1983.

Method
Design of study
This study was a cross sectional study of representative subsets of the Maltese population: a cohort of diabetic patients and a matched cohort for non-diabetic patients.

A questionnaire was used to assess basic participant characteristics such as height, weight, age, level of education, current job and treatment, level of physical activity and dietary history.

Sample
The sample was recruited on a voluntary and random basis. The diabetic cohort was collected from the Diabetes clinic at Mater Dei Hospital. A matched sample of normal participants, were recruited from other hospital clinics and general practice clinics across different locations in Malta. Recruitment of participants started in December 2012 and lasted 6 months.

The inclusion criteria for participants was an age between 20 to 80 years. T2DM is defined as per the WHO diagnostic criteria, of fasting plasma glucose ≥ 7.0mmol/l or 2-hour plasma glucose following an oral glucose tolerance test of ≥ 11.1mmol/l. Both previously diagnosed and newly diagnosed T2DM patients without a history of ketoacidosis were included in the project. Newly diagnosed type 2 diabetics needed to have had previous nutritional advice to be included in the cohort.

Exclusion criteria were patients who had Type 1 diabetes, coeliac disease, hypertension, hyperlipidaemia, pregnancy and any other patient on a special diet.

Both cohorts were matched for age, sex and locality.

Materials and apparatus
A questionnaire was used to assess basic participant characteristics and dietary history. This was taken in the form of a three day food diary. The nutritional data was analysed with Dietplan 6© from www.foresoft.co.uk. Results were then analysed using SPSS©.

Procedure
The questionnaire was filled in by interviewing the participant at the clinic during his or her visit or while they were waiting for their visit. The information was always collected by the same researcher who guided the participants as to portion sizes and weight of foods. These were predetermined from the pilot cohort. The estimate of amounts being ingested was calculated on standardized household measures (millilitres- ml and kilograms- kg).

Ethical issues
Ethical approval was obtained from the University of Malta Research Committee (UREC), and the University of Roehampton. All the data had to be collected within the provisions of the Data Protection Act. Informed consent was obtained from all the patients who accepted to participate in the research project.

Data analysis
The data was compiled on a Microsoft© Excel spreadsheet. Nutritional data was analysed with Dietplan 6© from www.foresoft.co.uk. From the information collected from the questionnaire, inputting the nutritional data in Dietplan 6© provided a report of the daily nutritional intake for each participant. The data collected from these reports were the total daily energy intake in kilocalories (Kcal); protein, fat and carbohydrate intake in grams (g) including sugar intake. The percentage amounts of daily intake of carbohydrates, protein, fats and alcohol were also calculated. SPSS© was then used for statistical analysis.

Means and 95% confidence intervals were calculated for baseline characteristics and also for the nutritional values of the different samples. For comparison of continuous variables between two groups, i.e. males and females and diabetics and non-diabetics, Mann-Whitney test was used. This test was used because the cohort was skewed and parametric assumptions were not met. A two-sided p value at 95% confidence interval was used for this test i.e. p value ≤ 0.05 would be significant. Nutritional values reflecting the current dietary habits of the Maltese cohort were compared with similar values from the 1983 study of Katona et al.
Results
A total of 166 patients were recruited for the analysis (Table 1). Of these 166, 75 had T2DM and 91 were nondiabetic (Table 2).

| Table 1: Baseline Characteristics of the cohort- Mean (± 95% confidence intervals) |
|---------------------------------|---------------------------------|-----------------|-----------------|-----------------|
|                                | Male and female (n=166)         | Males (n=83)    | Females (n=83)  | p value        |
| Age (years)                    | 56.92 (44.34-69.5)              | 56.75 (44-69.5) | 57.10 (44.61-69.59) | <0.01          |
| Weight (kg)                    | 78.58 (61.69-95.47)             | 87.60 (73.23-101.97) | 69.56 (55.32-124.88) | <0.01          |
| Height (cm)                    | 164.9 (156.79-173.01)           | 170.28 (164.39-176.17) | 159.51 (153.25-165.77) | <0.01          |
| BMI (kg/m^2)                   | 28.82 (23.32-34.32)             | 30.23 (25.37-35.09) | 27.41 (21.71-33.11) | <0.01          |

1Mann-Whitney test

| Table 2: Baseline characteristics according to diabetes status- Mean (± 95% confidence intervals) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | T2DM (n=75)     | Nondiabetics (n=91) | p value        |
| Age (years)                    | 59.28 (48.03-70.53) | 54.98 (41.65-68.31) | <0.01          |
| Weight (kg)                    | 83.93 (67.61-100.25) | 74.16 (58.03-90.29) | <0.01          |
| Height (cm)                    | 163.88 (156.37-171.39) | 165.74 (157.21-174.27) | 0.22          |
| BMI (kg/m^2)                   | 31.17 (25.91-36.43) | 26.89 (21.96-31.82) | <0.01          |

2Mann-Whitney test

There were statistically significant differences in weight, height and BMI between males and females (Table 1) and in weight and BMI in diabetics and nondiabetics (Table 2).

Prevalence of obesity was 43.4% (n=36) in males and 25.3% (n=21) in females while 49.3% (n=37) of the diabetic cohort were obese compared to the 22.0% (n=20) of the nondiabetic cohort.

Nutritional data showed there were significant differences between males and females in energy intake, protein, fat, carbohydrate and cholesterol intake (Table 3).

There were no statistically significant differences in the nutritional data for the diabetic and non-diabetic cohorts (Table 4).

The study performed by Katona et al 1983, presented the means and standard error of the mean (SEM) for different nutrients and from the data collected in this project, similar data was calculated and hence compared. Of note Katona et al 1983 presented data for the whole population of Malta. Table 5 and 6 show the 1983 data and the data from this cohort.

As can be seen from Table 5, the percentage protein intake is similar, percentage fat intake has decreased and percentage carbohydrate intake has increased. These changes were noted both in the male and female cohorts. From Table 6, it can be seen that the mean total daily energy intake is much lower in the current cohort compared to the 1983 cohort. This is reflected in all the mean daily macro-nutrient intake especially fat and cholesterol intake. There was a major decrease in dietary fibre intake for both males and females in the current cohort compared to the 1983 cohort.
**Table 3:** Baseline Nutritional values of the cohort - Mean (95% confidence intervals)

<table>
<thead>
<tr>
<th></th>
<th>Male and female</th>
<th>Males</th>
<th>Females</th>
<th>p value&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Energy (kcal/day)</strong></td>
<td>1708.27 (1249.04-2167.50)</td>
<td>1905.85 (1390.15-2421.55)</td>
<td>1510.68 (1481.93-1539.43)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Protein (g/day)</strong></td>
<td>71.35 (52.41-90.29)</td>
<td>78.51 (58.36-98.66)</td>
<td>64.19 (49.63-78.75)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Fat (g/day)</strong></td>
<td>63.70 (33.76-93.64)</td>
<td>74.99 (39.48-110.50)</td>
<td>52.40 (35.51-69.29)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Carbohydrate (g/day)</strong></td>
<td>213.41 (160.96-265.86)</td>
<td>227.50 (172.44-282.56)</td>
<td>199.32 (153.48-245.16)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Sugar (g/day)</strong></td>
<td>87.34 (51.73-122.95)</td>
<td>89.55 (52.58-126.52)</td>
<td>85.15 (50.88-119.42)</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Cholesterol (mg/day)</strong></td>
<td>184.04 (25.65-343.43)</td>
<td>222.55 (19.41-425.69)</td>
<td>145.53 (66.68-224.38)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Fibre (g/day)</strong></td>
<td>18.19 (11.86-24.52)</td>
<td>18.05 (11.01-25.09)</td>
<td>18.33 (12.75-23.91)</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>Poly/Sat fat ratio</strong></td>
<td>0.62 (0.32-0.92)</td>
<td>0.6 (0.29-0.91)</td>
<td>0.63 (0.34-0.92)</td>
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</tr>
</tbody>
</table>

<sup>3</sup>Mann-Whitney test

**Table 4:** Baseline Nutritional values for patients with T2DM and nondiabetics Mean (± 95% confidence intervals)

<table>
<thead>
<tr>
<th></th>
<th>T2DM</th>
<th>Nondiabetics</th>
<th>p value&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Energy (kcal/day)</strong></td>
<td>1723.82 (1248.14-2199.50)</td>
<td>1695.45 (1247.98-2142.92)</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Protein (g/day)</strong></td>
<td>71.84 (55.03-88.65)</td>
<td>70.95 (50.34-91.56)</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Fat (g/day)</strong></td>
<td>65.69 (36.82-94.56)</td>
<td>62.06 (31.19-92.93)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Carbohydrate (g/day)</strong></td>
<td>211.57 (156.92-266.22)</td>
<td>214.93 (164.11-265.75)</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Sugar (g/day)</strong></td>
<td>83.90 (45.35-122.45)</td>
<td>90.17 (57.23-123.11)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Cholesterol (mg/day)</strong></td>
<td>178.43 (92.26-264.60)</td>
<td>188.66 (-10.95-388.27)</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>Fibre (g/day)</strong></td>
<td>19.10 (12.87-25.51)</td>
<td>17.44 (11.17-23.71)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Poly/Sat fat ratio</strong></td>
<td>0.66 (0.32-1.00)</td>
<td>0.58 (0.31-0.85)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

<sup>4</sup>Mann-Whitney test
**Table 5:** Food intake as percentage of total energy- Mean ± SEM

<table>
<thead>
<tr>
<th></th>
<th>1983 data</th>
<th>Current cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td><strong>Protein percentage intake</strong></td>
<td>16.5 ± 2.5</td>
<td>16.5 ± 6.0</td>
</tr>
<tr>
<td><strong>Fat percentage intake</strong></td>
<td>41.5 ± 7.3</td>
<td>45.5 ± 8.0</td>
</tr>
<tr>
<td><strong>Carbohydrate percentage intake</strong></td>
<td>41.9 ± 7.8</td>
<td>38.0 ± 8.5</td>
</tr>
</tbody>
</table>

\(^5\)Katona et al, 1983

**Table 6:** Daily food intakes- Mean ± SEM

<table>
<thead>
<tr>
<th></th>
<th>1983 data</th>
<th>Current cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td><strong>Energy (kcal)</strong></td>
<td>3472 ± 1119</td>
<td>2785 ± 757</td>
</tr>
<tr>
<td><strong>Protein (g)</strong></td>
<td>139 ± 44</td>
<td>122 ± 28</td>
</tr>
<tr>
<td><strong>Total fat (g)</strong></td>
<td>156 ± 56</td>
<td>145 ± 53</td>
</tr>
<tr>
<td><strong>Carbohydrate (g)</strong></td>
<td>359 ± 136</td>
<td>267 ± 87</td>
</tr>
<tr>
<td><strong>Sugar (g)</strong></td>
<td>126 ± 73</td>
<td>108 ± 62</td>
</tr>
<tr>
<td><strong>Dietary cholesterol (g)</strong></td>
<td>1207 ± 494</td>
<td>1143 ± 656</td>
</tr>
<tr>
<td><strong>Dietary fibre (g)</strong></td>
<td>31.5 ± 11.8</td>
<td>25.6 ±9.0</td>
</tr>
</tbody>
</table>

\(^6\)Katona et al, 1983

**Discussion**

The aim of this study was to define the current diet of the Maltese population in particular the dietary habits of people suffering from T2DM and compare it with the 1983 data.

Significant differences between males and females were noted in weight, height and BMI. Males had a significantly higher BMI. T2DM patients weighed more and had a higher BMI than nondiabetics and this was a statistically significant difference with a \(p\) value < 0.01. The prevalence of obesity in the diabetic cohort was 49% compared to a 21% in the non-diabetic cohort. This means that T2DM in the Maltese population is strongly related to a higher BMI. Increased weight and obesity are associated with the metabolic syndrome and this in itself predisposes to an increased risk of T2DM.\(^7\)

Therefore lifestyle advice especially on weight loss and physical activity should be the primary focus especially in the newly diagnosed. Lifestyle advice should be given in a structured manner. A number of studies on lifestyle interventions have been published and all emphasize the importance of knowledge.\(^8\)-\(^9\)

This study showed that patients are not changing their diets after being given the diagnosis of T2DM. There seems to be a general difficulty in changing lifestyle habits when it comes to increasing exercise and eating healthier foods. Since these lifestyle habits are dependent on complex factors like socioeconomic status and attitudes determined by culture they are very difficult to change. It would be easier to instil healthier attitudes among children who will hopefully grow up to be healthier adults. There are multiple studies of interventions in schoolchildren\(^10\)-\(^11\), however
very little or no data about long term benefits.

**Comparison with the 1983 data- did the Maltese diet change over a 20 year period?**

From the current cohort, the percentage protein intake was noted to be similar, the percentage fat intake has decreased and percentage carbohydrate intake has increased. The mean total daily energy intake is much lower in the current cohort compared to the 1983 cohort.

Fat intake has decreased markedly. Katona et al in 1983 had commented about the extremely high fat intake in the Maltese population at the time. The levels have markedly decreased in males but more exponentially in females. The values for mean daily fat percentage intake are 41.5% for males which decreased to 33.85%, and 45.5% for females which decreased to 30.34%. Dietary cholesterol was also much higher in the 1983 cohort. This probably reflects a change in lifestyle habits and the Maltese are ingesting less saturated animal fats than they used to.

Total carbohydrate intake has increased considerably when compared to the intake in the 1980’s. Possibly this has happened because carbohydrates are now replacing the extra fat that the Maltese used to ingest at the time. Paradoxically the amount of simple sugars has decreased when compared to the 1983 data. This means that the carbohydrate intake of the Maltese today is mostly made up of complex carbohydrates as opposed to 20 years ago. Even though the types of food have not been looked into specifically, from simple observation we believe the most popular forms of carbohydrate now eaten in Malta are bread and pasta.

There was a major decrease in dietary fibre intake for both males and females in the current cohort as compared to the 1983 cohort. As previously mentioned this may show that the Maltese are eating less fruit and vegetables. There is a concomitant increase in carbohydrate intake and this suggests that fibre rich foods are being replaced by carbohydrates.

**Limiting factors**

The sample size was relatively small and this was limited by human resources and time. Data collection was a very long process in itself. There were also logistic problems.

All the participants were recruited through clinics inside the main government hospital and through general practice clinics. The majority were collected from hospital clinics. The whole cohort was a convenience sample and therefore it may not represent a normal distribution.

The figures quoted for the dietary intake levels obtained from the questionnaires may be an underestimate of some of the nutrients in the diet because patients were not exhaustive in their descriptions. This is a recognised problem with dietary histories and the reasons may be very varied. Knowledge of health and diet, perceived body image and perceived reasons of the study are among the possible reasons.

Another problem that arose during analysis was that the program used for the analysis, Dietplan 6, was not exhaustive in the list of foodstuffs which are typical of the area. Therefore adjustments were made by replacing some foodstuffs with other similar ones found on the program like for example capers were replaced with green olives.

**Conclusion**

Previous to this study, very little data had been collected about the nutritional habits of the Maltese population.

From the results one can note that the prevalence of obesity in the T2DM cohort was 49%, on average double that in the normal population which is 21%. Diabetics appear not to be changing their diets once they are given their diagnosis. Compared to the 1983 data, the Maltese seem to be eating more carbohydrates, less fat and fibre.

These results show that education is needed regarding all aspects of a healthy lifestyle including dietary advice. Lifestyle changes need to become a priority to achieve better outcomes and hence quality of life.

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A retrospective study on the Maltese population of the outcome of retinal detachment repair after the removal of silicone oil

Matthew T. Fenech, Thomas Fenech, James G. Diamond

Abstract

Background: Silicone oils of different viscosities are used in the treatment of retinal detachments of varying pathology.

Method: Seventy-two cases of retinal detachments managed with silicone oil were reviewed in a retrospective chart analyses. Eighty nine patients were reviewed from which data on primary pathology, type of silicone oil, duration of oil “in situ” and complications (including emulsification, increased intraocular pressure (IOP), re-detachment, cataract and presence of CME) were compiled. Of this number, 72 patients with post-operative follow-up of two years or more and documentation of the above parameters were included. The data was carefully analysed in an effort to determine the primary factor or factors of the varying silicone oil substitutes utilized responsible for the successful or non-successful re-attachment of the retina.

Results: Retinal re-detachment rate is greater when Silicone Oil (SO) is removed before 12 months. Complex vs non-complex retinal re-detachments in sub-group analysis indicates superiority of retention of SO for greater than 12 months. Emulsification is greater in low viscosity SO (1300cts).

Conclusion: The complication rates witnessed in this retrospective study are comparable to the findings of published studies present in the ophthalmic literature on an international scale. The findings of this study support the hypothesis that it is the duration of the SO “in situ” as opposed to the viscosity or other SO attributes which ultimately influences the re-detachment rate.

Keywords
Silicone Oil, Retinal Detachment, Emulsification, Intra-ocular pressure, Re-detachment

Introduction

Retinal detachment is the separation of the neurosensory retina from the underlying retinal pigment epithelium (RPE). Retinal detachment repair was first described in 1920 by Gonin, and has since undergone several advancements.1 The ultimate success of re-attachment is dependent on sealing any breaks in the retina and ensuring there is no longer any traction between the vitreous and retina itself. Uncomplicated rhegmatogenous retinal detachments may be treated through a number of modalities, the likes of which include pneumatic retinopexy, scleral buckling and pars plana vitrectomy.2,3 Advancements in vitrectomy techniques coupled with the introduction of silicone oil have allowed for the treatment of more complicated retinal reattachments, resulting in higher success rates and lower rates of re-detachment.

Introductions of heavy silicone oil (HSO),

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namely Densiron 68, has allowed for the management of inferior tears and recurrent re-detachments due to its physical properties, allowing it to tamponade lower tears due to its greater specific gravity when compared to water.\textsuperscript{4-5} It is the purpose of this study to determine the complications associated with retinal detachment repair managed with silicone oil at Mater Dei Hospital, Malta, Europe, when compared to the results of similar studies on an international level. We also aim to demonstrate our hypothesis that it is the duration of silicone oil “in situ” rather than the viscosity or other attributes of silicone oil which ultimately influences the rate of re-detachment.

Materials and Methods
SO with viscosities of Oxane1300cts, Oxane5000cts, Oxane5700cts and Densiron 68 (Heavy Silicone Oil (HSO)) were utilised as a vitreous substitute in 89 cases of retinal detachment. Seventeen patients were excluded because of lack of comparative data.

Seventy-two (72) cases of retinal detachments were used for the purpose of this study. Twenty-six patients fell into the rhegmatogenous retinal detachments (RRD) group, while the diabetic tractional retinal detachments (DTRD) and complex retinal detachments (CRD) groups included nineteen and twenty-seven patients respectively. Patients suffering from multiple retinal tears, proliferative vitreoretinopathy and large inferior retinal tears were included within the CRD group.

The study was approved by the appropriate patient safety and ethics approval boards. Strict inclusion and exclusion criteria were established. The surgical register at Mater Dei Hospital Malta was used as the source of all the data for surgical patients undergoing retinal detachment repair. Data of procedures performed by the same consultant vitreoretinal surgeon between the years 2007 and 2013 was used. Eighty nine (89) patients were reviewed from which data on primary pathology, type of SO, duration of oil “in situ” and complications (including emulsification, increased intraocular pressure (IOP), re-detachment, cataract and presence of CME) were compiled. Of this number, seventy two (72) patients with post operative follow-up of two years or more and documentation of the above parameters were included in this study.

Patients in which 5000cts and 5700cts SO was used were grouped together in view of the fact that the structural make up was essentially identical (Table 1).

The data was carefully analysed in an effort to determine the primary factor or factors responsible for the successful or non-successful re-attachment of the retina.

\begin{table}[h]
\centering
\caption{Representation of the various silicone oils used and their individual properties}
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{Properties of Silicone Oils} & \textbf{Oil} & \textbf{Density (g/cm$^3$)} & \textbf{Viscosity (mPa.s)} & \textbf{Surface Tension (mN-m)} & \textbf{Refractive Index} \\
\hline
Oxane1300 & 0.98 & 1000 & 44.9 & 1.4 \\
Oxane5000 & 0.975 & 5000 & 43.01 & 1.4035 \\
Oxane5700 & 0.98 & 5000 & 44.9 & 1.4 \\
Densiron 68 - HSO & 1.06 & 1500 & 40.82 & 1.387 \\
\hline
\end{tabular}
\end{table}

Results
Retinal re-detachment rate is greater when SO is removed before 12 months (Table 2). The overall re-detachment rate in this series was 26.4\%. SO “in situ” for 12 months or less resulted in a re-detachment rate of 18.1\% and a re-detachment rate of 8.3\% for all cases where SO was present for greater than 12 months (Table 2). Of the complex cases, 61.5\% re-detached when SO was left “in situ” for less than 12 months and 38.5\% re-detached when SO was “in situ” for greater than 12 months (Table 3). Of the non-complex cases, 83.3\% re-detached on removal of SO at less than 12 months and 16.7\% re-detached when SO was retained for longer than 12 months (Table 3).

Complex vs non-complex retinal re-
detachments in sub-group analysis indicated the superiority of retention of SO for greater than 12 months (Table 3). Complex cases making use of 1300cts SO had a re-detachment rate of 15.4% when kept “in situ” for less than 12 months compared to a re-detachment rate 7.7% when retained for longer than 12 months (Table 3). 5000/5700 and Heavy SO however had a re-detachment rate of 46.2% when retained for less than 12 months and 30.8% when longer than 12 months (Table 3). Furthermore, separation into presence or absence of PVR supports the recognised poor success rate of re-attachment in cases of severe PVR (Tables 4).

Table 2: Representation of the various silicone oils used, their re-detachment rates and the time in situ.

<table>
<thead>
<tr>
<th>Silicone Oil</th>
<th>#Pts</th>
<th>Duration of Oil in Situ</th>
<th>&lt;12Mo</th>
<th>&gt;12Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1300 cts</td>
<td>34</td>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5000/5700 cts</td>
<td>31</td>
<td></td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Densiron 58 - HSO</td>
<td>7</td>
<td></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>72</strong></td>
<td></td>
<td><strong>13</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>

**Total Percent** 18.1 8.3

Table 3: Sub-analyses of the re-detachment rate of complex and non-complex cases per silicone oil used separated in a period of < or > 12. This shows a greater rate of detachments in the period less than 12 months irrespective of whether the detachment was complex or non-complex.

<table>
<thead>
<tr>
<th>Silicone Oil</th>
<th>Complex RD</th>
<th>Non-Complex RD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;12Mo</td>
<td>&gt;12Mo</td>
</tr>
<tr>
<td>1300 cts</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5000/5700 cts</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Densiron 58 - HSO</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Sub-total</strong></td>
<td><strong>8</strong></td>
<td><strong>5</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>13</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total Percent</strong></td>
<td><strong>61.5</strong></td>
<td><strong>38.5</strong></td>
</tr>
</tbody>
</table>
Table 4: Sub-group analyses showing presence of PVR primary cause for decreased detachment rate in complex group

<table>
<thead>
<tr>
<th>Complex RD +/- PVR</th>
<th>Pathology</th>
<th>Silicone Oil</th>
<th>#Pts</th>
<th>% Attached</th>
<th>% Detached</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complex RD +PVR</td>
<td>1300</td>
<td>9</td>
<td>4</td>
<td>69.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50/57</td>
<td>5</td>
<td>6</td>
<td>45.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heavy</td>
<td>2</td>
<td>1</td>
<td>66.7</td>
</tr>
<tr>
<td></td>
<td>Group Total</td>
<td></td>
<td>16</td>
<td>11</td>
<td>59.3</td>
</tr>
<tr>
<td></td>
<td>Complex RD - PVR</td>
<td>1300</td>
<td>9</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50/57</td>
<td>5</td>
<td>2</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heavy</td>
<td>2</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Group Total</td>
<td></td>
<td>16</td>
<td>3</td>
<td>84.2</td>
</tr>
</tbody>
</table>

Total emulsification rate in the series was 18.1%. Emulsification is greater with low viscosity SO (1300cts) resulting in minimal consequences. 1300cts SO retained for less than 12 months accounted for 15.4% of emulsification cases and 53.8% of cases if retained for longer than 12 months. 5000/5700 and Heavy SO accounted for 7.7% of emulsification cases when retained for less than 12 months and 23.1% when retained for longer than 12 months.

Total increased IOP rate in the series was 30.6%. Increased IOP is greater with 5000/5700 cts Silicone oil as opposed to 1300cts. 1300cts accounted for 36.4% of cases of increased IOP when retained for less than 12 months and 4.6% when “in situ” for longer than 12 months. 5000/5700 and Heavy SO “in situ” accounted for 18.1% of increased IOP cases when retained for less than 12 months and 40.9% when retained for longer than 12.

Discussion

Silicone oil is a non-expansible clear fluid, commonly used in the treatment of retinal detachment, providing a safe, inert medium to provide endotamponade. Silicone oil has served as a vitreous substitute for many years. Numerous studies have been performed to identify the beneficial effects of silicone oil tamponade whilst also establishing the chemical and physiological properties which may be applied to different clinical scenarios.

Silicone oil management is not without complications. One of the most commonly seen complications with the use of silicone oil is emulsification. Emulsification rates usually vary from anything between 17.2% - 38.4% from the literature reviewed, occurring in 18.1% of patients within our series. Emulsification may occur between 5 months to anything up to 24 months, usually occurring within the 1st year or so.

Emulsification in itself is clinically significant because of the structural and physiological implications it has on the functioning of the eye. Emulsification refers to the inability of small bubbles to coalesce into larger bubbles after dispersion from the main silicone oil body has occurred. Such a phenomenon results from the alteration in oil surface tension, changes in oil viscosity as well as prolonged duration of said oil “in situ.” Intrinsic surfactants such as fibrin, fibrinogen and serum, resulting from intra-ocular manipulation, cause a decrease in surface tension, resulting in increased droplet dispersion and ultimately increased emulsification. Several studies have also shown that less viscous silicone oils emulsify faster than oils with greater viscosities. Our series demonstrates that the highest rate of silicone oil emulsification was also seen in the 1300cts group, comprising 69.1% of all cases of emulsification.

When selecting silicone oil, one must balance the benefits of prolonged tamponade with the risks posed by emulsification of the oil itself. While low
Increased by 13% it may hence be argued before 12 months. It is the duration of new retinal breaks and the likelihood of re-attachment of the use of SO is the fluctuation of IOP, no statistical difference was seen with greater viscosity are more likely to result in emulsification, which is why they are more commonly used in cases of complex retinal detachment.

Although surface tension and viscosity influence the rate of emulsification, it is the duration of silicone oil “in situ” which has the strongest influence on the occurrence of emulsification. Emulsification may occur between 5 months to anything up to 24 months, usually occurring within the 1st year or so. Results from our series reveal that 23.1% of all cases of emulsification occurred before 12 months of SO “in situ”, while 76.9% of cases occurred when SO was retained for greater than 12 months. That being said, it should be noted that silicone oils of various viscosities have similar tamponading effects as long as emulsification of the oil has not taken place.

From conclusions made in our study, the rate of re-detachments is significantly increased if silicone oil is removed before 12 months. Unfortunately, most surgeons insist on retaining SO for no longer than 12 months, in an attempt to reduce complications associated with SO “in situ”, one of which includes emulsification. Another commonly faced complication associated with the use of SO is the fluctuation of intra-ocular pressure (IOP). IOP was increased in 30.6% of all patients within this series with 54.5% of cases being in patients where SO was retained for less than 12 months and 45.5% of cases where SO was “in situ” for greater than 12 months. Our values are greater than average values in other studies, which range from 1.5% to 27.7%. Although SO with greater viscosity are more likely to result in increases in IOP, no statistical difference was seen with the patients in our series.

The benefits of silicone oil extraction must be outweighed by the risk of retinal re-detachment. The results of this study regarding the similarity of various SO viscosities in retinal re-attachment rates are comparable to the findings of published studies present in the ophthalmic literature on an international scale. The overall re-detachment rate in our series was that of 26.4%, comparable to a similar study by Soheilein et. al, quoting a re-detachment rate of 28%. That being said, retinal re-detachment rates are quoted in the literature to lye anywhere between 9% and 34%, with such discrepancies being due to the number of patients studied or the underlying disease.

The findings of this limited retrospective study support the hypothesis that it is the duration of the SO “in situ” as opposed to the viscosity or other SO attributes which influences the re-detachment rate. Our findings support that a minimum period of 12 months for SO retention “in situ” is associated with a higher rate of re-attachment. In a similar study by Falkner et. al, it was felt that after a period of 3-6 months, the chances of retinal re-detachment after silicone oil removal were minimal. While this may hold some ground, our findings push us to postulate that a period 12 months or more reduce the rates of re-detachment significantly.

It is interesting to note that whilst most studies in the literature have shown no real difference between the tamponading effects of silicone oils of varying viscosities, our limited study highlights a significantly higher re-detachment rate in the 5000cts silicone oil when compared to other viscosities used. Also of note is that complex retinal re-detachment case success is similar to other categories when PVR is excluded (Table 4). Comparable results were also obtained by Mazareei et. al, where higher rates of re-detachments were found in the rhegmatogenous retinal detachment group with PVR treated with 5000cts silicone oil. Such findings suggest that the higher re-detachment rate in the 5000cts group was not due to the viscosity of the oil itself, but due to the underlying complex pathology for which 5000cts oil is used, where residual traction and re-development of proliferative vitreoretinopathy could have led to reopening or formation of new retinal breaks and the ultimate re-detachment.

The ultimate goal for all retinal surgeons is to establish a stable, re-attached retina, free from any risk factors that may promote its re-detachment. Whilst the possibility of this may be increased by silicone oil with greater viscosity, this must be balanced by the greater risk of failure within that
sub group.

Acknowledgements
This paper is done in conjunction with the University of Malta Medical School, Malta Europe, Tulane University Medical School and Department of Ophthalmology New Orleans, LA and the Veterans Administration Hospital New Orleans, LA.

References
Abstract
Folate is essential for normal cell division and as intrauterine fetal growth involves a process of rapidly dividing cells, there is a consequent increased requirement for folate at this time. Folate, and the synthetic form folic acid, is thus vital for the early development process of a healthy fetus and there is indisputable evidence that it can significantly reduce the risk of neural tube defects (NTDs). Further ongoing research suggests that folic acid supplementation in pregnancy is also associated with a decreased risk of other birth defects. This review gives an overview of the current literature related to the use of folic acid in the peri-conceptional period and prevention of birth defects, in particular NTDs.

Keywords
folic acid, neural tube defects, birth defects.

Introduction
It has long been acknowledged that “a healthy start in life must be a top priority for any society” (WHO, 1998 p.21). Achieving optimal maternal and infant health is an important goal for all health care systems and is emphasized in the WHO Millennium Development Goals. Today, congenital anomalies are among the major causes of perinatal and infant mortality and morbidity in developed countries. It is known that avoidance of certain environmental exposures, adequate nutrition, folate and other vitamin intake, cessation of smoking and alcohol consumption, prevention and control of maternal infection and disease are among the interventions that may avoid congenital anomalies. Nevertheless, many fetuses still suffer from potentially avoidable birth defects and this is an important area where public health initiatives and interventions can be effective in the primary prevention of congenital anomalies.

This review outlines the current knowledge related to the use of folic acid in the prevention of severe birth defects.

Folate and folic acid
Folate is one of the water-soluble B vitamins; Folic Acid (FA) is the synthetic form of this vitamin and is only minimally different from folate. FA has the advantage of being better absorbed by the body and having a much higher bioavailability than naturally occurring folate.

Being water soluble, folate is easily excreted by the body and is not stored, such that an adequate daily intake is necessary to maintain the required blood levels of this vitamin. The National Institute of Health – Office of Dietary Supplements in the UK gives the daily recommended dietary allowance (RDA) of folate for an adult male or female as 400 micrograms, this requirement increases to 600 micrograms of dietary folate in pregnancy. Folate is found naturally in several

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foods including liver, yeast, leafy green vegetables, such as spinach, various fruits including oranges, eggs and beans.\textsuperscript{6}

Folate is known to be important for the formation of red and white blood cells, proper development of the fetus and the formation of nucleic acids in DNA (deoxyribonucleic acid) and RNA (ribonucleic acid).\textsuperscript{5} Folates also play an important role in homocysteine metabolism, with folate having a homocysteine lowering effect.\textsuperscript{7}

Adequate blood folate levels have been documented to be associated with several beneficial health effects; however, the most notable are the health benefits associated with maternal and fetal health.\textsuperscript{8}

**Folate and maternal, fetal and perinatal health**

Low maternal blood folate levels have long been implicated in increased risk of megaloblastic anaemia necessitating treatment with FA.\textsuperscript{9} More recently, low folate levels have been associated with low birth weight,\textsuperscript{10} the effect believed to be mediated through plasma homocysteine metabolism, with folate acting to decrease harmfully high homocysteine levels.\textsuperscript{11} Low birth weight is associated with poor perinatal outcomes including higher mortality and morbidity as well as long term motor and cognitive disorders\textsuperscript{12} and increased risks of cardiovascular and metabolic disease later on in the infant’s life.\textsuperscript{13}

Bergen et al. (2012)\textsuperscript{11} showed that “women with high homocysteine and low folate concentrations have lighter placentas and lower birth weight by 110 and 124g, respectively” (p.748). These are significant findings as “these estimates are of similar magnitude to, for example, smoking, which is a well-established risk factor for impaired fetal growth” (p.748).

Other adverse pregnancy outcomes that have been associated with low maternal folate include prematurity, pre-eclampsia and spontaneous pregnancy loss,\textsuperscript{14} however these associations have not been confirmed.\textsuperscript{15}

Inadequate maternal blood folate levels have also recently been associated with poorer infant neurodevelopment including language delay,\textsuperscript{16} impaired attention function and autism.\textsuperscript{17} The results of these studies are, however, conflicting and inconclusive and further research to determine the exact association, if any, is required.

The most significant and widely researched associations of low maternal folate levels have been with the occurrence of certain birth defects namely neural tube defects (NTDs).

**Folic acid and neural tube defects**

NTDs are major birth defects resulting from inappropriate development of the neurological system in early embryonic growth (Fig. 1) and occur with a prevalence of around 1 in 1,000 births in Europe.\textsuperscript{18} The major NTDs encountered are anencephaly and spina bifida, which occur when the neural tube fails to close. These defects are associated with severe morbidity and mortality, causing distress to both the individual and his family and presenting a significant burden to public health.\textsuperscript{19}

**Figure 1: Embryonic development and spina bifida**

Obladen (2011),\textsuperscript{20} in his paper titled ‘Cats, Frogs and Snakes: Early Concepts of Neural Tube Defects’, describes the colourful history of the various beliefs regarding the causation of these defects. He describes how in the past these infants were considered as ‘human monsters’. In the 16th century such defects were attributed to “imagination, God’s glory, God’s wrath and demons and devils” (p.1454); in the 18th and 19th centuries the predominant belief was that these defects resulted primarily from the mother’s...
imagination and experiences during pregnancy. However, in spite of this generally held idea, some eminent scientists of the time did doubt that imagination would impinge so significantly on the formation of the infant.\textsuperscript{20} It was only in the late 18\textsuperscript{th} and early 19\textsuperscript{th} century that the embryogenetic formation and closure of the neural tube was described.\textsuperscript{21} In the 20\textsuperscript{th} century, several epidemiological studies observed regional and socioeconomic differences in the prevalence of NTDs, implicating the role of environmental factors in the causation of NTDs.\textsuperscript{22} It was not until 1965 that folate deficiency was associated with the occurrence of NTDs.\textsuperscript{23} Current understanding is that NTDs are associated with folate deficiency and disturbed methylenetetrahydrofolate reductase (MTHFR) metabolism.\textsuperscript{24} However, as Blom et al. (2006)\textsuperscript{25} describe, “the case is far from closed” (p.724) and further research into the causation of NTDs is ongoing.

Evidence of a possible relationship between defective folate metabolism in the mother and embryopathy was first raised in the mid-1960s\textsuperscript{23} and the possible role of blood folate deficiency in the occurrence of NTDs was described by Smithells et al. in 1976.\textsuperscript{36} In 1981, Smithells et al.\textsuperscript{27} published the results of a multicentre, case-control study in which women who had previously given birth to an infant with NTD and were planning to become pregnant again were offered a multivitamin containing, amongst others, 360ug of FA. These women were advised to take the multivitamin at least 28 days prior to conception. Results of this study showed a 4\% recurrence rate of infants with NTDs in those women who had no vitamin supplementation as opposed to a 0.4\% recurrence in those women who had vitamin supplementation. The authors concluded that “the most likely explanation is that supplementation has prevented some neural tube defects” (p.911).

Further corroborating these findings, Laurence et al. (1981)\textsuperscript{28} report on a double-blind randomised controlled trial conducted in Wales, which engaged 111 women who had had a previous child with NTD. In this study, it was not a multi-vitamin, but specifically FA that was given to these women. Sixty women were advised to take 4mg of folic acid daily before and during early pregnancy (of these 44 complied while 16 defaulted) and 51 women were given a placebo. The researchers reported that there were no recurrences in those mothers who had complied with treatment (n=44), 2 recurrences in mothers who had not complied (12.5\%, n=16) and 4 recurrences in those women taking a placebo (7.8\%, n=51); these findings were significant, \(p=0.04\).\textsuperscript{28} These studies were followed by a number of others demonstrating the prevention of recurrence of NTDs using FA supplementation.\textsuperscript{29-30}

In July 1983, the Medical Research Council Vitamin Study Research Group\textsuperscript{31} launched a large randomised double-blind prevention trial involving 33 centres from 7 different countries to determine whether peri-conceptional supplementation (before and until 12 weeks of pregnancy) with FA and/or other vitamins could prevent recurrence of NTDs in women with a history of NTD infants. Results of this landmark trial were published in The Lancet in July 1991. This trial clearly showed that FA had “a 72\% protective effect” (p.131) for recurrence in those women who had had a previous infant with NTD.\textsuperscript{31}

In 1992, Czeizel and Dudas\textsuperscript{32} carried out a double blind randomised controlled trial in women planning a pregnancy and not having a history of an infant with NTD. The women were randomised to either having a multivitamin supplement (containing, amongst others, 800ug of FA) or a mineral-only supplement starting at least one month before the intended conception. Pregnancy outcomes of the two study groups were evaluated and a significantly lower rate of NTDs was encountered in the group taking multivitamins. None of the 2,394 mothers taking multivitamins including FA had a baby with NTD whereas 6 of the 2,310 mothers taking minerals without multivitamins had a baby with NTD whereas 6 of the 2,310 mothers taking minerals without multivitamins had a baby with NTD whereas 6 of the 2,310 mothers taking minerals without multivitamins had a baby with NTD, with \(p=0.029\).\textsuperscript{32} In this milestone study, the authors concluded that “peri-conceptional vitamin supplementation reduced the incidence of a first occurrence of neural tube defects” (p.1834).

Following these breakthrough findings in the 1980s and early 1990s, a large number of studies further establishing the protective role of FA in preventing NTDs, have been published.\textsuperscript{33-35} Berry et al. (1999),\textsuperscript{36} carrying out community-based intervention studies in two regions of China, demonstrated that daily supplementation with 400ug of FA alone could prevent these defects both in areas of high incidence as well as in areas with low incidence of NTDs. The reduction being more marked in the areas of high incidence.

Three Cochrane Systematic Reviews with
Review Article

meta-analyses examining the relationship between FA and NTDs have been carried out by De-Regil et al. in 2010, Lumley et al. in 2011, and De-Regil et al. in 2015, all concluding that periconceptional FA has a protective effect against NTDs.

In summary, research has convincingly shown that periconceptional FA intake (from at least one month before conception to 12 weeks of pregnancy) can decrease the rate of NTDs by 50% for the first occurrence and up to 70% for recurrence if taken at the correct time, giving good scope for action to actively prevent these defects.

To obtain maximum benefits the optimal time of taking FA to avoid preventable NTDs is to start supplementation at least one month before conception until at least one month after as the development of the neural tube occurs early in embryological development. The dose of periconceptional FA advised for women to reach the required blood folate status is 400ug daily in women with the lowest risk of NTDs and 4mg daily in high-risk women with a history of NTDs or women with certain chronic disease, including epilepsy treated with anti-epileptic drugs. Recent research also shows benefits of folic acid supplementation for the male partner with a personal history of NTDs.

Folic acid and other birth defects

Ever since the protective influence of periconceptional FA supplementation on the occurrence of NTDs was described, interest in possible associations between maternal FA supplementation and the occurrence of other birth defects has grown. In an extensive systematic review of studies investigating associations between multivitamins containing FA and various birth defects, Botto et al. (2004) found that periconceptional multivitamin use was associated with an over all decreased risk of congenital anomalies which was not due solely to the decrease in NTDs. There is evidence that FA may decrease the occurrence of congenital heart defects. A European registry-based case-control study by Van Beynum et al. in 2010 analysing birth defects in the Northern Netherlands over a 10-year period (1996 to 2005) showed a decreased risk of all types of congenital heart disease with periconceptional FA use. The authors conclude that FA may decrease the prevalence of congenital heart disease by approximately 20%.

There is emerging evidence of a protective role of FA in the prevention of orofacial clefts and abdominal wall defects namely gastroschisis and omphalocele. However, these claims have not been conclusively confirmed and remain debatable.

Conclusion

Evidence for the protective function of FA in the prevention of NTDs, when taken prior to conception and throughout the first trimester of pregnancy, is indisputable. Research showing protection against other birth defects including congenital heart, orofacial clefts and abdominal wall defects is less so, rendering definitive conclusions at this time premature.

Maximising the intake of folic acid in the peri-conceptional period is truly an area where public health action can concretely contribute to the decrease of severe, disabling and potentially lethal NTDs.

References


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Leiomyosarcoma of the Distal Ureter: a Case Report

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Abstract
Leiomyosarcoma of the genitourinary tract is a rare malignancy generally having a poor prognosis, with scarce literature having been published. This case report outlines the clinical progression of a 43-year-old that presented with macroscopic haematuria and was subsequently diagnosed with leiomyosarcoma of the distal ureter.

Keywords
Leiomyosarcoma, ureter, haematuria

Introduction
Leiomyosarcoma of the ureter is an uncommon urological malignancy which is as yet rather poorly understood, with consequent scant coverage in current literature. This malignancy has been always associated with a poor prognosis, although 5-year survival rates have improved over the years. The following describes a ureteric leiomyosarcoma in a 43-year-old woman.

The patient is a 43-year-old lady with no previous medical history who presented to the emergency department with a one-month history of loin to groin pain radiating to the back and over 10 episodes of haematuria with clots in the previous two months. An ultrasound of the urinary tract showed severe hydronephrosis of the left kidney with a hydroureter that could be followed down to the bladder. This was followed up by a non-contrast CT scan that identified a well-defined, lobulated soft tissue mass at the left vesicoureteric junction that was causing the ureteric obstruction (Figure 1).

Figure 1: well-defined, lobulated soft tissue mass at the left vesicoureteric junction.

At cystoscopy, a soft tissue mass originating from the left distal ureter and involving the bladder wall in the vicinity of the ureteric orifice was resected and the left ureter was stented with a double J stent. An initial diagnosis of high grade urothelial carcinoma involving the muscle wall (pT2G3 WHO classification 1973) was made on histological examination of the resected tissue. A positron emission tomography scan using fludeoxyglucose tracer did not show any regional or distant metastases. Because of the exceedingly rare incidence of these tumours, a specific staging system for sarcomas of the ureter does not exist and the TNM staging for transitional cell carcinoma of the ureter is used as published by the American
Joint Committee on Cancer in 2009. Clinical staging of our patient using this system would be T2N0M0 at presentation.

After discussion at a multi-disciplinary meeting it was decided to proceed to open left nephroureterectomy. On histological examination of the operative specimen, the diagnosis was revised to pleomorphic leiomyosarcoma (Figure 2) obstructing the ureter with invasion of the bladder wall (with positive surgical margins).

**Figure 2:** Pleomorphic tumor composed of irregular sheets of poorly-differentiated neoplastic cells with occasional bizarre nuclei which are SMA and CD99 positive, p63, CK7, CK20, Desmin, HHF-35, CD117 and CD34 negative. (HE stain, x200)

The patient presented again a year after her surgery with multiple episodes of haematuria. CT scan showed locally recurrent disease with another lobulated mass close to the original site of the left ureteric orifice with extensive involvement of the bladder wall (Figure 3). Repeat transurethral resection and histological examination confirmed recurrence of the original disease process.

**Figure 3:** CT showing local recurrence of disease

Repeat fludeoxyglucose PET scanning this time showed multiple metastases to liver and lung (Figure 4), consequently ifosfamide and epirubicin chemotherapy was commenced.

**Figure 4:** PET imaging showing liver involvement by disease

This was shortly followed by an episode of severe haematuria requiring multiple blood transfusions and bilateral embolization of the anterior division of the iliac arteries. Local pelvic progression of the malignant process resulted in contralateral renal obstruction and renal failure which was treated with percutaneous nephrostomy diversion, followed by pelvic external beam radiotherapy in an effort to control local symptoms.

Over the following 6 months, the patient was admitted multiple times for blood transfusions following recurrent episodes of gross intractable haematuria, progressive general deterioration and renal dysfunction eventually resulting in death.

**Discussion**

Soft tissue sarcomas are the commonest mesenchymal tumors of the urinary tract, accounting for 1-2% of malignant genitourinary tumors and 2.1% of all sarcomas, with leiomyosarcomas comprising 50% of cases, rhabdomyosarcomas 20% and the rest being rare histological subtypes. In view of the rarity of this malignancy, published literature on the subject is scarce. Understanding of the etiology and pathogenesis of the disease is rather limited, with retinoblastoma 1 gene mutation, previous pelvic radiotherapy and use of cyclophosphamide being considered as likely aetiological agents.

Most case reports published to date have involved young female patients, however with less
than 20 cases documented in the literature it is difficult to establish definitive epidemiological patterns.

Most data available pertains to the prognosis of the disease, derived from several case series and multicentre studies over the years.\(^4\) Mackenzie et al in 1968 reported that the disease has a poor prognosis, with 10% 3-year overall survival.\(^7\) Survival has improved over the years with recent studies reporting 5-year disease specific survival in the order of 55 – 60%, most likely related to early diagnosis with the more frequent use of cross sectional imaging.\(^5\) The most important factors determining prognosis are metastases at presentation and free margins on surgical resection.\(^2\) Rosser et al showed that the most common symptoms at presentation are gross hematuria (81% of patients), followed by increased urinary frequency (28%), and dysuria (19%).\(^8\) As diagnosis is often late, with less than 15% of patients presenting at T1 clinical stage.\(^9\) Indeed, our patient was staged at T2 at presentation, patients presenting with muscle invasive disease are considered to have locally advanced disease and invariably their prognosis is poor.

As no randomized controlled trials comparing treatment options in leiomyosarcoma of the urinary tract have ever been published, treatment is largely empirical, with extrapolation of methods used in treatment of epithelial tumors of the ureter. In the above case, surgical excision of the kidney, neighboring lymph nodes and ureter was performed.\(^10\)

In addition to this, the role of adjuvant chemotherapy using multimodal sarcoma chemotherapy protocols using doxorubicin or epirubicin, ifosfamide, cisplatinum and docetaxel and external beam radiotherapy have also been advocated, especially in cases of partial cystectomy.\(^5\)

Spiess et al (2007) showed that local recurrences occur in about 16% of cases, whereas metastases, most commonly in lung, liver brain and bone, occur in 53% of cases. In metastatic disease, chemoradiation remains the only palliative option available in patients with good performance status who can tolerate such regimens.\(^5\)

This case report outlines the salient features of leiomyosarcoma of the ureter and adds to the published literature on such a rare entity, which should be part of the differential diagnosis in patients presenting with soft tissue masses in the region, especially in young female patients.

References