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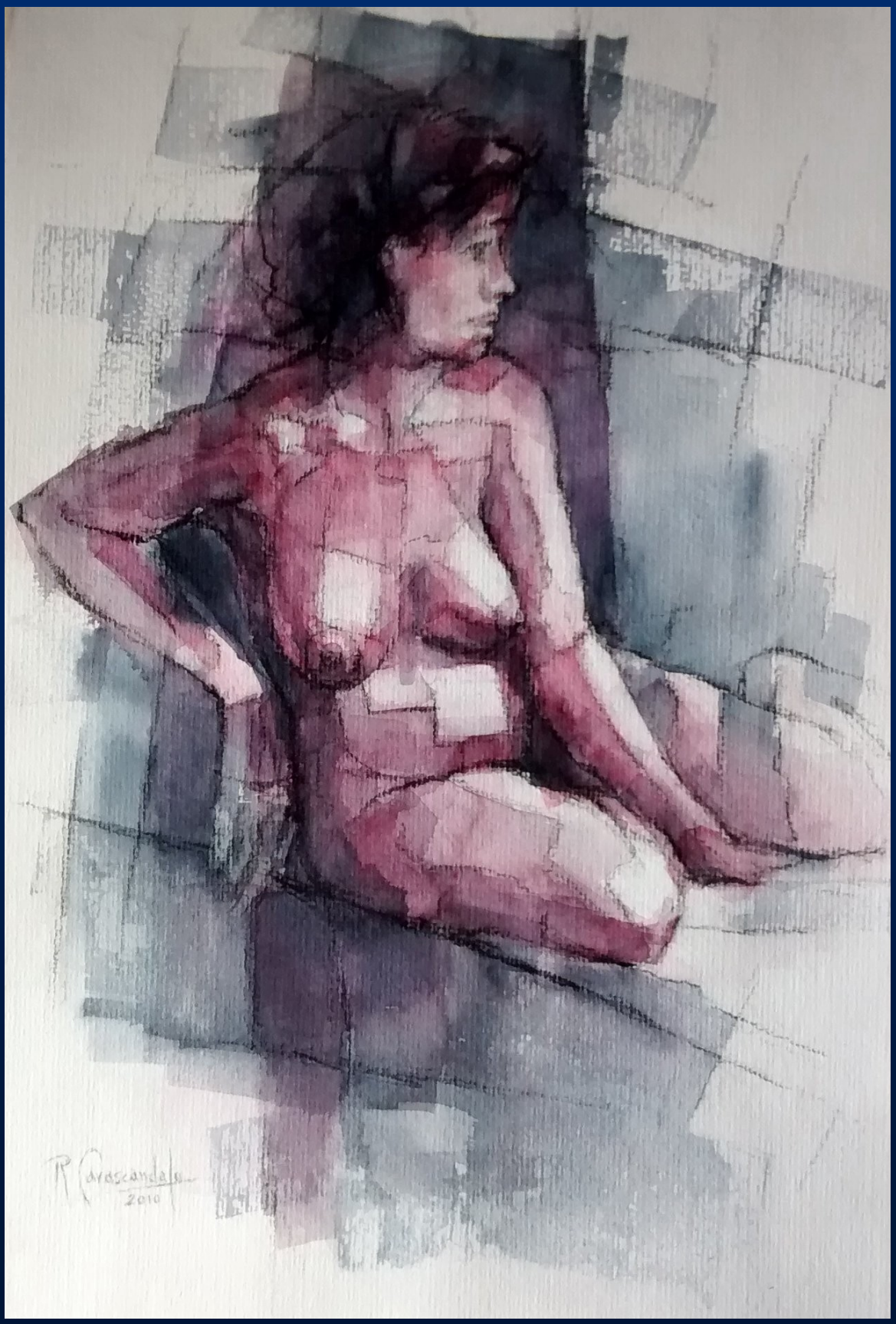

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Editorial

Victor Grech

"Man's inhumanity to man, makes countless thousands mourn!" Robert Burns, 1784.

"It is a frightening thought that man also has a shadow side to him, consisting not just of little weaknesses and foibles, but of a positively demonic dynamism. The individual seldom knows anything of this; [...] a raging monster." Carl Jung, 1912.

Syria's civil war constitutes the worst humanitarian disaster of our time and it is estimated that over four million refugees will have fled the country by the end of this year. These have already had huge impacts on neighboring countries.

The crisis began with anti-government demonstrations in March 2011, part of the Arab Spring. These triggered a violent crackdown by the regime. By July, army defectors had become the Free Syrian Army and were joined by many civilians. Matters are further complicated by divisions between secular and Islamist fighters, and between ethnic groups. Over 190,000 people (half of whom were civilians) have died. Human rights violations are widespread and basics such as food and medical care are sorely lacking.

Over half of the country's pre-war population of 23 million requires urgent humanitarian assistance, whether they still remain in Syria or have escaped from the country. Thousands flee daily after witnessing their neighborhoods bombed or family or friends killed. This course of action is as risky as remaining, with families having to walk many miles at night in order to avoid being killed by snipers or being apprehended by soldiers who kidnap young men to fight for the regime.

The majority of refugees are currently living in Jordan and Lebanon, the region's two smallest countries whose weak infrastructures and limited resources are approaching their breaking points. Iraq and Turkey are also hosting an increasing number of Syrians. More than half of the refugees are children and most have been out of school for months or years.

The World Health Organization has estimated that 35% of the country's hospitals are out of service and in certain regions, up to 70% of health care professionals have fled. Cases of diarrhoea and hepatitis A have doubled since the beginning of the year and routine vaccination has been abandoned, implying that displaced refugees also may pose health risks to the countries to which they have fled.

Furthermore, the lack of clean water and poor sanitation in crowded and makeshift settlements further threatens health by increasing the risk of outbreaks of diseases such as cholera and polio. Exactly one year ago, the United Nations issued its largest ever appeal for a single crisis, asking for $6.5 billion.

International humanitarian aid for this tragedy is being coordinated by the United Nations. The United States is providing food aid, medical supplies, emergency and basic health care, shelter materials, clean water and hygiene and education supplies. Islamic Relief has stocked 30 hospitals and sent hundreds of thousands of medical and food parcels. Iran has been exporting between 500 and 800 tons of flour daily to Syria. Malta is only peripherally involved, hosting some refugees and providing other assistance as it can.

It is abundantly clear that medicine's global efforts to reduce morbidity and mortality pale into insignificance when compared with the death and destruction meted out by man on himself in the name of religious fundamental extremism.

Detrimental long term effects by extremism on global population growth are also possible. It is estimated that the global population will perhaps level off around the year 2050-2075, at 9 to 11 billion, perhaps even slowly decline thereafter since education and health care tend to reduce fecundity.

However, extremism tends to reduce women to virtual slavery (as uneducated male chattels in patriarchal societies). A global rise in extremism therefore threatens humanity with Malthusian scenarios, leading to collapsing food supplies and widespread famines. It would therefore behoove developed countries to control extremism in their own long term interests.

Cover Picture:
'Nude'
Charcoal and Watercolour.
By Parascandalo Raymond

Ray Parascandalo is a Consultant Paediatrician and Neonatologist. He started drawing at an early age and later was tutored by Harry Alden and the late Esprit Barthet at the School of Arts (1973-4). From 2000 to 2008, Dr Parascandalo furthered his studies in drawing and painting under Anton Calleja. Subsequently, in 2009 he joined Patrick Dalli's Art Group. His preferred medium is acrylic but he also works in watercolour, terracotta pencils and charcoal. His favourite style is impressionism. Dr Parascandalo has participated in seventeen collective art exhibitions between 2001 and 2014.

Original Article

The attitudes, knowledge and practices of Maltese family doctors in disease prevention and health promotion

Lynn Pace, Mario R Sammut, Charmaine Gauci

Abstract

Introduction: Family doctors are in a unique position to advocate health promotion and disease prevention**,** though it is known that this is not always given its due importance due to various reasons.

Aim: To assess the knowledge, attitudes and practices of Maltese family doctors in health promotion and disease prevention. The results of the study were compared with a similar study in 2000.

Methodology: A validated questionnaire was sent in 2011 to all Maltese general practitioners (GPs) and GP trainees. The results were analysed statistically. A focus group was conducted to discuss the results and develop a set of recommendations.

Results: An improvement was seen in health promotion practice since 2000. Family doctors look after their own health better. However, they have difficulties regarding which prevention guidelines they should follow. Time constraints remain the biggest obstacle to promoting health. GPs who are involved in post-graduate teaching activities find it easier to promote health ($p<0.05$), while doctors working in both private and public settings find it most difficult ($p<0.05$). GPs who smoke find it harder to advise on smoking cessation ($p<0.05$), while doctors who are obese find it more difficult to recommend exercise ($p<0.05$).

Conclusions and recommendations: Health promotion practice by family doctors is on the increase, yet there is clearly room for enhancement of their service. Web-based training, lectures and seminars would help family doctors to enhance their knowledge. Flyers, posters and video-clips in waiting areas could increase patient awareness on healthy lifestyles.

Keywords:

Health promotion, attitudes, disease prevention, lifestyle

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Introduction

Chronic lifestyle diseases are responsible for increasing morbidity and mortality.[1] Health promotion and disease prevention are crucial to control this ever-growing pandemic, which is caused by a variety of lifestyle risk factors including unbalanced diet, sedentary lifestyle and tobacco, apart from biological risk factors.[2] Family doctors, being in direct contact with patients in the community, have an important role to play in promoting healthier lifestyles and reducing risk factors. However, it is known that health promotion and disease prevention is not always given its due importance in primary health care due to a number of factors.[3]

The study aims to assess the knowledge, attitudes and practices of family doctors in disease prevention and health promotion. It also explores barriers in implementing health promotion. The main outcome from this study is in suggesting ways of improving the practices of family doctors (both in the private and public sector). The results of the study were also compared with the Maltese results of a similar study

carried out in 2000 by EUROPREV (European Network for Prevention and Health Promotion in General Practice/ Family Medicine).[4] This survey was carried out in 11 European countries, including Malta.[5]

The study was supported by the Health Promotion and Disease Prevention Directorate (HPDPD), EUROPREV and the Primary Health Care Department.

Methods

A tool (adapted from the EUROPREV questionnaire used in 2000) was mailed in 2011 to Maltese general practitioners (283 in total) as per list available at the Health Promotion and Disease Prevention Directorate and to 17 GP trainees (undertaking the Specialist Training Programme in Family Medicine at the time of the study). The questionnaire was sent by the Health Promotion and Disease Prevention Directorate together with a stamped addressed return envelope. A reminder was sent to all by post. The response sheets were anonymous ensuring complete confidentiality.

The questionnaire included demographic and professional data, two clinical scenarios, questions related to barriers in implementing preventive medicine and questions concerning personal health behaviour. Data were analysed by SPSS. *p* values were calculated using the Exact Test (for a 2xK table).

Following analysis of the questionnaires a focus group was conducted to discuss the results. Participants were nominated from organisations of GPs, GP trainers and trainees, patient non-governmental organisations and public health specialists within the HPDPD. The results from the postal study were presented and discussed, with recommendations put forward by participants being collected in writing by a secretary.

Ethical permission was obtained from the Health Ethics Committee.

Results

The study had a response rate of 30.3% (91 out of 300). The male/female ratio was 70% / 30% with a similar ratio in 2000 (74% / 26%). Details of the GPs' professional characteristics (working and teaching activities) are shown in Table 1.

GPs were presented with two clinical scenarios of a 52 year old male who presents with a trivial cough and a 57 year old female who presents with a trivial dermatological problem. Both patients were visiting the doctor for the first time and had no previous "check-ups" or tests, no known risk factors and no personal or family history of any major disease. Tables 2 and 3 show the GPs' response to these scenarios. The tables compare the results of this study with the local results of the EUROPREV 2000 study.

***Table 1**: GPs' professional characteristics (working and teaching activities)*

Working and Teaching Activities	Percentage (this study)	Percentage (study 2000)
Work in : Primary health centre	40.7%	16%
Solo Practice	53.8%	58%
Public Centre	30.8%	19%
Private Centre	53.8%	55%
Postgraduate Teaching Activities	41.8%	26%

***Table 2**: Examinations done and investigations ordered by GPs in reaction to the clinical scenario where a 52 year old male presents with a trivial cough.*

Exam/ investigation/advice	Should it be done? Yes % (this study)	Do I do it? Yes % (this study)	Should it be done? Yes % (study 2000)	Do I do it? Yes % (study 2000)
Blood pressure	98.9%	97.4%	99.0%	88.0%
Glucose level	94.0%	88.3%	80.0%	80.0%
Cholesterol level	93.1%	93.0%	73.0%	74.0%
Faecal occult blood	95.8%	50.0%	23.0%	21.0%
Chest X ray	91.7%	68.8%	52.0%	44.0%
Digital rectal exam	93.9%	73.0%	43.0%	45.0%
Advise quit smoking	98.9%	87.8%	99.0%	66.0%
Advise less alcohol	98.8%	87.5%	97.0%	62.0%
Advise exercise	98.9%	89.2%	97.0%	62.0%
Advise weight loss	98.9%	90.5%	97.0%	61.0%
Body mass index (BMI) estimation	98.6%	84.6%	58.0%	39.0%

***Table 3**: Examinations done and investigations ordered by GPs in reaction to the clinical scenario where a 57 year old female presents with a trivial dermatological problem*

Exam/ investigation/advice	Should it be done? Yes % (this study)	Do I do it? Yes % (this study)	Should it be done? Yes % (study 2000)	Do I do it? Yes % (study 2000)
Blood pressure	97.4%	89.3%	95.0%	81.0%
Glucose level	96.9%	86.9%	88.0%	78.0%
Cholesterol level	96.3%	82.1%	76.0%	75.0%
Faecal occult blood	90.9%	56.5%	22.0%	20.0%
Cervical cytology	94.4%	81.0%	77.0%	64.0%
Breast examination	97.0%	87.5%	88.0%	73.0%
Advise quit smoking	95.2%	89.5%	95.0%	61.0%
Advise less alcohol	97.4%	86.5%	95.0%	60.0%
Advise exercise	97.6%	87.0%	95.0%	59.0%
Advise weight loss	96.4%	86.8%	95.0%	60.0%
BMI estimation	95.7%	82.8%	59.0%	37.0%

When asked about their attitudes to disease prevention and health promotion, about one third of GPs found some (36.3%) or great (1.1%) difficulty, while about two thirds of GPs found little (20.9%) or no (41.8%) difficulty. In 2000, nearly half the GPs found some (44.5%) or great (4.5%) difficulty while the other half had little (30.3%) or no (20.7%) difficulty respectively.

The main barrier perceived by GPs to the implementation of prevention and health promotion activities was heavy workload in their practice and hence lack of time (45.1%). This compares well with what 56% of the doctors studied in 2000 stated. 17.6% of GPs found lack of consensus and discrepancies in recommendations to be another barrier. 11% of GPs believe that patients have doubts about effectiveness of prevention measures while 9.9% of GPs have insufficient personal training.

GPs found themselves reasonably effective at promoting tobacco reduction (53.8%), alcohol reduction (41.8%), weight loss (53.3%) and regular exercise (69.2%).

Regarding the health behaviour of GPs themselves, 14.3% stated they smoked on a daily basis (cigarettes – 7.7%, cigars/pipe – 6.6%) compared to 15% in 2000 (cigarettes: 12% and cigars/pipe: 3%). 17.6% admitted they were former smokers compared with 29% in the 2000 study. While 37.3% of GPs reported that they do not drink alcohol, 16.% consume 1-2 drinks a week, 44% 3-14 drinks/week and only 2.2% drink 15 units or more (with 1 drink or unit consisting of 100ml wine, 200ml beer or 25ml whisky). The consumption of alcohol by GPs in the 2000 study showed 25% consuming 1- 2 drinks per week, 31% consuming 3 -14 drinks per week and 6% consuming 15 units or more per week.

On a more positive note, 58.3% of GPs exercise regularly (daily or 2-3 times a week), 29.7% exercise rarely (just once a month or week), while 12% of GPs never exercise at all. This shows an overall improvement compared to 2000 where 37% of GPs exercised regularly, 39% exercised rarely and 24% never exercised.

Once a year, 79.1% of GPs check their own blood pressure and 54.4% check their own serum total cholesterol. This also shows an improvement compared to 2000 where 74% of GPs checked their blood pressure yearly and only 37% checked their cholesterol levels yearly.

Family doctors were also asked regarding self screening procedures and vaccinations. There was good feedback for vaccinations. (Table 4).

***Table 4**: Self-screening procedures and vaccinations undergone by GPs*

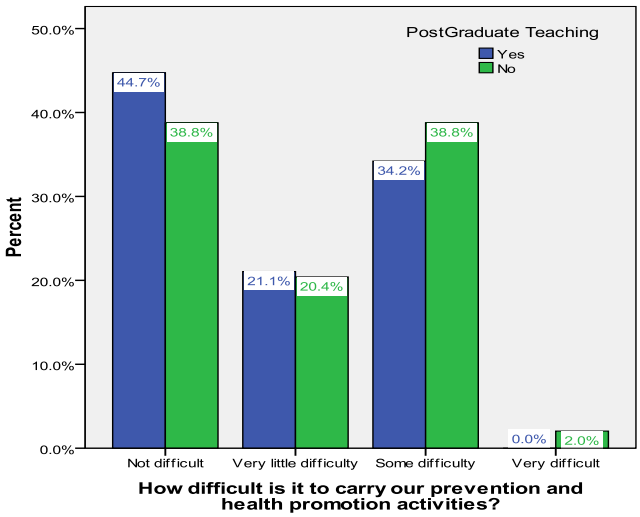
Underwent screening procedure/vaccination	Yes (%) (this study)	Yes (%) (2000 study)
Hepatitis B	93.3	84
Cervical Cytology	85.2	83
Rubella (females)	96.3	91
Clinical breast exam (females)	70.4	83
Digital rectal examination (males)	21	19
Influenza	84.6	62
Tetanus	91.2	89
Test for faecal occult blood	6.6	7

GPs were also requested to provide their weight and height so that the mean body mass index (BMI) could be determined.

The mean BMI for female GPs at 23.9% fell within normal limits (normal range – 20 – 24.9), while the mean BMI for male GPs at 26.7% fell within the overweight category (overweight range – 25-29.9). These values were very similar to the mean BMIs of GPs in 2000 (mean BMI for female GPs – 23.9% and mean BMI for male GPs– 27%).

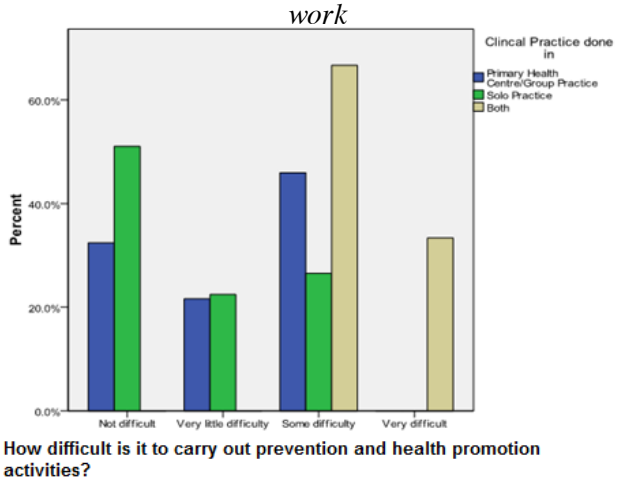
From the cross-tabulations, it is noted that GPs who are involved in post-graduate teaching activities find it easier to do health promotion and disease prevention (p<0.05) (Figure 1).

***Figure 1**: Cross-tabulation*
difficulty in carrying out health promotion with post graduate teaching activities



Doctors in private practice find it easier to promote healthier lifestyles than those working in public centres (p<0.05). Doctors working in both private and public settings find it most difficult (p<0.05) (Figure 2).

Figure 2: Cross-tabulation
difficulty in carrying out health promotion with place of work



As expected, GPs who smoke find it harder to advise smoking cessation (p<0.05) (Figure 3) and doctors who are obese find it harder to advise on exercise (p<0.05) (Figure 4).

***Figure 3**: Cross-tabulation*
smoking history versus effectiveness of smoking cessation

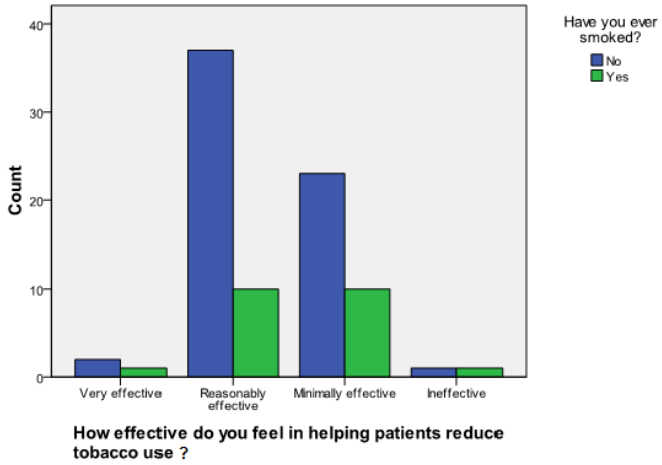
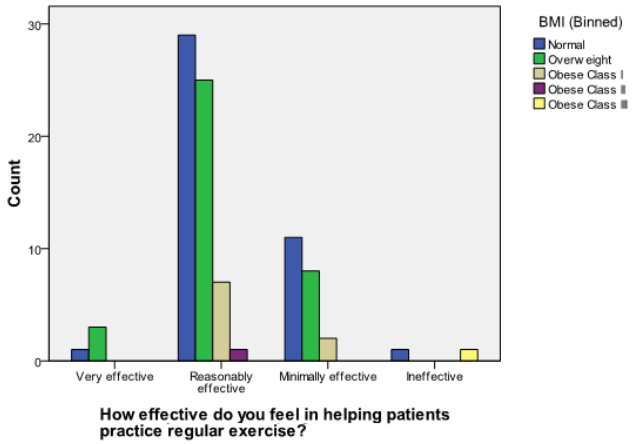


***Figure 4**: Cross-tabulation*
BMI versus effectiveness at helping patients practice exercise



Discussion

This study attempted to evaluate the health promoting service provided by general practitioners. From the two clinical scenarios it was noted that there is a difference between the belief that certain health promotion activities should be done (e.g. decrease in smoking, alcohol and weight) and the GPs actually doing them. In the 2000 study this difference is more drastic. This implies that health promotion is being practised more in 2011 than in 2000; however, there is still room for improvement. This compares well with results of another European project – Health promotion in primary health care: general practice and community pharmacy.[6]

A study in the Netherlands concluded that there was greater awareness of a healthy lifestyle in 2008

compared to 1975, but there were only limited lifestyle behaviour discussions during GP consultations.[7] Another study in Australia suggested that patient-reported GP management of smoking, nutrition, alcohol, physical activity and weight is "less frequent than is optimal", as GPs provide education or advice to "between one-quarter to one-third of those at risk for each risk factor".[8] As regards barriers to health promotion, 10 years down the line, doctors still find their heavy work load and time constraints a major obstacle. The introduction of specialised clinics run by other health care professionals can help here. GPs also have difficulties regarding which guidelines to follow and what to recommend to patients.[4] A possible solution to this obstacle is the distribution to patients of leaflets with specific guidelines on disease prevention which can assist GPs in their busy practices. A similar study conducted in the Netherlands concludes that the main barriers to health promotion include lack of motivation to make lifestyle change, insufficient re-imbursement, lack of proven effectiveness of interventions and lack of overview of health promoting programmes in the neighbourhood.[9] On the other hand, patients in Malta are finding it easier to access health promotion activities.[10]

When it comes to GPs' own health, it seems that family doctors have become more health conscious and looked after their own health better in 2011 than they did in 2000. More doctors check their own cholesterol and blood pressure levels yearly, perform exercise and take vaccinations (Hepatitis B, Rubella, Influenza, Tetanus). Less doctors smoke cigarettes and consume $\geq$ 15 alcoholic drinks per week. Overall, male doctors are still more obese than female doctors. GPs' healthy behaviour helps to encourage patients to improve their lifestyles as they see their family doctors as role models.

From the cross-tabulation results, it is a bonus to see that GPs who are involved in post-graduate teaching activities carry out health promotion activities as they pass this on to GP trainees. A study conducted in Switzerland concludes that the integration of health promotion in medical education may be needed to increase knowledge as well as attitudes of GPs regarding health promotion.[11] Doctors working in both private and public settings find it most difficult to put into practice disease prevention, possibly due to heavy workloads.

Moreover, GPs who smoke find it harder to advise smoking cessation. A European Project (General Practitioners and the Economics of Smoking Cessation in Europe), which explored the extent of GPs' engagement in smoking cessation, reported that various factors are involved, including GP's own smoking status and their attitudes towards smoking cessation advice.[12] On a similar note, doctors who are obese find it harder to advise exercise.

Limitations of the study

The study's response rate was low at 30.3%. Hence it is limited in generalisability. There could also be some desirability bias where doctors reported on what they feel they should do than what they actually do.

Moreover, those GPs who did reply probably had a greater interest in health promotion and disease prevention compared to family doctors in general and this could have affected the results.

Another limitation is lack of analysis of the difference between male and female GPs regarding the percentage difficulty of promoting health and the reason/s for such.

Furthermore, the qualifications of GPs were not recorded. Therefore the association between GPs having insufficient personal training in health promotion and their professional academic roles could not be studied.

Concluding recommendations from focus group

General practitioners would benefit from some training on health promotion, be it in the form of web-based training or seminars as part of Continuing Professional Development (CPD) meetings.

Information from the Health Promotion and Disease Prevention Directorate provided on the website of The Malta College of Family Doctors (MCFD) would also be helpful. Leaflets (both soft and hard copies) can serve as an asset to distribute or share with patients. Buying or renting monitor screens for waiting rooms to display health promotion videos on topics like exercise, nutrition, alcohol, hypertension, hypercholesterolemia, diabetes etc. could also help. GPs should ideally be role models to their patients, through their own healthy lifestyles.

GP trainees would benefit from an optional 2 month placement in the Health Promotion and Disease Prevention Directorate as part of the Specialist Training Programme in Family Medicine.

The Health Promotion and Disease Prevention Directorate (HPDPD) can help by providing flyers/ leaflets (soft and hard copies) and video clips with short clear messages for the public. Moreover, the provision of training for family doctors (e.g. through the MCFD website or through lectures given at CPD meetings) would also help.

The Primary Health Care Department (PHCD) in collaboration with the HPDPD can introduce special clinics to counsel patients wishing to change unhealthy lifestyles. Weight management and smoking cessation classes are already available; however these do not involve a GP in the team. New clinics introduced so far by the PHCD include Lifestyle Clinics, Chronic Disease Management Clinics and Chronic Kidney Disease Prevention Clinics, which models would benefit from being evaluated for their effectiveness.

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Review Article

Suicide rates in Maltese Islands (1955-2009) analysed in European context using WHO data

Samuli Helema, Jari Holopainen, Timo Partonen

Abstract

Aim: To calculate the suicide rates (for males and females) in Malta and other European countries with long series of suicide mortality as recorded in the WHO (World Health Organization) database, and compare the Maltese suicide rates with European rates.

Method: Suicide rates were computed from the WHO database as rates (suicides per 100,000 persons) using the reported suicide and population counts in Malta and ten other European countries for a common period 1955-2009. Suicide rates were age standardized following the WHO recommendations. These calculations were carried out separately for both sexes.

Results: Compared to other European counties, the suicide rates (both male and female) in Malta have remained at considerably low level as calculated over the full period. Maltese suicide rates have however multiplied since the 1980s. European data exhibit clear decrease in suicide rates towards the present consistently in several countries. Malta is the only European country showing its highest suicide rates during the 2000s.

Conclusions: Although the suicide rates in Malta remain at considerably low level, they have exhibited a notable increase towards the present, whereas the European suicide rates are in decline. Becoming aware of this fact and the issue may help in building a suicide prevention programme to mitigate the situation.

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Keywords

Suicide, Mortality, Europe, Database, World Health Organization

Introduction

Suicide is one of the major causes of death world-wide.[1] Suicide rate is not, however, constant in a given region, but varies with time. Another characteristic of suicide mortality is that males are more prone to commit suicide than females. Apart from temporal variations, the suicide rates differ between regions and generally exhibit diverging levels in different countries.[1-3] Several studies have aimed at revealing the temporal post-war trends and levels of suicides in different European countries.[1-2, 4-6] A feature common to these studies is the peak in European suicide mortality in the 1980s, with declining rates thereafter[1,5], possibly occurring on a global scale apparent for the last 20 years.[6] Despite this decline, the studies conclude that suicide remains a significant public health problem.

In comparison to other European countries, the suicide rates in southern Europe are low and tend to be lowest in Mediterranean countries.[2,5] Notably, the suicide rates have remained at very low levels in Malta.[2] However, the most recent international comparisons have not included the mortality figures of Malta in their estimations.[1, 4-6]

In this study, we have performed a comparison of suicide rates in 11 European countries including Malta. These analyses were to depict the temporal trends of suicide mortality in these counties, with emphasis on the development of Maltese mortality, and compare the trends in Malta with those of other countries. The figures were constructed from the updated database of World Health Organization (WHO) and age standardized for neutral comparisons between the countries. The main aim of this study was to evaluate the development of suicide rates in Malta and their recent changes in the European context.

Method

Mortality and population data of Austria, Finland, France, Hungary, Iceland, Ireland, Malta, Netherlands, Norway, Sweden, and Switzerland, covered the common period (1955-2009) as derived[7] from the WHO mortality database. Typically, the mortality and population data

was available for age groups of 5-10, 11-15 …81-85 years, and these age groups were used in further calculations. Suicide counts of these age groups and the population figures were adopted from the database, and transformed into sex-dependent suicide rates (suicide deaths per 100,000 persons) for each calendar year. Moreover, the suicide rates were age standardized following the WHO recommendations.[8] Following previous suicide comparisons[1], the suicide rates were averaged for pentads (1955-1959, 1960-1964 … 2005-2009).

In this study, we aimed to reveal the suicide rates in Malta, and place them in the context of European suicide mortality, whereas pan-European comparison of suicide rates will be presented elsewhere. We have previously compared the development of Finnish suicide rates with the corresponding rates in other European countries, but that analysis[7] did not focus on suicide rates of any other particular country. In contrast, the temporal development of suicide rates in Malta were compared here to the corresponding rates available in the abovementioned 11 countries.

Results

Suicide rates in 11 European counties, including Malta, exhibited temporal variations through the study period (Fig. 1). In general, the suicide mortality appeared to rise from the 1950s until the 1980s, after which several counties exhibited a decline towards the 2000s. For males, this pattern of change was confirmed for all studied countries except Finland, Ireland, and Malta, showing their highest suicide rates over the following decades (Fig. 1a).

A similar pattern was evident for females. That is, the suicides rates ascended towards their peak values in the 1980s, and declined thereafter, except in Finland, and Malta, where the peak values occurred later. For both sexes, the suicide rates reached their maximum in Finland during the pentad 1990-1994. In Malta, the highest male and female suicide rates were obtained for 2005-2009 and 2000-2004, respectively (Fig. 1b). Comparison between the studied countries (Fig. 1) showed that the suicide rates were clearly at their lowest levels in Malta, this observation being sex-independent. For females, no suicides were registered in Malta during the periods 1955-1959 and 1970-1979.

For males, the long-term trend in suicide rates, depicting the change in suicidal mortality since 1955, rose in only four counties, including Ireland, Netherlands, Norway, and Malta (Fig. 2a). By contrast, the suicide rates in the 2000s increased only in Malta (Fig. 2b).

For females, the long-term trends in suicide rates rose only in Ireland, Norway, and Malta (Fig. 2c). In fact, Ireland and Norway showed rising suicidal mortality also in the 2000s, as depicted by the short-term change in suicide rates, in addition to Sweden. Overall, the recent (i.e. short-term) changes in suicide mortality were relatively subtle, in comparison to the post-war change (1955-2009), as evident for both sexes and for all studied counties.

Figure 1*: Temporal variations in suicide rates as computed for pentads over the study period (1955-2009) for males (a) and females (b) in Malta (open circles) and ten other European countries (filled symbols).*

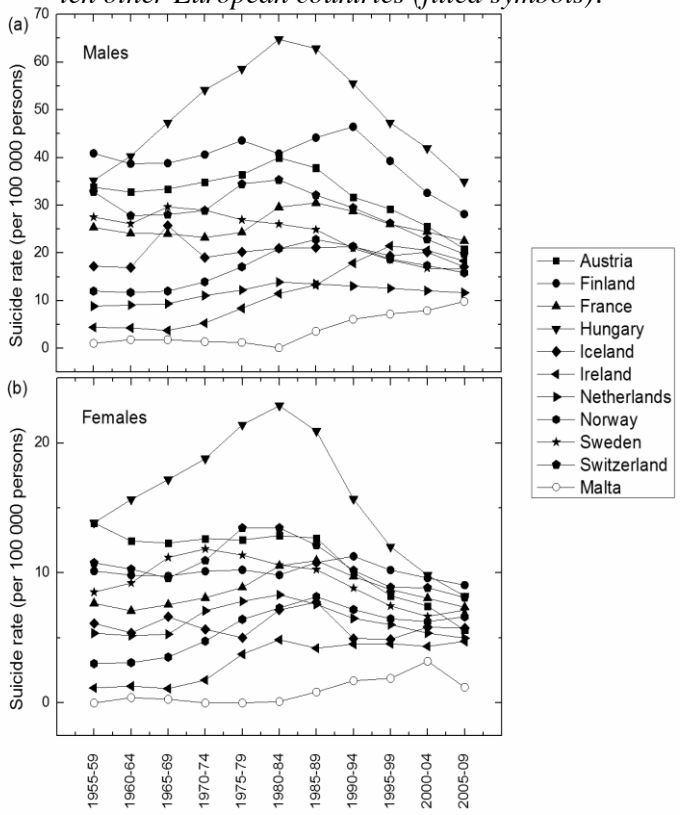
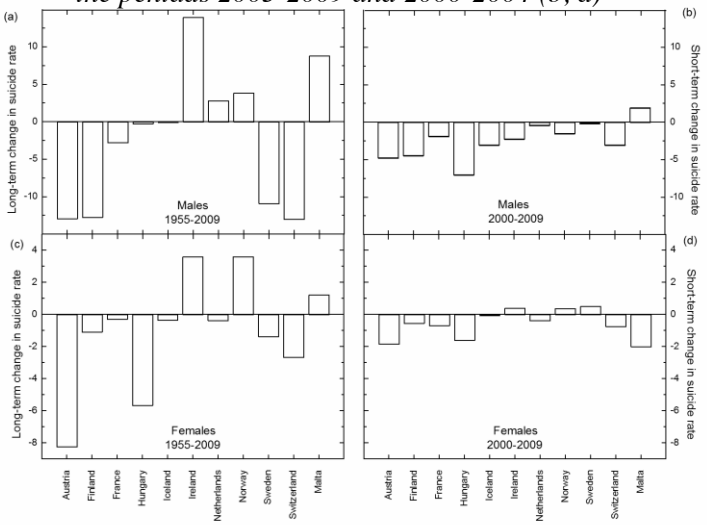


Figure 2*: Change in suicide rates (corresponding deaths per 100 000 persons) computed as long-term trend using the difference between the rates during the pentads 2005-2009 and 1955-1959 (a, c) and as short-term trend using the difference between the rates during the pentads 2005-2009 and 2000-2004 (b, d)*



Considerable changes were observed for Malta also when comparing the suicide rates from the early 1980s (here, 1980-1984) until the last pentad (2005-2009). During the former period, the male and female suicide rates remained at level of 0.134 and 0.111 (suicide deaths per 100,000 persons), respectively, whereas during the latter period the rates of 9.845 and 1.208 were obtained.

Discussion

Suicide is a complex problem receiving world-wide attention.[3] Suicide rates vary between countries, including Europe. The fact that the suicide rates were in Malta clearly at the lowest level among the studied counties followed the geographical picture, whereby the rates are higher in northern countries, in general, than in southern European countries.[3] Moreover, the Mediterranean countries have generally lower suicidal mortality than the other countries in Europe.[2,5] In fact, no female suicides had been registered for Malta in the WHO database over three pentads in the 1950s and 1970s.

Although the suicide rates vary between countries, their temporal trends may indeed show similarities. The decadal and longer trends deciphered in this study followed the previously detected a rise in suicidal mortality towards the 1980s, common to several European countries, whereas the subsequent decline in suicide rates occurred towards the 1990s and 2000s.[1,5-6] In this respect, Malta was no exception, but the suicide rates ascended during the 1980s (Fig. 1). However, it appeared that the country did not experience the decline in suicide rates during the 1990s and 2000s, unlike several other European countries. On the contrary, the overall low level of suicides in Malta were contrasted by the increase in suicide rates since those years, especially in the case of males (Figs 2a, b).

As previously alluded to, a feature common to Malta and Finland was that their highest suicidal mortalities were not observed in the 1980s but during the following decades. In Finland, the high level of suicide rates during 1980s evoked a parliamentary committee on suicide, and a suicide prevention program was initiated by a nation-wide research (1986–1991) and implementation phases (1992–1996).[9] At the end of the research phase, the national suicide prevention target and action strategy was published and distributed throughout Finland.[10]

Corresponding combination of suicide research and prevention was the first nation-wide effort of its kind.[11] In Finland, the post-programme suicide rate of 24.3 over the period 1991-2005 is contrasted by the predicted 32.6 (suicide deaths per 100,000 persons).[12] In Malta, the suicide rates of males and females were seventy and nine times higher during the most recent pentad (2005-2009) than they were in 1980-1984. Considerations presented here imply that becoming aware of the suicidal behaviour at national level may help at building a suicide programme to mitigate the situation.

Acknowledgements

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Original Article

Treating the patient not just the disease? Delving deeper into the possible link between affective disorders and coronary heart disease through statistical analysis of a random sample of Maltese people

David Debono, Neville Calleja

Abstract

Background: Ischemic heart disease is the leading cause of death in Males in Malta and globally. Affective disorders are the commonest psychological problem. This cross-sectional study utilizes a multiple regression model utilizing binary logistic to delve deeper into the link between affective disorders and coronary heart disease and also the link between coronary heart disease and anxiety and depression separately.

Methods: The study was performed in the small Mediterranean island of Malta through the European health interview survey (EHIS), at a national level involving 5500 participants. The response rate attained in the actual field work was 72%. Statistical analysis involved performing chi-squared tests on all contributing variables and retaining those variables that were significant to both diseases. These were then placed in a multiple regression model using forward stepwise binary logistic to retain only the most significant variables.

Results: Age, gender, BMI, diabetes prevalence, depression prevalence, anxiety prevalence, hypertension prevalence, affective disorders(having either anxiety or depression), smoking status, frequency of alcohol intake, and educational level all had a significance of <0.05, some; than less than 0.01. On fitting a multiple regression model, Anxiety (p=0.033), age (p=<0.001), gender (p=<0.001), hypertension (p=0.016) retained their significance in the model. Diabetes could not be analyzed due to power issues.

Conclusion: BMI was not retained in the model having been replaced by associated conditions such as hypertension, together with age and gender as strongly associated risk factors. Anxiety nevertheless retained its independent association with coronary heart disease, in spite of the presence of the other stronger predictors described above.

Keywords

anxiety, depression, coronary heart disease, public health, multiple regression model.

Abbreviations

p: Probability value, CI: confidence interval. EHIS: European health interview survey, sig: significance

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Background

Ischemic heart disease has been the top cause of mortality one killer in middle aged to old men for many decades.[1] In this study we consider the link between coronary heart disease and affective disorders (ie with either anxiety or depression prevalent), and also the link between coronary heart disease and anxiety and depression separately.

In Malta studies studying the association between mental and cardiovascular health are lacking. The aim of the paper is to raise awareness on the physiological importance of mental health and hence help to soften the undeniable taboo surrounding mental health on this tiny island. This cross-sectional study makes use of data

collated by the local national European health interview survey (EHIS) in 2008 and utilizes a multiple binary logistic regression model to explore better the possible link between affective disorders and coronary heart disease.

Literature review

Depression and anxiety in coronary heart disease.

Affective disorders have for a long time been reported to be associated with abnormal functioning of the body; a specific example being stress as implicated in irritable bowel syndrome.[2] Chronic depression and stress bring about biochemical changes in the body which may affect cardiac health as has been observed in a study concerning medical students during examinations.[3] Evidently during examination period, students' cholesterol levels were found to be elevated when compared to relaxed controls.

Mental depression seems to increase blood clotting, inflammation and hyper-coagulability, increases the risk of hypothyroidism, increases oxidative stress, and hyperactivity of the sympathetic system. All these factors associated with depression lead to increased predisposition to atheroma and hence myocardial infarction and congestive cardiac failure.[4] Therefore dealing with depression is important to prevent these lethal metabolic changes but it is more complex than just treating the patient pharmacologically as the use of antidepressants has not reduced the risk of coronary events.[5]

The Type-d personality is related to probability of long term development of general heart disease.[6]A type-d personality is used in medical psychology to refer to an irritable, stressed person, a person with negative affectivity; this concept was developed by John Denollet. Evidently distressed patients are much more likely to develop heart disease in the long run.[7]

Findings on this topic are not always consistent. In a particular study, men with pre-existing clinical depression did not differ inbaseline blood pressure, serum cholesterol levels, smoking status, physical activity, obesity, or family history of coronary artery diseasebut depression was still associated with increased incidences of heart disease even several decades after the onset of the clinical depression.[8] Strangely enough in another study[9] blood pressure and cholesterol levels were found to be increased in anxious and depressed subjects.

Depression is considered to be a major a risk factor as much as lack of physical activity and diabetes in causing heart disease, though the exact nature of the relationship remains unknown.[10] Depression may predispose to development of adverse behaviors.[11] Chronic anxiety has also been related to destructive behaviors. In Malta chronic anxiety has been statistically linked to unemployment, marital status, low education level, income and age.[12] In other studies anxiety has also been linked to increased incidences of smoking [13] and drinking [14] low socioeconomic status[15] and increased rates of obesity.[16]

Many other variables have also been statistically proven to be contributors of depression and anxiety. According to Peter M. McEvoyet al[17], the incidence of chronic depression and anxiety is related to age and individuals in the oldest age range are at the greatest risk of developing anxiety.

Therefore to summarize the above, when analyzing current literature on the subject, it is safe to say that even though a link evidently exists between both diseases, the exact nature of the mechanism behind the link still remains relatively unknown.

Methodology

The type of study used is a cross-sectional study that utilizes a multiple regression model with binary logistic. A European health interview survey was conducted by EHIS at a national level involving 5500 participants, the youngest being of 15 years of age. The sample was drawn from the population register obtained from the Maltese national statistics office and was stratified by age, gender and locality. Before the actual fieldwork, field testing was carried out on 430 individuals, 310 responded. The response rate attained in the actual field work was 72%. The survey was carried out in June 2008. It consisted of two questionnaires. It was made sure that the questionnaires were adapted to highlight important local issues at the same being comprehensible and not too lengthy. The first interview carried out by an interviewer and the second interview which contained more sensitive topics was filled in by the interviewee. Questionnaires were available in both Maltese and English depending on the preference of the interviewee.

Randomly selected interviewees received a letter of introduction from the Directorate for Health Information and Research and a phone call from the interviewers to arrange a suitable appointment to meet face to face. Interviewees below age 18 were accompanied by a guardian. Interviews and questionnaires were held in complete confidentiality.

***Figure 1**: Variables significant to coronary heart disease and at least one affective disorder*

	Coronary heart disease	Depression	Chronic Anxiety	Affective disorders (depression or anxiety)
Age	**	**	**	**
Gender	**	**	**	**
BMI	**	**	**	**
Hypertension	**	**	**	**
Coronary heart disease prevalence	**	**	*	**
Do you smoke?	*	**	*	*
Alcohol frequency during the past 12 months	*	**	*	*
Educational level	**	**	**	**

*p<0.05 *
**p<0.01

***Figure 2**: Variables retained in the multiple regression model*

Variables	Confidence interval Lower-Upper	Odds ratio	Significance of the change
Hypertension	0.392-0.905	0.596	0.016
Chronic anxiety	0.276-0.912	0.502	0.033
Age	0.309-0.708	0.468	<0.001
Sex	0.928-0.955	0.941	<0.001

Statistical analysis

Using the statistical package SPSS version 19, chi-squared tests were used for the association between coronary heart disease prevalence and for all the categorical variables namely, depression prevalence, chronic anxiety prevalence, coronary heart disease prevalence, present day smoking, past smoking, alcohol frequency, binging, gender, educational level and average range of income, hypertension prevalence and medication use for all diseases and environmental variables such as noise pollution, discrimination bullying, time pressure violence in the area of residence, smells and air pollution. This was done to see which variables were statistically significant in contributing to depression and/or coronary heart disease. For age and BMI, which are continuous variables, the independent samples T-test was used to evaluate significance.

Diabetes could not be analyzed due to power issues. Variables were grouped into 4 categories; first category was for those variables significant to coronary heart disease and at least one affective disorder. The second category included those significant only to heart disease, the third category for those significant to the affective disorder (chronic anxiety or depression) and the 4th category was for those significant to none of the diseases. Only the variables in the first category were further analyzed. These are shown in Figure 1.

The variables in the first category were then placed in a multi-variate binary logistic regression model to assess the independent effect of each of the variables in the presence of confounders, the dependent variable being coronary heart disease. Only the variables that retained their significance were kept in the model. This is shown in Figure 2.

Results

When smoking was analyzed it resulted that significantly less people with coronary heart disease tend to smoke at the time of the survey (p=0.014) but a statistically significant amount of people used to smoke

daily in the past (p=<0.001). In contrast significantly more people with chronic depression (p= 0.025) and chronic anxiety (p=0.030) were found to smoke at the time of the survey but these affective disorders were not found to be statistically associated with past smoking as was the case for coronary heart disease. Similar results were obtained for alcohol use. People with coronary heart disease tending to drink less (p=0.022), while people with affective disorders tending to drink more (p<=0.001).

Alcohol consumption is positively related to chronic depression and anxiety (p<=0.001) as is binging with chronic depression (p=0.027).

During our analysis educational background was found to be strongly linked to chronic anxiety and depression as well as coronary heart disease. This has been already been described by other studies.[18]

Affective disorders, that is the presence of either chronic anxiety or depression or both were also found to be statistically linked to coronary heart disease when analyzed independently (p=<0.001).

Age was also significantly linked (p=<0.001) for both chronic depression and anxiety and coronary heart disease. When adjusted, age remained in the model suggesting that it exerts an independent influence in the development of coronary heart disease.

These variables were placed in a multi-variant binary logistic regression model with coronary heart disease as the dependent variable. Figure 2 shows the variables that remained in the final model.

Hypertension was also found to be strongly linked to coronary heart disease (p=<0.001).

Chronic anxiety remained clinically significant even when put amongst other variables that one would commonly think about as being the more relevant risk factors, when adjusted, chronic depression and affective disorders did not retain significance within the model.

Discussion

The hypothesis statistically proven for this case has already been suggested by other papers.[19-20]Although the relationship is not as strong as that with variables such as age, sex, and hypertension, a statistically significant relationship is still present for chronic anxiety. Diabetes had to be excluded from this part of the analysis because of power issues. Depression and affective disorders did not statistically hold up in this particular case indicating that their effect is probably governed by variables retained in the model.

Smoking and alcohol abuse

Smoking has been long known to cause adverse cardiovascular effects [21,-22] as has been alcohol abuse [23-24]. The main findings on smoking in this study tend to support the findings of other studies. Referring to the above results, in this study, since people with coronary heart disease are statistically linked to having smoked daily in the past and not linked to smoking much nowadays and since people with chronic depression statistically smoke more nowadays one can therefore speculate a temporal link that when examining the role of smoking as follows an affective disorder may be occurring first predisposing towards smoking which may then accelerate coronary heart disease, which smoking may have been curtailed following the diagnosis of heart disease.

Referring to the above results in the case of alcohol similar events occur, people with coronary heart disease tend to drink less, but alcohol consumption is positively related to chronic depression and anxiety as is binging with chronic depression hence pointing towards affective disorders as a possible culprit for these unhealthy destructive behaviors. A similar model could therefore be proposed for alcohol. With chronic anxiety, a similar statistically significant relationship is observed but chronic anxiety is not associated with alcohol binging.

The effect of low education and socioeconomic status

Low education is associated with low income, and low income is statistically linked to increased incidences of affective disorders as has been shown in Figure 1. Therefore a tough economical situation may predispose to development of affective disorders [25] and hence predispose a person to heart disease.[26] This does not exclude a direct link between low education and income to heart disease, independent of mental health.[27] The mechanisms of how affective disorders could bring about heart disease remain to be explored and are likely to be multiple. In this study chronic depression was most prevalent in people who had stopped their education at primary level or upper secondary level of education.

The effect of other contributing diseases

Hypertension and diabetes could be considered as precursors for coronary heart disease.[28- 29]In this study it was found that affective disorders are linked to hypertension and diabetes further solidifying the original hypothesis; that affective disorders are in some way linked to coronary heart disease be it directly or indirectly.

The effect of age

The risk of heart attack increases significantly with age.[30]This has been further supported by this study. Affective disorders also appear to be more to be more prevalent with increasing age, but so are most other diseases. In this case hypertension, diabetes, coronary heart disease and chronic depression were all linked with age. Therefore one can say that since older people are more likely to be suffering from conditions that cause

some degree of suffering or limitation, it would be foolish to assume that depression on its own increases with age. Depression prevalence is more likely to increase as a co-morbid factor.[31]

The effect of BMI

BMI has been linked with increased incidences of depression and coronary heart disease.[32]The above results also show this.The fact that BMI was not retained in the model shows that its effect is probably governed by the presence of variables retained in the model. These are likely to be predisposing psychosocial variables together with the presence of conditions whose onset may have been facilitated by the presence of obesity.

Limitations

The major limitation of this paper is that the data is self reported. This means that the data can't be independently verified. The paper being self reported means that selective memory, attribution or simply awareness might have all inadvertently affected the results of this study. One other limitation is that the study is a cross-sectional one and therefore one can only speculate on potential hypothetical temporal links between variables.

Conclusion

When adjusted, depression lost its independent influence suggesting that its prevalence is almost entirely explained by the presence of other risk factors. The findings from this study seem to support the consistent findings of other studies that affective disorders are in some way linked to heart disease. When it comes to chronic anxiety, this paper should act as a step towards solidifying the hypothesis that, chronic anxiety and coronary heart disease are indeed linked and to further exemplify the importance of the title of this paper, which is; to treat the patient not just the disease.

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Original Article

Assessing the outcome of patients who underwent a primary percutaneous coronary intervention

Sarah Cuschieri, Mark Sammut

Abstract

Introduction: Patients presenting with acute ST-elevation myocardial infarction (STEMI) of less than 12 hours from onset of chest pain are candidates for primary percutaneous coronary intervention (PPCI).

Aim: To assess the patients' outcome after 12 months of their admission by a retrospective observational study.

Methodology: Data of patients admitted with STEMI and preceding to PPCI between 1st of January 2011 to 30th of June 2011 were analyzed. A total of 105 patients were recruited, identified and analyzed by using Cardiac Investigation and Patient Record (CIPR) software. Survival outcomes were determined by mortality data obtained from the Department of Information, Health and Research.

Results: Out of the 105 patients having PPCI, the majority were men (81%). 8.6% died within one year. 20% had scheduled repeat coronary angiography, 9.5% requiring further PCI. 0.95% had target vessel revascularization while another 0.95% was referred for coronary artery bypass grafting (CABG) due to triple vessel coronary disease.

Unplanned re-admissions rate due to another episode of chest pain was of 5.7%, out of which one presented with another STEMI requiring PPCI. The other patients underwent inpatient coronary angiogram, with 2 proceeding to PCI.

The remaining 63% did not experience any other cardiovascular related episodes.

Conclusion: This analysis showed that the re-admission rates over a year requiring further interventions were low as was the death rate. Only one target vessel revascularization was performed suggesting that the majority of the PPCI's performed were successful. This is important when assessing the quality of cardiovascular interventional service provided by our state health system.

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Keywords

Cardiology, Percutaneous Coronary Intervention, Myocardial infarction, Thrombolytic Therapy, Chest pain

Introduction

Acute ST-segment elevation myocardial infarction (STEMI) is an emergency condition, which results from a thrombotic occlusion of a coronary artery. Impairment of vascular supply to the myocardium occurs, leading to an eventual infarction.[1]

Primary percutaneous coronary intervention (PPCI) is the gold standard for STEMI management[2] provided that a PPCI center is within a reasonable geographical distance to ensure a rapid revascularization as possible. The other alternative to treat acute STEMI is thrombolysis. The earlier the patient presents to the Emergency department after onset of chest pain, the better results would be obtained by PPCI. When comparing PPCI to thrombolysis, it had been found that PCI is superior to thrombolysis when undertaken between 3 and 12 hours from the onset of chest pain, as it significantly leads to a more rapid and effective revascularization. It had been reported that in particular women[3] and elderly patients[4] benefit more from undergoing PPCI as compared to thrombolysis.

The PPCI procedure involves acquiring arterial access (originally through the femoral artery but nowadays the use of the radial or brachial arteries are also possible) under local anaesthesia, where a seldinger technique is used to guide a catheter up to the coronary artery. Visualization by means of intracoronary contrast medium injections and fluoroscopy would enable the catheter to be passed through the stenosis and into its distal branch[5]. The stenosis would then be dilated and stented, resulting in the return of blood flow through the vessel to the distal myocardium. The outcome depends

on the presence of co-morbid factors such as pre-existing heart failure or renal failure, previous myocardial infarction, the degree of vessel collateralisation and the presence of multi-vessel disease[5]. These in addition to the duration of the door-to-balloon time, a prognostic factor in its own right.

This study was undertaken at Mater Dei Hospital, which is equipped with a PPCI facility and experienced team. Due to the relatively small size of the islands, patients experiencing acute chest pain have a greater chance of reaching the hospital within the first few hours of the onset and so the door-to-balloon time is generally short. The local protocol is that patients presenting to the Accident and Emergency department of Mater Dei Hospital with acute STEMI up to 12 hours duration are candidates for PPCI. Circulatory system diseases including ischemic heart disease[6] constitute the major cause of death in Malta over recent years (38% of the death rate for 2010). This retrospective observational study was performed to assess the outcome of patients' cardiovascular interventional outcome at 12 months of having undergone PPCI.

Method

Over a 6 month period between the 1st of January 2011 to 30th June 2011, a total of 105 patients presented to the Accident and Emergency department of Mater Dei Hospital, Malta, with acute onset of chest pain, where an electrocardiogram in each case showed acute STEMI. These subjects were candidates to undergo PPCI.
Permission for PPCI data covering this period was obtained from the cardiologist consultants, the Mater Dei hospital administration and the data protection office. The researchers kept no personal data of the subjects in this study.

A total of 105 patients were identified and analyzed by using the Cardiac Investigation and Patient Record (CIPR) software available at the time of presentation and during data collection. The CIPR software was Maltese designed software used at Mater Dei Hospital to log in and save all data from angiograms and angioplasties performed[7], along with any other re-admissions requiring further interventions for each patient. Using this software, each patient under study was individually screened to assess for any additional interventions in the following 12 months. Nowadays, this software has been superseded by international software.

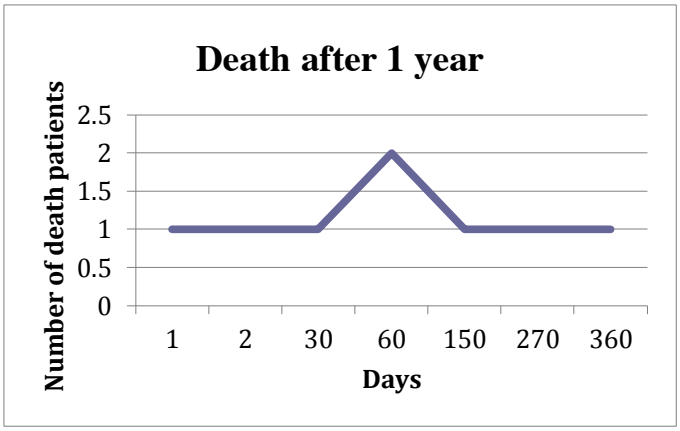
Special attention was given to those patients that were admitted again for additional target vessel revascularization after their STEMI admission. Survival outcomes of these patients were determined using mortality data obtained from the Department of Information, Health and Research, Ministry of Health, the Elderly and Community Care, Malta.

Results

Of the 105 patients having undergone PPCI in the studied period, 81% of the patients were men (n= 85).

The death rate in this cohort after a year was 8.6% (n=9), with 4.8% being men (n=5) and 3.8% female (n=4), with their age varying between 67 years and 95 years. Graph 1 shows the time of death after PPCI.

***Graph 1**: Time of death after PPCI*



20% of the patients (n=21) had a scheduled repeat coronary angiogram 1 to 3 months after the PPCI. 9.5% (n=10) did not require any further intervention, while one -0.95% was found to have triple coronary artery disease and was referred to the cardiothoracic surgeons for coronary artery bypass grafting (CABG). Of the remaining 9.5% (n=10), one - 0.95% needed target vessel revascularization (i.e. PCI to the same vessel that had the initial PPCI) while the other 8.6% (n=9) had had PCI to other coronary vessels. One of these patients died 3 months following the scheduled PCI.

There was a re-admission rate of 5.7% (n=6) who presented to the Accident and Emergency department again with another episode of chest pain, out of which 0.95% (one) presented with another acute STEMI requiring PPCI due to an in-stent thrombosis. The other 4.75% (n=5) patients underwent an inpatient coronary angiogram, with 2 proceeding to PCI. 0.95% (n=1) out of the patients undergoing inpatient coronary angiogram had previously undergone scheduled repeated coronary angiography, which had taken place 15 days prior to the re-admission with chest pain.

The majority of the patients - 63% (n=66) did not experience any cardiovascular related episodes requiring interventions within one year of having had PPCI.

Discussion

In certain STEMI cases such as those with onset of chest pain exceeding 12 hours, thrombolysis is usually undertaken at Mater Dei hospital.

The majority of the subjects presenting with STEMI were men. This may be due to the fact that men are more at risk to develop cardiovascular disease throughout the

world especially when compared to premenopausal women.

In a recent meta-analysis, a significant death reduction was found in patients having undergone PCI as compared to thrombolysis though no significant reduction was found in cardiac deaths and myocardial infarction[8]. In the DANAMI-2 trial it was shown that a significant reduction in the primary endpoint of death, re-infarction and stroke after 30 days with PPCI was evident[9].

Nowadays, as per latest guidelines, patients need to be on dual antiplatelet therapy (Aspirin and Clopidogrel) for a period of 1 year after a myocardial infarction in Malta. In 2010, the practice was slightly different, where patients were discharged on aspirin and ticlopdine. Ticlopidine is not as effective as an antiplatelet agent as clopidogrel, where at the time it was not yet available on the NHS drug formula.

Scheduled angiograms after PPCI are usually booked for patients having extensive coronary disease either to the culprit vessel or to other coronary vessels.

The re-admission rate after the initial PPCI was low due to cardiovascular-related conditions requiring further intervention. There was only one re-admission related to stent restenosis and required target-vessel re-vascularization. Stent thrombosis is a relatively rare complication.[10]

Two studies were found on re-admissions after PPCI, stating that re-admissions due to associated cardiovascular complications are more likely to occur within 30 days of the PCI.[11-12] When implementing this to our study, only 1 subject was re-admitted with chest pain within the 30-day window post-PPCI. The remainder 5 patients were re-admitted beyond the 30-days of PPCI. The 30-day re-admission rate in some countries has now become a "quality indicator" for congestive heart failure as well as to acute myocardial infarction and being used as a means to assess health systems.[13]

Possible closer follow-up after PPCI might have identified some of these cardiovascular problems at an earlier stage and prevented the re-admission.[14] Assessing compliance to medications might prevent re-infarction, bleeding and stent thrombosis.[15]

The majority of the subjects that had undergone a PPCI in this study did not present to hospital in need of further cardiovascular associated invasive procedures within the one-year follow-up. This could be interpreted, as suggesting that the majority of the PPCI's performed was successful.

Study limitations

None of the patients were actually contacted nor was their medical file reviewed; therefore one cannot say whether their deaths were directly linked to cardiovascular consequences. Also, this does not allow for further discussion on the effects of other therapies and co-morbidity. Any data missing from the software used would also have been left out from this study. Due to lack of electronic medical records for outpatient visits, any patients presenting to the cardiac medical outpatients within the follow-up period was not included in this study. Only patients having undergone invasive procedures at the hospital were taken into consideration. All subjects presenting to private hospitals were excluded.

The study lacked information on the medical history and presence of any co-morbidity that may have been present for each patient and which may have led to their differing prognosis.

Conclusion

This study documented that re-admission rates over a 1-year follow-up period requiring further interventions were low. The majority of the re-admissions were for scheduled angiograms. The possible strategy for the other unplanned re-admissions would be shorter duration to follow-ups at the medical outpatients to prevent development of complications as well as monitor treatment compliance. Interestingly to notice is that the majority of the studied cohort needed no further cardiovascular interventions over 1-year. Additionally the death rate was relatively low. This information is important when assessing the quality cardiovascular interventional service provided by our state health system.

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Original Article

Motor Neurone Disease (MND/ALS) among Maltese in Malta and Australia: many sporadic cases were related

H. V. Wyatt

Abstract

Objective: to look for genetic links between cases of MND.

Method: to search for ancestors of Maltese cases dying in Malta and Australia and to record dispensations for consanguineous marriages.

Results: the median age of death was similar in both countries and in Malta was similar for men and women. Almost 45 % of the cases were related to one or more other cases: however, more than half were sporadic and widely dispersed.

Conclusions: MND is not affected by emigration to the southern hemisphere and different life styles. Many MNDs are related and may represent a sub-group.

Keywords

amyotrophic lateral sclerosis, Australia, consanguinity, kinship, Malta, motor neurone disease.

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Introduction

'The clinical and biological evidence that ALS [amyotrophic lateral sclerosis] or motor neurone disease, MND) cannot be a single disorder…allows for a novel approach to pharmacological strategies.'[1] This study suggests that many of the sporadic cases are related to other cases and may form a sub-species of the disorder.

The islands of Malta and the smaller Gozo lie between Sicily and Africa and have a compact population with good medical services and marriage records. Until WWII all were Roman Catholic, most lived in small villages and often married within local groups. The Maltese are a blend of Arab and South European peoples with some from the Knights Templar and more recent additions from eg Italy. With the British dockyard and administration, some British men married Maltese girls, mainly in Valletta, Senglea and Cospicua. When infant mortality fell dramatically in the late 1940's, Maltese children were encouraged to emigrate, especially to Australia where death certificates record the place of birth (eg Malta). Before 1990 few Maltese death certificates recorded motor neurone disease (MND/ALS).

Materials and methods

This study comprises 196 Maltese whose death certificates included a diagnosis of MND and six whose diagnosis has been confirmed by their neurologists. Forty eight had emigrated to Australia, two had been born in the USA, but had returned to Malta, and one was resident in England. Twelve had been born in Gozo, two of whom died in Australia. One death in the USA and three in Britain were found from Maltese newspapers. The two earliest births were in 1898 and the latest was in 1979 (he died age 20 yr). The Health Information Unit (Malta) kindly gave me verified deaths from MND since 1990 and Dr Geoffrey Dean provided earlier cases from Malta and Australia. State registries in Australia sent photocopies of deaths from MND of those born in Malta. Data Protection Law as interpreted by Victoria State, Australia has meant that the last case was from November 2004. Initially, all were traced to their great-grand parents, but some rare surnames suggested that cases might be linked, so I followed their ancestors to about 1820 or so. Marriages and births were traced in the

Public Registry and, before 1863, in parish records. Some marriages were never registered, others were made overseas (Egypt, Crete, Gibraltar, Libya, etc), a few were not blessed by the church, some children were adopted and others were born without naming the father. Some parish registers omit the mother's maiden name. One father was untraceable, one great grand-parent was 'unknown' and one case was adopted. One Italian and four British cases were excluded. Marriages were checked for dispensations for consanguinity in the Curias of Malta and Gozo and in parish records. Consanguinity is shown by roman numerals eg II is a marriage of two first cousins, and by double lines between bride and groom. All marriages to foreigners were followed, as many had ancestors who had married Maltese. Some marriages in Gibraltar, Tunis and USA were traced, but Egyptian records were destroyed in 1956.

Results

Diagnosis

All cases were diagnosed as 'MND'. Cases 34 and 132 were diagnosed as 'pseudo bulbar palsy', cases 38 and 111 as 'progressive MND' and 32 as 'mixed bulbar and pseudo bulbar palsy'.

Age at death

The median age at death was very similar for men and women in Malta, for those from Gozo and for the emigrants to Australia although the ranges were different (Table 1, Fig. 1). Most of the emigrant children to Australia were boys and the median domicile was 31 yr (Table 1). The age at death was probably typical (Fig. 1) although the two youngest were possibly rare.[2] Of those in Malta, 36 died in the three months December (13), January (12) and February (11) and only 52 in the other nine months

***Table 1**: Median age at death of MNDs*

		N	Median age	Range yr	Median domicile
Gozo		16	64 yr	28 - 80	
Malta	Men	84	64 yr 5m	20 - 88	
	Women	57	63 yr 7m	34 - 84	
Australia	(34 men, 14 women)	48	64 yr	36 - 90	31 yr range 11–57

Kinship

There were 80 (45%) cases with links to at least one other. I have used kinship as a neutral term to describe these links. There are probably 22 (11 %) familial cases in Kinship 2 (Fig. 2) and Kinship 1 (Fig. 4). Only Kinships 1, 2 and 17 had cases in two generations. There were groups with 16, 10, 9, 6 and 4 cases, five groups with three cases and 14 groups with two in each (see Figures).

Location

I have used the 1901 populations to compare the incidence in different parishes, based on the homes of the grand-parents. Some kinship groups were based on one parish, while some were from eight or more villages. A few older parishes were very large and have since been reduced. Where parish boundaries are adjacent, a marriage from two parishes might be between near neighbouring farms. The four areas with the greatest incidence included the three large kinship groups (Table 2).

Table 2: Incidence of grand-parents of MNDs by parishes

Parish or town	Population	No. of cases	No. of cases		Cases 0/00
	1901 census	sporadic	kinship	Total	
Area Y#	c 6,000	8	9.5	17.5	2.7
Village F+	c 6,000	1	10.5	11.5	2
Area H	c 6,000	3.5	9	12.5	1.95
Villages I and J#	c 8,000	7	7	14	1.75
Village D	c 8,000	8.5	3.5	12	1.45
Village E	c 7,000	2.5	7.5	10	1.4
Parish V *	c 2,000	1	2	3	1.25
Valletta, Floriana	22,680	19	9.5	28.5	1.25
Village C	c 3,000	3	0.5	3.5	1.1
Cospicua, Senglea	20,241	10	3	13	0.58
Hamrun	10,293	1,5	-	1.5	0.15

Note:

 # These adjacent parishes were extensive with one large kinship group common to both (kinship 1, Fig. 3)

+ This was the centre of kinship 2 (Fig. 1).

** This isolated parish shared links with Gozo (kinship 20, Fig. 2).*

The population of Malta in 1901 was 164,952.

The next four areas were similar, with two other areas with far fewer cases. Many sporadic cases (Table 2) were widely dispersed. Kinships 5 (six cases) and 9 (two cases) were from a large village, with Kinship 17 (three cases) from and Kinship 4 (two cases) from neighbouring small villages. Nearby were Kinships 3 (four cases) and 10 (two cases) and Kinships 2 (12 cases) and 8 (two cases) at large villages.

***Figure 1**: The age incidence at death of MND cases in Malta and Australia.*

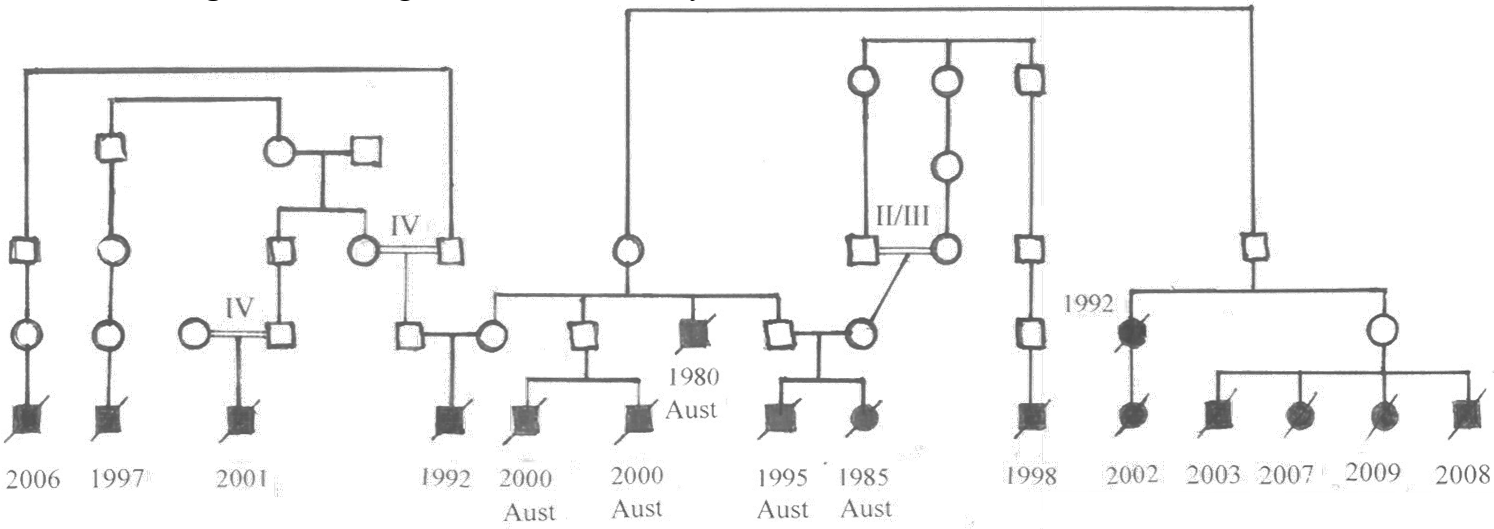
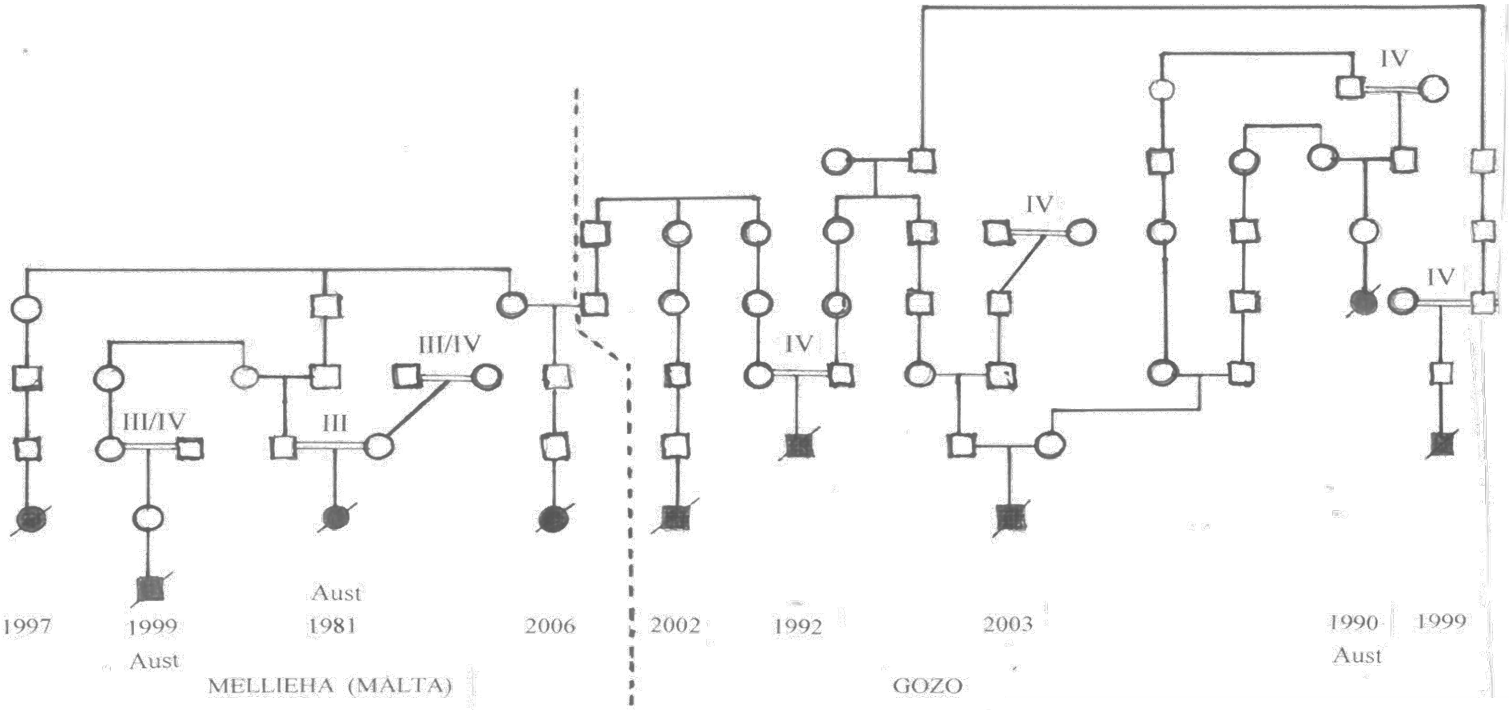


***Figure 2**: Kinship group #2. Seven and perhaps others are probably familial.*



Kin #20

***Figure 3**: Kinship group #20 which had cases from Malta and from the island of Gozo.*

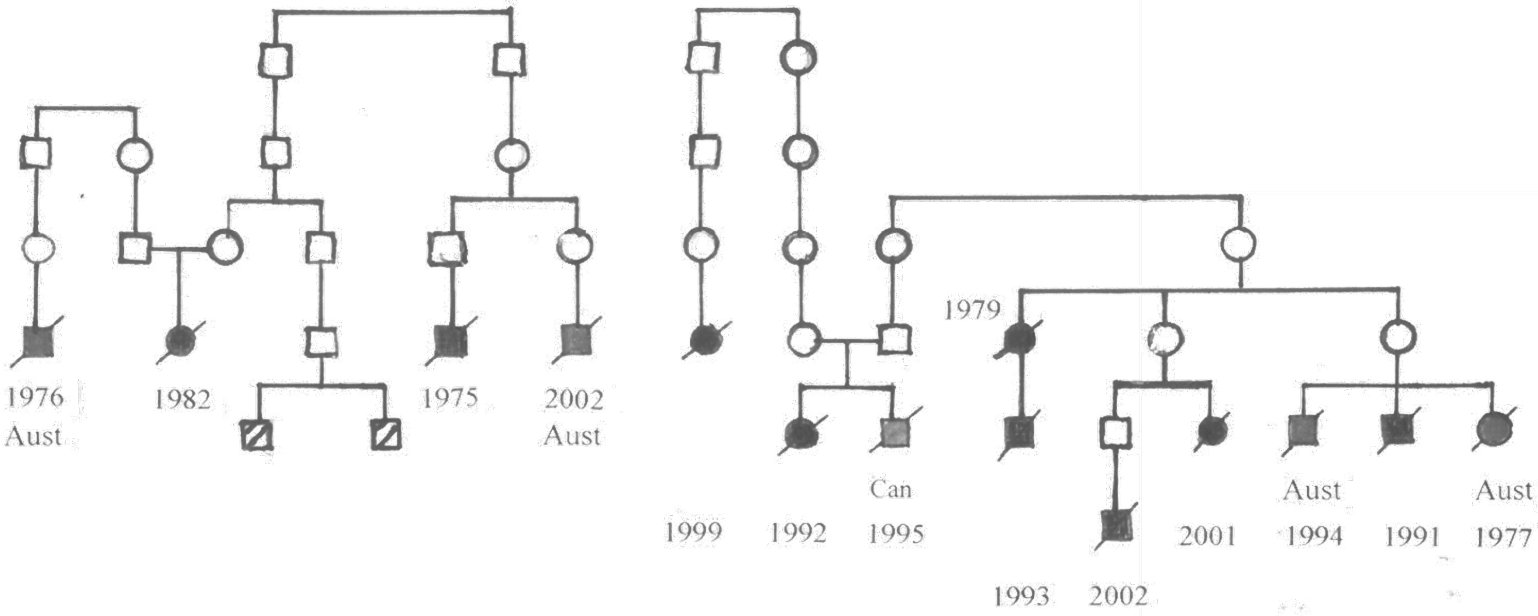


***Figure 4**: Kinship groups #3 and #1. Kinship1 on the right may be familial. The two hatched sibs were paralysed by poliomyelitis.*

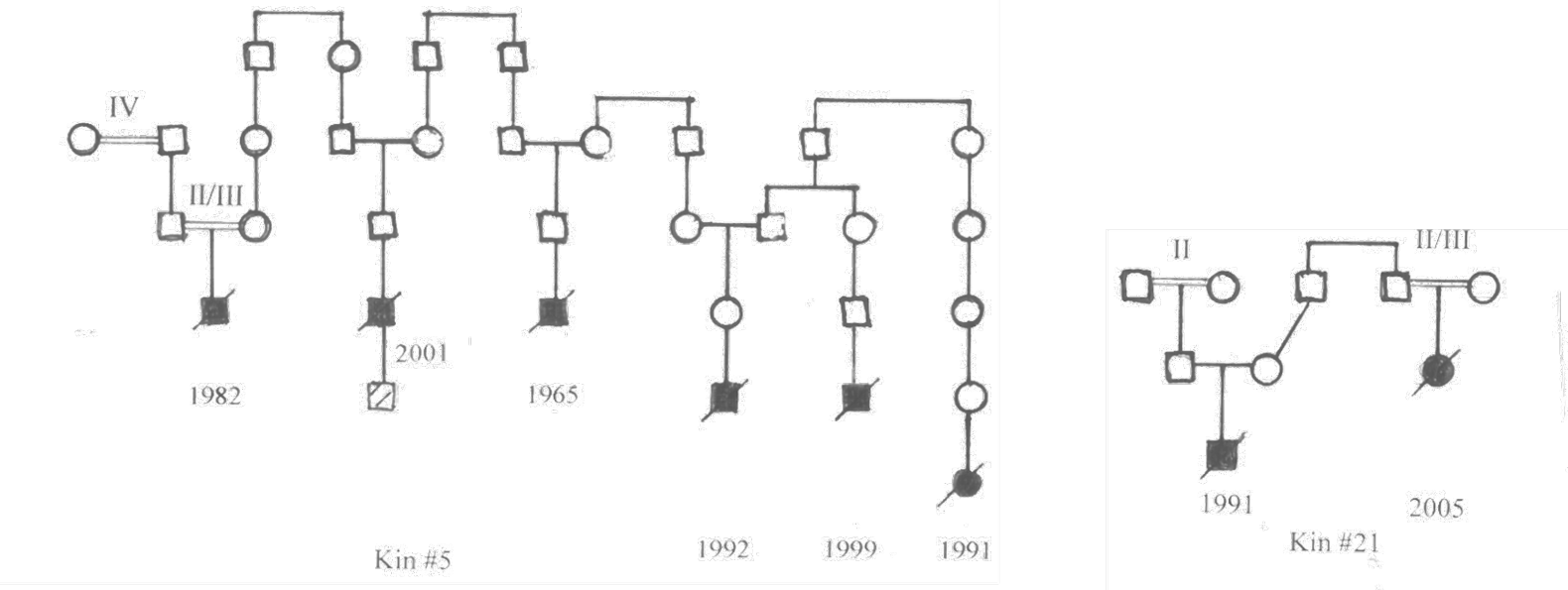


***Figure 5**: Kinship groups #5 and #21.*
The MND who died in 2001 was the father
of a boy with polio (hatched). Kinship groups with 2, 3, or 4 cases in each group. Kinship groups 8 and 11 each have a long term survivor.

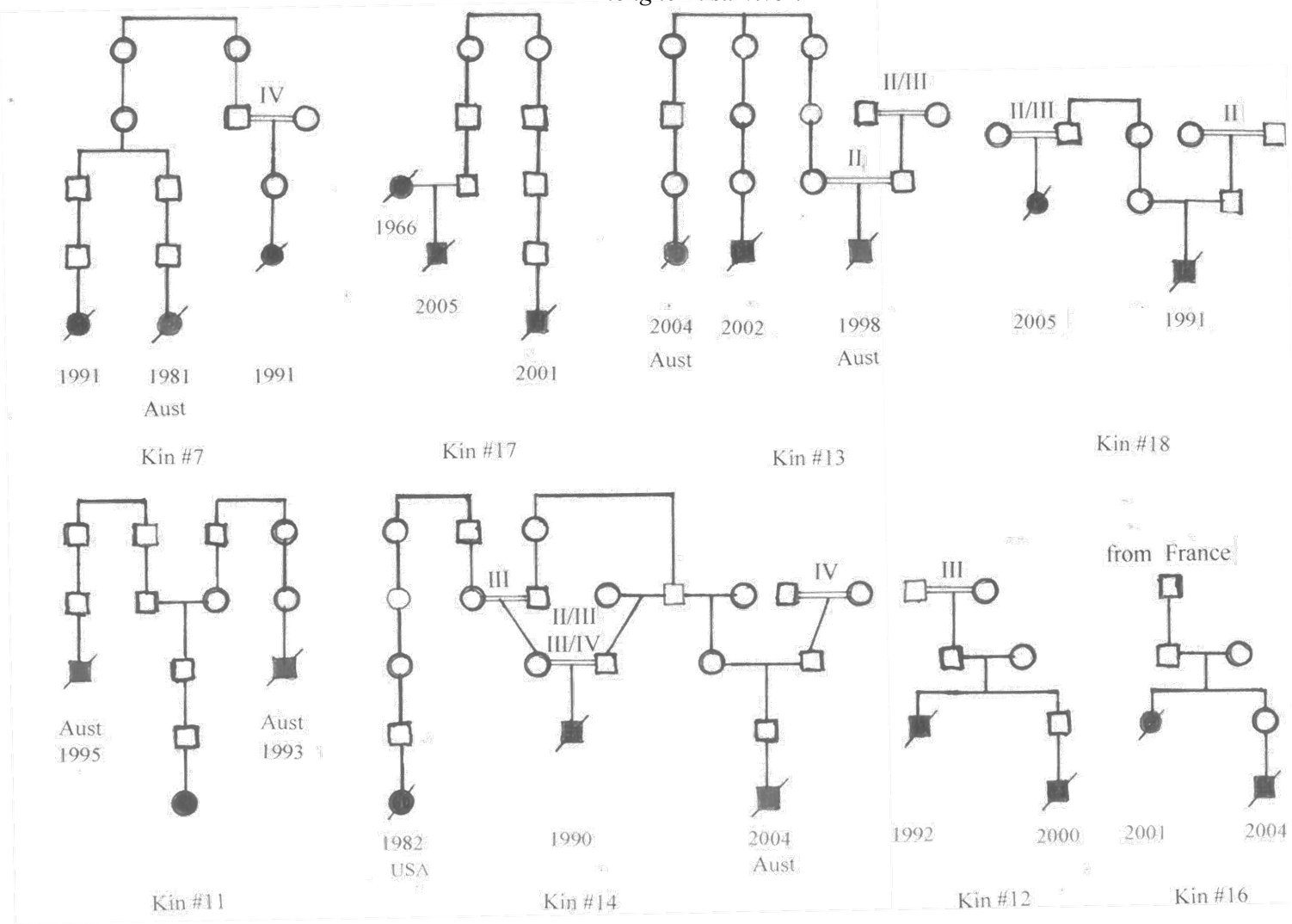
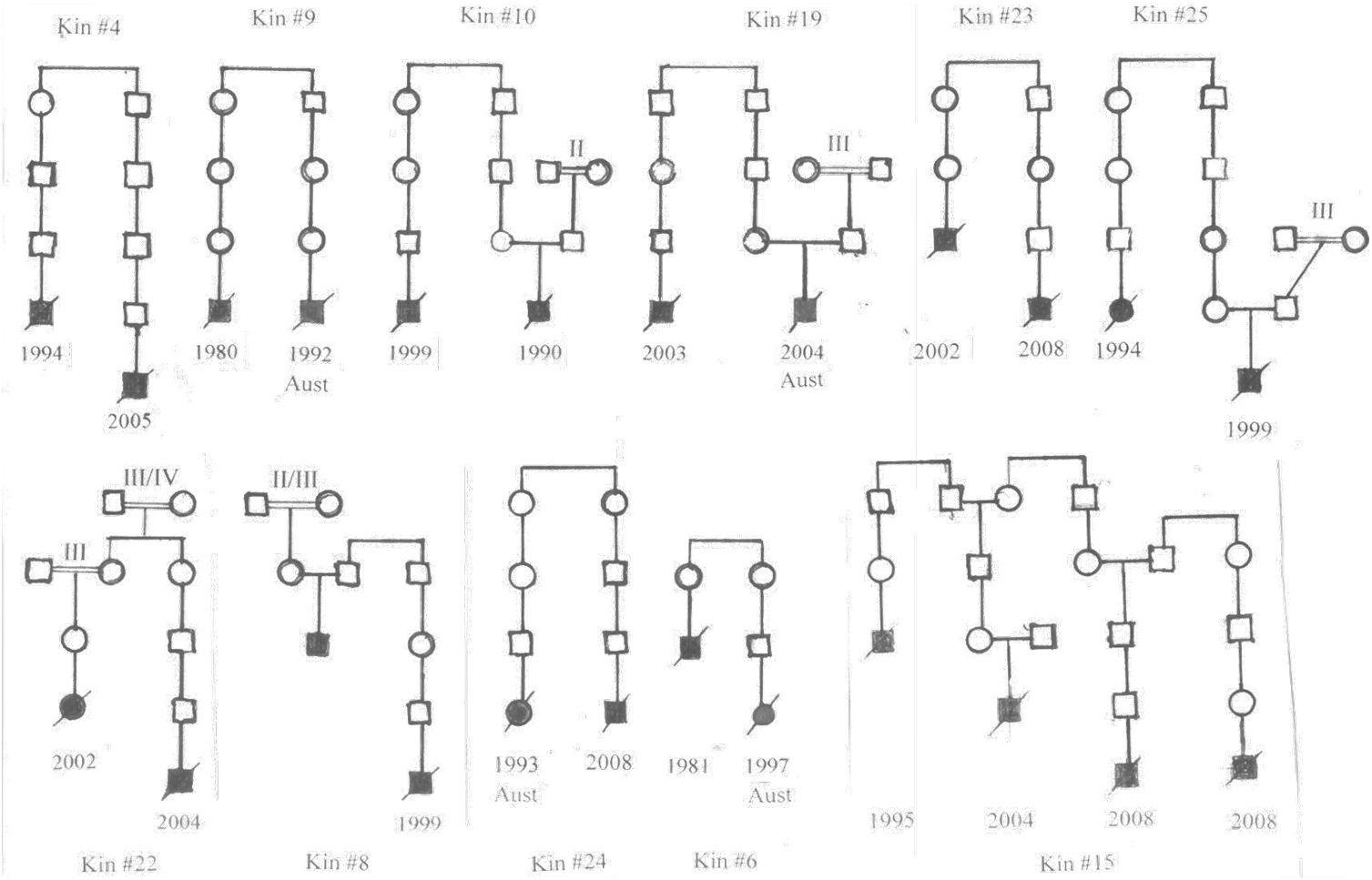


***Figure 5**: Kinship groups #5 and #21.*
The MND who died in 2001 was the father
of a boy with polio (hatched). Kinship groups with 2, 3, or 4 cases in each group. Kinship groups 8 and 11 each have a long term survivor. (Cont.)



Consanguinity

The numbers of consanguineous marriages have changed over the years, peaking at the end of the 19th century, with higher rates in Gozo. Among the MNDs, there was more than twice the proportion on Gozo than on Malta, although there was little difference in each between the two generations (Table 3). Four MNDs had multiple consanguinities of parents and grand-parents (Table 4), including two cases among Kinship 13.

***Table 3**: Consanguinity among marriages of parents and grand-parents of MNDs*

	N marriages	II	II/III	III	III/IV	IV	Total
MND Parents Malta	163	4	3	1	1	3	12
Gozo	15		1			1	2
Grand-parents Malta	313	3	4	7	2	11	26
Gozo	33	1	1	2		1	5

***Table 4**: Multiple consanguinity among parents and grand-parents.*

	Parents	Grand-parents	Kinship group
MND 10	II/III + III/IV	III	13
MND 149	II	II/III	13
MND 27	II/III	IV	4
MND 131	II/III	IV	

Foreign ancestors

Some surnames suggest foreign origin eg Catania and Genovese with many others common in Italy: two cases (Kinship 15) were probably of recent Italian origin. In Kinship 16 the grandfather of the aunt and her nephew were French and the mother of a great grand-parent (case 6) was probably also. Six of these were among the linked cases. One had a Spanish mother. Three had British grand-fathers and six had British great grand-fathers (one of whom had been born in Corfu). One mother was born in Turkey of a British father and a Maltese mother from Egypt. Two cases had British fathers and another, a British mother. Of these 14, only four belonged to linked family groups (see below).

Maltese from abroad

Five had a Maltese grand-parent from Tunisia, Benghasi, Sicily, Kephalonia or Corfu and one father was from Tunis. One father whose mother was probably Italian, was from Tripoli and the mother was probably British from Italy. One case (from Australia) was omitted: his non-Maltese father was from Sicily although his mother, from Tripoli, had a Maltese father.

Incidence of MND

I have only 25 cases who died in Malta from 1965 to 1989. MND was rarely diagnosed or put on the death certificate until consultant neurologists were appointed. From 1990 to 2009 there were 58 686 deaths in Malta (excluding Gozo) of which 122 were MND giving an incidence of 2.1 per thousand. For New South Wales (NSW) from 1991 to 2006, there were 3 298 deaths of those born in Malta, of which nine were MND, an incidence of 2.7 per thousand. The populations were not entirely comparable: the Maltese deaths included all ages with a few foreigners, whereas the NSW deaths were mainly middle-aged males who had come to Australia as young immigrants.

Discussion

Although ten per cent of cases are familial, the remainder are sporadic and the diagnosis with a single name is now thought to conceal a number of different groups with different causes. Without a starting point, a priority is to find what these groups might be. [2] In large countries it is not easy to retrospectively survey families as many are spread over multiple boundaries. Malta, on the other hand, had a population which can be traced, but relatively few MND cases. The population was stable with some addition of foreign genes. It is not possible to find earlier MND cases as there were few hospital notes and the diagnoses will be doubtful: of the first 11 cases, five were subsequently changed on death. Several large 'villages' had no cases in this study, although several villages like B'kara and Sliema grew considerably around 1900.

The median age of death in all the groups was very similar at about 64 yr [3] and would seem to be lower than the ages for England and Wales (see [4]) and lower than the mean age of onset of 65.2 yr for males and 67.2 for females in Scotland. [4] The distribution of familial and other cases suggest no hot spots of special causal factors. The age of death was unchanged by emigration to new lifestyles in a different hemisphere.

The relationships of these MNDs may be due to the small population, about 250,000 in 1940, or may be more obvious than in widely dispersed populations. A marriage of cousins affects only their children, but numerous marriages with consanguinities of grand-parents and great grand-parents may have significant later effects on many children. There are several different groups: familial cases, kinship groups, sporadic cases and six with long-term survival. In other studies, from five to ten per cent of cases are familial, but in Malta may be higher. [5]

With the first 100 and the final 206 cases, there were similar proportions of 46 %. Whether these different Maltese groups represent different clinical entities can only be suggested from this study, which should be continued in both Malta and in Australia with genetic testing of relatives of these and new cases.

This research was approved by the Medical Ethics Committee, Malta and by the Curias of Malta and Gozo. A poster showed earlier results at an MND meeting. [6.] The data on cards, computer print-outs and notes etc will be deposited in the Melitensis Collection of the University of Malta.

I have no interests to declare. My annual stays in Malta were funded from my pension.

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Review Article

An update on pharmacotherapy for type 2 diabetes

Rachel Agius

Abstract

Glucose lowering drugs have been available for clinical use for over the past 60 years or so with the last 2 decades seeing a significant number of new agents being developed making treatment increasingly complex and also somewhat controversial. This stems from the fact that while it is now known that patients with diabetes have an increased risk for cardiovascular disease and mortality there are mounting concerns with regards to the cardiovascular effects of certain antihyperglycemic agents leading to uncertainties when it comes to drug prescription. This has left many clinicians perplexed with respect to optimal strategies for management for management of such patients leading to many regulatory bodies to issue recommendations for antihyperglycimic therapy in adults with type 2 diabetes. These all uniformly advocate an individualised approach, keeping in mind each patients' unique health profile (such as age and weight) and their cardiovascular risk factors vis-a-vie the specific attributes, side effects and adverse effects of each antihyperglycemic agent. This article will focus on the ten major categories of diabetic therapies looking specifically at their mode of action, safety profile as well as key trial data and where possible the long-term outcome studies for each class.

Keywords

Type 2 diabetes, Antihyperglycemic agents, Cardiovascular risk, hypoglycemia

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Introduction

The last few decades have seen a considerable increase in the therapeutic armamentarium for the management of patients with type 2 diabetes (T2 DM). As the incidence and prevalence of diabetes continues to increase worldwide so has been the struggle to find the ideal antihyperglycemic agent which is cost-effective at achieving and maintaining near-normal blood glucose levels, but also has a favourable safety profile, has good tolerability with limited side effects and possibly also exerting positive effects on surrogate markers of cardiovascular risk[1-3] This stems from the fact that patients with T2 DM have an increased risk of cardiovascular morbidity and mortality and while data from recent key trials have shown that tight glycaemic control results in sustained reductions on microvascular event rates (including nephropathy, neuropathy and retinopathy), strict and aggressive blood glucose control does not necessarily exert beneficial effects on macrovascular events and may actually increase mortality.[2-9] Thus, keeping in mind that the ultimate aim for diabetic patients would be to reduce this excess cardiovascular risk one should look at other characteristics of anithyperglycemic agents independent of glycemic control which may influence cardiovascular outcomes in such patients.[2] In fact over the past few years, many questions have arisen regarding the cardiovascular safety or otherwise of drugs used to treat diabetes. This occurred following the results of a highly publicized meta-analysis in 2007 concerning the thiazolidinedione rosiglitazone. Here the authors demonstrated a significant increase in risk of myocardial infarction (odds ratio 1.43) and death from cardiovascular (CV) causes (odds ratio 1.46) with rosiglitazone use fuelling a lot of controversial issues with respect to prescribing this drug as well as stimulating the debate on whether diabetes drugs should have long-term trials showing cardiovascular safety [10-11]). This eventually led the U.S. Food and Drug Administration (FDA) to issue a 'boxed warning in the drug's labelling about potential increased risk for heart attacks'. Furthermore in 2008 it also issued new recommendations with respect to evaluation of cardiovascular risk in the premarketing and postmarketing assessment of novel antidiabetic therapy defined as the upper bound of the 95% Confidence Interval for major adverse cardiovascular events

(MACE) of < 1.3 leading to profound changes to the way new antidiabetic drugs are developed.[6,12-15] Keeping all this in mind, this article will focus on the ten major classes of drugs used to treat T2DM focussing on their mode of action, their safety profile as well as key trial data and where possible the long-term outcome studies for each class.

Sulphonylureas

Sulphonylureas (SU) have been in use for the past 50 odd years making them the oldest class of oral antihyperglycemic agents. They are the major insulin secretagogues and their mode of action is well understood. These exert their effect by binding to the adenosine triphosphate (ATP)-sensitive potassium channels situated on the Beta (β)-cells inhibiting potassium efflux leading to subsequent depolarization of the β-cell, which ultimately results in insulin secretion.[16-19] Interestingly these ion channels are also present in cardiac myocytes and have been implicated for the adverse effects of SU on the heart.[2] There are a number of agents available in this class with the major difference between them being in their side-effect profile and their duration of action. SU reduce HbA1c by around -0.9 to -2.5% and have thus been advocated for use as monotherapy and first line agents in non-obese individuals or in combination with other antihyperglycemic drugs.[1,16-18] The well-known side-effects of these drugs include the risk of hypoglycaemia and weight gain. Much of our knowledge on SU comes from the United Kingdom Prospective Diabetes Study (UKPDS). This landmark multicentre study which was carried out over 20 years between 1997 and 1999 in the UK randomised more than 4000 newly diagnosed type 2 diabetic patients to either intensive treatment with insulin or SU (with a small subset of overweight patients being given metformin instead) or to conventional therapy consisting of dietary and lifestyle modification. Patients randomised to intensive treatment with SU/insulin showed a lower risk of microvascular complications (25%) then conventional therapy as well as a non-significant (16%) reduced risk of myocardial infarction (p=0.052), however, this was at the expense of significantly greater weight gain which however was less than in those treated with insulin. Hypoglycaemic episodes were more frequent in the intensively treated group however patients assigned to SU treatment exhibited lower rates of both minor and major hypoglycaemia when compared to those on insulin therapy.[18-22] On the other hand, the specific effects of SU therapy on CV outcomes is still conflicting. Previous studies (including the University Group Diabetes Program [UGDP] which used the older generation SU tolbutamide) have implied that SU treatment may be associated with adverse CV effects.[23] Conversely in the UKPDS, this suggestion was not reproducible as none of the SU used showed an increased rate of adverse CV outcomes.[22, 24] Furthermore, in the 10-year post trial follow-up of the UKPDS, the sulphonylurea-insulin group continued to have significant risk reductions for any diabetes-related end point, microvascular disease, all-cause mortality as well as significantly reduced risk for myocardial infarction despite convergence in glucose control between the different treatment arms after one year.[21, 22] This implies a legacy-effect and that early aggressive glycaemic control led to sustained benefits after 10 years of follow-up with respect to microvascular disease with the added benefit of reduced macrovascular events which were not seen during the interventional phase of the trial.[19,21-22,24] Recently meta-analysis looking at cohort and case-control studies showed that SU monotherapy or in combination treatment was associated with higher all-cause and cardiovascular mortality risks when compared to patients receiving non-SU treatment. The authors explain that the potential causes for this could be due to four specific effects of SU therapy namely hypoglycaemia, weight gain, increased proinsulin release and activation of SU receptors on myocardial muscle cells. However they caution that these results should be interpreted carefully not only because data from randomised controlled trials was missing but also because the data had high treatment group heterogeneity.[25] Interestingly these findings were also echoed in another meta-analysis by an Italian group of authors published in the same year.[26] Another important issue that emerges from the UKPDS is the effect of SU on β-cell function. The widely held view that SU are associated with loss of β-cell function is not reproducible in this study as it was found that the percentage mean β-cell function decreased in all groups irrespective of the treatment modality used[19] Thus while treatment with SU has been established over the last 5 decades or so, they should be used judiciously within a multi-factorial risk reduction strategy and treatment tailored according to the patients characteristics (such as age and weight), presence of co-morbidities and other risk factors [25].

Biguanides

The widely available drug in this class is metformin and its use has been around for the past five decades or so, thus establishing itself as a safe and cost-effective glucose lowering agent such that most guidelines now uniformly advocate its use as a first line agent in the management of overweight or obese type 2 diabetics[1]). Metformin has been classified as an insulin sensitizer but its mode of action has only recently been understood. This involves activation of an adenosine monophosphate (AMP)- kinase enzyme which plays an important part in carbohydrate and lipid metabolism as well as inhibition of mitochondrial respiration leading to inhibition of hepatic glucose production, increased

glucose uptake in contracting muscle, increased fatty-acid oxidation, decreased lipolyisis and enhanced insulin sensitivity without the undesirable side effects of weight gain or hypoglycaemia.[17, 1, 27-29] Metformin, when used as monotherapy has been associated with a reduction in glycated haemoglobin (HbA1c) of between -1.1% to -3% [18](). Two important clinical trials using metformin are the Diabetes Prevention Program (DPP) and the UKPDS. In the DPP, metformin showed a 31% reduction in diabetes incidence over approximately 3 years and this effect was sustained in the ten-year follow up of the DPP suggesting that metformin is a good long-term strategy for diabetes prevention.[27,29-30] In the UKPDS trial, patients randomised to treatment with metformin achieved similar FPG and HbA1c levels to those randomised to treatment with insulin or sulfonylurea however with the added benefit of no weight gain and reduced risk of hypoglycaemia[31]). With respect to complications, in the UKPDS metformin was associated with a 32% lower risk of developing any diabetes related end-point, a 36% lower risk of all-cause mortality, a 42% risk reduction for diabetes-related death and 39% lower risk of myocardial infarction then in the conventionally treated group.[27-31] Moreover, these results were sustained in the 10 year follow-up study albeit differences in glycemic control were blunted after the first year of follow-u [21, 28] This study thus implies that metformin has numerous advantages notably amelioration of macrovascular risk that make it the ideal first choice treatment in obese diabetics [27,30]). Metformin has also been associated with a reduced incidence of the metabolic syndrome (by 17% when compared with placebo) in the DPP.[29] Moreover several meta-analysis have also shown that metformin exerts favourable effects on surrogate markers of CV risk with reduction in fasting and postprandial plasma triglycerides, low density lipoprotein (LDL)-cholesterol, and free fatty acids.[18, 28] Another important landmark of metformin is its effects on heart failure. It has been shown that metformin monotherapy is associated with reduced mortality rates as well as lower hospitalization rates in subjects with heart failure when compared with other anti diabetic drugs.[28, 32] Another important feature of metformin is its role in fertility in women with Polycystic Ovary Syndrome (PCOS) with recent studies showing that therapy with metformin significantly improves pregnancy rates as well as live-birth rates.[28] Metformin has also been associated with anti-neoplastic properties due to its action on AMPK which leads to inhibition of the mammalian Target Of Rapamycin (mTOR) causing inhibition of the cell cycle.[28] Metformin's anti-neoplastic effects range from solid to haematological malignancy, however further research is required in this field. The main documented side effects of metformin include gastrointestinal adverse effects, notably bloating, diarrhoea, flatulence, and abdominal cramps.[1,27-28] These are usually off-set by introducing metformin at a low dose and increasing it gradually over a few days to weeks. The risk of lactic acidosis is actually very rare with studies showing that this event may occur in situations associated with a tendency for hypoxia or acidosis – such as sepsis or acute heart failure.[27,29] Metformin has also been associated with vitamin B deficiency, however, this too is a rare event but should be sought in patients with macrocytic anaemia, peripheral neuropathy or cognitive impairment.[27,29] With respect to long-term outcome studies on metformin, the UKPDS trial and its 10-year follow up show convincing evidence that metformin is as good as sulfonylureas or insulin on glycemic control and it was the only drug to show a reduction in myocardial infarction rates which persisted in the 10-year post trial follow-up. Meta-analyses have shown that the benefits of metformin on cardiovascular risk were observed in those trials compared with placebo or no therapy (CI 0.64-0.98, p=0.031) but disappeared when compared to active comparator trials suggesting that the cardiovascular protection is due to the improved glycemic control.[22, 33] Taking all this into account metformin is still considered a safe drug and given its low cost is an ideal agent for first line treatment in type 2 diabetes.

Thiazolidinediones

Thiazolidinediones (TZDs) are insulin sensitizing agents and work primarily by activating the peroxisome proliferator-activated receptor (PPAR)-γ leading to increased transcription of genes involved in glucose and lipid metabolism as well as energy balance. One of these is the glucose transporter GLUT-4 which in the presence of insulin is associated with increased glucose uptake. PPAR-γ is also expressed in adipocytes and endocrine signalling from adipocytes results in enhanced adipognensis and decreased fat breakdown (mediated by signalling factors such as free fatty acids and TNF-α) leading to a reduction in liver fat and improvement in insulin sensitivity in liver and muscle.[1, 18, 22] The two available TZDs are rosiglitazone and pioglitazone however, concerns associating rosiglitazone with increased risk of ischemic cardiac events (as already mentioned in the introduction of this article) led to the withdrawal from marketing authorisation of this drug within the EU in 2010 by the European Medicines Agency (EMA) and highly restricted access within the States by the FDA.[1, 10, 12, 18, 34] Over the last few years TZDs have been studied in a number of trials, mostly to assess efficacy and durability of these drugs as well as their long-term outcomes and safety profile. TZDs are comparable to metformin and SU when it comes to glucose lowering, with an approximate HbA1c reduction of between -1.2% to -2.3% over a period of 3 to 12 months.[18, 22] They are not associated with increased risk

of hypoglycaemia and the A Diabetes Outcome Progression Trial (ADOPT), showed that rosiglitazone was associated with a lower cumulative incidence to monotherapy failure at 5 years then did metformin or glyburide suggesting that it had greater glycemic durability over the other drugs.[22, 35] The most common side-effects of these drugs include weight gain, fluid retention leading to peripheral oedema as well as contributing to heart failure, effects on lipid profile as well as an associated increased risk of bone fractures in women in the long term.[1, 22, 34] Weight gain is dose-dependent and more pronounced when TZDs are used with insulin. With respect to their effect on lipid profile and other biochemical parameters, several studies have shown that TZDs are associated with an overall improved lipid profile with respect to HDL-C and TG, however in one study rosiglitazone was associated with significant increases in LDL-C. Other improved cardiovascular parameters include a lowering of highly sensitive (hs)-CRP (anti-inflammatory effect) improved endothelial function and a reduction in procoagulatory state.[18] The side effect of fluid retention with TZDs is widely recognised as is the associated consequence of heart failure, however, their effect on other cardiovascular end-points have been of much debate over the last few years. When looking at individual clinical trials as well as meta-analyses of RCT and observational studies with respect to cardiovascular events, studies on rosiglitazone seem to show an increased risk while studies on pioglitazone show a possible cardiovascular benefit.[10, 36-40] Although the meta-analysis by Nissen and Wolski in 2007 showed that there was a significant increased risk of myocardial infarction, angina and cardiovascular mortality in patients taking rosiglitazone when compared with metformin, SU or placebo, this meta-analysis was heavily criticised for excluding studies with no relevant events and that some trials were too short to assess cardiovascular outcomes.[10, 41] On the other hand the RECORD (rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes) study (which was a multicentre, randomised, open-label non-inferiority trial) showed that rosiglitazone did not increase the risk of a composite end point of MACE when compared with SU or metformin, but it did not rule out an elevated risk of myocardial infarction.[37, 42] The results of this study were also questioned partly in view of the open-label, unblinded design as well as concerns regarding data integrity which led to the FDA to ask for readjudication of the data. Following this, the results which emerged were reassuring that rosiglitazone was not associated with excess cardiovascular risk which eventually led the FDA in 2013 to remove some of the prescribing and dispensing restrictions on rosiglitazone.[15, 43] With respect to pioglitazone, several leading studies have shown a benefit of this drug on cardiovascular end-points. The notable PROactive (PROspective pioglitazone Clinical Trial In macrovascular Events) randomised controlled study found that in patients with prior evidence of macrovascular disease, pioglitazone was associated with reduced risk of all-cause mortality, myocardial infarction (MI) and stroke.[39] These differences on cardiovascular risk between pioglitazone and rosiglitazone are thought to be brought about by their differences on blood lipid profile – with pioglitazone having better effects on TG and HDL-C.[6] However, the PROactive study did show an increase risk of oedema and congestive heart failure (CHF) in the pioglitazone treated groups when compared with placebo. An important feature not to be missed but is seen in most of the studies mentioned above is the fact that TZDs all have a decreased incidence of stroke.[22] With respect to fracture risk the ADOPT study showed an increased risk of distal bone fractures in women above the age of 60 with more fractures of the upper-limb and foot rather than femoral neck or vertebrae thus stating that care should be taken when prescribing TZDs to female patients with regards to fracture risk.[6] The fact that pioglitazone is both a PPAR-γ and α agonist, it has been linked to possibility of bladder cancer. A recent cohort study showed that short term use of pioglitazone was not associated with increased bladder cancer incidence, however increased risk is seen if treatment is given for more than 2 years.[44] In light of all this one may wonder what is the place of these drugs in treatment strategies for patients with type 2 diabetes. Judicious use on an individualised basis should be the way forward with the hope that ongoing studies may shed more light and provide definitive answers.

'Glinides' (Meglitinides)

This class of antihyperglycaemic agents is also classified as insulin secretagogues, however they have a more rapid onset and shorter duration of action when compared to SU. Their mode of action is similar to SU in that they also bind to the ATP-dependent K^+-channel on cell membranes of pancreatic β-cells, however they exert their actions via a different binding site.[45] The fact that glinides have a short metabolic half-life (< 1 hour) with a fast onset of action makes them suitable as a prandial glucose regulators and hence ideal agents to cover the glucose load associated with meals. Thus, repaglinide allows for flexibility of dosing such that if a meal is missed then so is the corresponding dose and this will in turn lead to a reduced risk of hypoglycaemia. One study on repaglinide assessed glycemic control after patients were randomised to treatment with either this drug or placebo. Use of repaglinide was associated with significantly lower values of HbA1c, fasting and postprandial glucose (FPG, PPG) then placebo and at the end of the study there was a mean group difference in HbA1c of -1.7%. The commonest adverse event

encountered in both treatment groups was mild-to – moderate hypoglycaemia with most of the events in the repaglinide treated group occurring during the dose-adjustment period.[45] In another study, repaglinide was administered to patients uncontrolled on metformin monotherapy. This led to significant reductions in HbA1C and FPG then when repaglinide or metformin were given on their own suggesting synergism when metformin is combined to repaglinide however, there was a significant increase in body weight with repaglinide use.[46] Thus this agent appears to be an ideal component in managing type 2 diabetes as it has desirable characteristics which make it advantageous for use in certain patients such as the elderly (due to decreased risk of hypoglycaemia) or in patients with renal impairment due to its preferential metabolism in the liver.[45]

α-glucosidase inhibitors

This class of drugs suppresses glucose levels by preventing the digestion and absorption of complex gut carbohydrates (starch and sucrose) secondary to inhibition of intestinal α-glucosidase, thus lowering the post- prandial blood glucose level. These agents are used more infrequently nowadays, globally, mostly due to their renowned gastrointestinal side effects of flatulence and diarrhoea.[1, 18, 22] They commonly reduce HbA1c by around -0.6 to -1.3% and are approved for use both as monotherapy and in combination with other anti hyperglycaemic drugs.[18] With respect to weight, a Cochrane review stated that treatment with acarbose (the most commonly used α-glucosidase inhibitor) is associated with around -1.2kg weight loss in patients with prediabetes compared to placebo treatment. Furthermore there were nonsignificant ameliorations in serum lipid levels as well as BP.[18] A commonly cited meta-analysis on acarbose (which included 7 placebo-controlled RCTs) found that this drug was associated with reduced risk of 'any cardiovascular event' and also MI.[47] Another RCT called the STOP-NIDDM assessed the effects of acarbose on development of frank diabetes in patients with impaired glucose tolerance. Here the authors found that decreasing the post-prandial hyperglycaemia was associated with a 49% risk reduction in developing any cardiovascular event with the major reduction occurring in the risk of MI. There was also a statistically significant reduction in BP, even though it must be acknowledged that there were a significant number of patients who discontinued treatment due to side-effects.[48] However in a substudy of the UKPDS, patients randomised to acarbose did not have any significant differences on the risk of major clinical events.[49] Thus, although there is no doubt about the benefits of acarbose on blood glucose lowering, data with respect to cardiovascular risk is still conflicting.

Amylin analogues

Amylin is a peptide hormone which is co-secreted with insulin from pancreatic β-cells following ingestion of nutrients of which secretion is either absent or diminished in diabetic patients. Pramlintide, which is an amylin - receptor agonist is an equipotent synthetic analogue to amylin and has been approved for treatment of both type 1 and type 2 diabetes since 2005. It is thought to exert its glucose lowering effects by suppression of endogenous postprandial glucagon production leading to suppression of postprandial hepatic glucose production, by reducing gastric emptying time as well as induction of satiety through centrally mediated mechanisms leading to a reduction in postprandial glucose levels.[1, 18, 50-51] Treatment with Pramlintide has proven to be efficacious in both type 1 and 2 diabetes with beneficial effects on various metabolic parameters including HbA1c, weight and lipid levels. Since pramlintide is a peptide, it must be administered via the subcutaneous route (like insulin) to avoid degradation by gastrointestinal acids. In type 2 diabetes, it has been approved for use as adjunctive treatment to mealtime insulin in patients with or without concurrent use of SU and/or metformin in patients not achieving adequate glucose control. The observed reductions in HbA1c were around -0.6% and this was not accompanied by any increases in hypoglycaemia as well as proportionately lower total daily insulin doses in type 2 diabetics.[50] With respect to weight, pramlintide was associated with significant reductions in weight (of around -0.5 to 1.4kg) despite reductions in HbA1c, with more pronounced weight loss occurring when baseline BMI > 40kg/m².[8, 50] When it comes to its effect on biomarkers of cardiovascular disease further studies are need to elucidate the effect of pramlintide on the complications of diabetes. However, a study in type 2 diabetics showed significant reductions in total and LDL-cholesterol compared with placebo, with the greatest reductions seen when pramlintide was used at the highest dose.[18, 51] The side-effect profile of pramlintide includes nausea as well as vomiting and anorexia, however all these occur most frequently during initiation of therapy and tend to ease off with continued use. There is also an increased risk of severe postprandial hypoglycaemia occurring within 3 hours of administration of pramlintide, and thus it is advisable for patients to increase the frequency of monitoring in order to detect hypoglycaemia.[51]

Incretin based therapies

The incretin system consists of gut hormones notably glucose-dependent insulinotropic polypeptide (GIP) and glucagon like peptide-1 (GLP-1). GIP is synthesised in the enteroendocrine K cells of the proximal ileum whereas GLP-1 is released from the enteroendocrine L cells of the distal ileum and is rapidly inactivated by the enzyme didpeptidyl peptidase IV

within the circulation. However administration of a dipeptidyl peptidase IV inhibitor prevents degradation of this peptide hormone allowing it to have a more prolonged action. It is thought that these hormones are responsible for the enhanced insulin secretion seen in the postprandial phase. However, in patients with type 2 diabetes this incretin effect is either lost or blunted, with a more pronounced impairment in GLP-1 secretion.[1-2, 16-17, 52-53] Consequently the two available drugs in this category are thus the GLP-1 agonists and the DPP IV inhibitors. Some studies have shown that the insulinotropic effects of GLP-1 are preserved, such that infusion of GLP-1 may completely normalize beta and alpha cell sensitivity to glucose leading to potential novel pharmacotherapy in patients with type 2 diabete.[53]

Glucagon like peptide-1 receptor agonists (GLP-1 RA)

The most commonly available agents in this class are exenatide (twice daily), exenatide extended-release (once weekly) and liraglutide. These agents are peptide hormones and thus need to be injected via the subcutaneous route. As already stated, GLP-1 analogues are responsible for the stimulation of insulin secretion which is regulated by the intracellular glucose level as well and also reduce glucagon secretion from the alpha-cells leading to a robust HbA1c lowering of around 0.8-2.0%. However GLP-1 RA are associated with other beneficial effects including a delay in gastric emptying as well as early satiety resulting in decreased oral intake which may explain the modest weight loss seen with this treatment. GLP-1 RA also exerts positive effects on β-cells, namely it enhances β-cell proliferation and is also capable of inhibiting β-cell apoptosis.[2, 52, 54] Looking at the cardiovascular effects of these drugs it is thought that GLP-1 RA exert beneficial effects on the cardiovascular system due to the presence of GLP-1 receptors in the heart and this happens independent of glucose control. Studies have shown that administration of GLP-1 resulted in improvement in the ejection fraction and both global and regional wall indices in patients who had had an acute myocardial infarct with associated low left ventricular ejection fraction, and that exenatide treatment was associated with lower rates of CV disease event rates when compared with other agents.[2, 52-53] It is also well known that GLP-1 RA have a beneficial effect on the metabolic profile in type 2 diabetics. Exenatide therapy led to reductions in total cholesterol and triglycerides as well as reductions in systolic and diastolic blood pressure after 16 weeks of therapy.[2, 18, 52] With respect to weight loss all studies report a positive effect of GLP-1RA on weight with a reduction in BMI by around – 0.44kg/m² when compared to placebo or insulin therapy.[54-55] With respect to adverse effects, GLP-1R analogues have been associated with lower risk for hypoglycaemia when administered as monotherapy or when compared to insulin.[52, 55-56] Other adverse side effects include an increased incidence of gastrointestinal effects including nausea, vomiting and diarrhoea when compared to placebo or insulin therapy.[52, 54-55] Regarding long term cardiovascular outcome studies, one meta- analysis did not find any evidence to suggest an increase in cardiovascular morbidity when compared to placebo or other drugs.[57] There have been reports of short-term risk of acute pancreatitis as well as potential for long-term risk of chronic pancreatitis in patients taking this class of drugs, however, patients had other potential causes for this and the data available to date does not convincingly prove this risk. Even so, the FDA asks for vigilance when prescribing these drugs to patients and to report any such cases.[58] Concerns have also been raised on GLP-1R analogues with regards to their propensity to cause proliferative changes in rodent thyroid C cells including C-cell hyperplasia, adenomas, and medullary thyroid carcinomas although data in human subjects did not show any elevations in serum calcitonin levels and there have been no case reports describing medullary thyroid carcinomas in patients receiving GLP-1R agonist treatment. However more long term trials need to be available concerning the above issues as till now the data is not robust enough.[52] Finally there is limited data with respect to mortality with GLP-1 analogues, however studies to date suggests that there is no increased risk during treatment with such drugs.[59]

Dipeptidyl peptidase-4 (DPP-4) Inhibitors

This class of drugs are also part of the incretin system of gut hormones. These work by preventing breakdown of endogenous GLP-1 and GIP leading to enhanced circulating concentrations of these hormones which in turn lead to glucose dependent insulin secretion as well as inhibition of glucagon secretion. The four widely available agents are all orally active and include sitagliptin, vildagliptin, saxagliptin and linagliptin.[1-2, 18, 22, 52, 60] Studies have shown that these drugs are generally well tolerated, reduce HbA1c by around -0.8% are weight neutral and by themselves are not associated with hypoglycaemia, thus the FDA has approved them for both monotherapy as well as in combination with other anti-hyperglycaemic drugs in the treatment of type 2 diabetic patients.[1, 18, 52, 58, 60] Their pharmacodynamic and pharmacokinetic properties are what make DPP-4 inhibitors attractive for use especially in certain groups of people. The fact that they cause glucose dependent insulin secretion and thus decreased risk of hypoglycaemia when compared to SU, as well as the fact that saxagliptin and vildagliptin are metabolised by the liver implies that they may be used in elderly patients or patients with renal failure. They also enjoy good overall tolerability (when compared with metformin they are associated with lower

gastrointestinal adverse effects) and are not associated with the weight gain seen with SU and TZD use.[18, 22, 59, 61] Moreover they are also associated with positive effects on surrogate parameters of cardiovascular risk. Studies have shown a favourable trend with regard to triglyceride, HDL-C and LDL-C levels[52-53] and emerging data from recent studies and meta-analysis also show that DPP-4 inhibitors have a positive effect on the cardiovascular system. One study has shown that administration of sitagliptin to patients with coronary artery disease led to increased ejection fraction and improved contractile function of the ischemic areas.[62] Also, it has been shown that DPP-4 inhibitors reduce blood pressure in a number of studies and in animal studies gliptins seem to exert a positive effect on the evolution of heart failure which was independent of blood glucose control.[63] When looking at the effects of DPP-4 inhibitors on cardiovascular events two recent meta-analyses state that DPP-4 inhibitor reduce the risk of major adverse cardiovascular events – in particular myocardial infarction as well as decreased all-cause mortality and are thus reported as having a safe profile from a cardiovascular standpoint which is not seen with certain other anti-hyperglycaemic agents.[64-66] Several other large-scale trials are in the making specifically designed to assess the cardiovascular effects of each gliptin. One such study, the SAVOR-TIMI 53, has recently published data which states that saxagliptin found no excess or reduction in rates of ischemic events. It was noted, however that patients randomised to the saxagliptin arm had increased rates of hospitalisation for heart failure, which warrants further investigation.[67] With respect to the association of DPP-4 inhibitors with the risk of pancreatitis, pancreatic cancer and C-cell proliferation, data is very minimal and not uniformly reproducible in human studies thus further data is required in this area.[59] Thus the literature available implies that these novel drugs are proving to be pivotal in the treatment of type 2 diabetes, and that the benefits of DPP-4 inhibitor therapy by far outweigh the risks, making them key agents in the therapeutic armamentarium for type 2 diabetes.

Insulins

Insulin is the mainstay of treatment in type 1 diabetes and is an option in type 2 diabetes when other hypoglycaemic agents fail to maintain adequate blood glucose levels.[16-17, 34, 52, 58] With respect to other antihyperglycemic agents, insulin delivers superior glucose reductions and this is consolidated by the fact that it offers up to 4.9% reductions in HbA1c levels.[18] There are various different types of insulins available depending either on the source (animal, human or analogue insulins) or their action profile (short-, intermediate- and long-acting insulins).[17] Short acting insulins include those with a rapid onset and short duration of action such as soluble insulin (Humulin S®) or the newer analogues (such as aspart or gluisine) and notably these are used to cover prandial glucose excursions.[16-17, 52] Intermediate acting insulin such as isophane insulin (neutral protamine Hagerdon [NPH] has an onset of action within 1-2 hours and lasts for around 8-14 hours whereas long acting insulins (notably the analogues glargine or detemir) have a longer duration of action of around 22-24 hours and provides a consistent release of insulin during the day reminiscent of natural basal insulin release without any peaks of activity.[68-69] Insulin therapy in type 2 diabetes can be administered in different ways. Usually, insulin initiation takes the form of bedtime insulin using either isophane insulin or a once daily long-acting insulin analogue (such as glargine) and step-up treatment with either bi-daily injection of premixed biphasic insulin or short-acting insulin before meals (in a basal –bolus fashion) occurring if adequate glucose control is still not achieved.[34, 52] In the United Kingdom Prospective Diabetes Study (UKPDS) tight glycemic control with a combination of insulin and oral hypoglycaemic agents was associated with lower HbA1c values then those in the conventionally treated group and also had significantly decreased risk of microvascular complications, and furthermore, in the 10 year post trial follow up there was also a significant reduction in myocardial infarctions thus implying that insulin use is indispensable in type 2 diabetes and is also effective at preventing onset of complications. However, these results came at the expense of an increase in the rate of both hypoglycaemia and weight gain.[20-21, 69-70] With the development of long acting insulin analogues there is an improvement the insulin profile such that when injected subcutaneously there is a constant release of insulin into the bloodstream and without any peaks in insulin concentration over 24 hours (as opposed to isophane insulin) thus providing the basal component in the basal-bolus regime with the added benefit of once daily dosing.[69, 71] Thus, these inherent pharmacokinetic and pharmacodynamic properties of insulin analogues have been thought to be responsible for the decreased risk of hypoglycaemia especially nocturnal hypoglycaemia.[69, 71] Several studies have shown that long-acting insulin analogues achieve comparable glucose control to NPH insulin with lower rates of symptomatic and nocturnal hypoglycaemia with detemir also showing significantly less weight gain.[34, 68-69, 72-73] With respect to long term outcome trials, in the 10-year post-trial follow-up of the UKPDS, patients subjected to an intensive treatment regime continued to show a reduction in microvascular risk by 15% as well as reductions for any diabetes-related end point and death from any cause (9% and 13% respectively) even though the differences in HbA1c levels attained were lost after the first year. This 'legacy-effect' implies that early aggressive glycemic

control is associated with a sustained reduction in microvascular risk and in any diabetes-related end point. Furthermore, there was also a significant reduction in risk of either myocardial infarction or death from any cause which was not seen during the interventional phase of the trial.[18, 21] Finally, the UKPDS also investigated the concerns that exogenous insulin may potentially be harmful by enhancing atheroma formation due to the high insulin concentrations. This was unproven in the study since patients assigned to intensive insulin treatment did not have an increase in myocardial infarctions suggesting that inherent treatment with insulin did not pose a cardiovascular risk.[20] There have also been insinuations that high concentrations of insulin and thus increased binding of insulin to IGF-1 receptors may promote tumorigenesis. Insulin glargine has increased potency at the IGF-1 receptor then regular human insulin, however studies in rats and mice as well as a recent review of glargine-treated patients did not support an increased risk of carcinogenicity.[69- 70]

Conclusion

Thus as one can see the clinician has at his disposal a number of antihyperglycemic agents available for the management of hyperglycemia. As with all chronic medical conditions an individualised approach within a comprehensive care framework should be the way forward with many regulatory bodies advocating pharmacotherapy to be used as an adjunct to lifestyle modification. It is now universally acknowledged that management of diabetes does not only involve lowering of blood glucose but also the management of other cardiometabolic parameters such as serum lipid levels, blood pressure and platelet aggregation which have all been associated with adverse cardiovascular events. It is understood that most patients will eventually require more than one antihyperglycemic agent for optimum control of their diabetes, and thus the risks and benefits of each drug should be considered when prescribing a treatment regime as should the individual patient characteristics (such as age, weight, presence of comorbidities, risk of hypoglycaemia and so forth) in order to be successful at achieving optimum glycemic control without the occurrence of undesirable effects.

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Review Article

Spare the rod, spoil the child? A literature review of outcomes of physical punishment in relation to recent changes to Maltese Law

Kevin Borg, Deborah Hodes

Abstract

A literature review of outcomes of physical punishment in children confirms the polarised views resulting from various studies. This is mainly attributed to the limitations in the methodology and study designs used, confounding factors that were unaccounted for and the different ways in which physical punishment was defined by researchers. Researchers that provide evidence to discourage the use of physical punishment highlight the risk that this mode of discipline can easily cross over to physical abuse. This is challenged by other researchers who argue that alternative disciplinary techniques investigated with similar analyses to physical punishment have similar outcomes. Malta recently became one of the 39 countries worldwide that outlawed the use of physical punishment in children, in keeping with the United Nations Convention of the Rights of the Child. The focus of legally banning the use of physical punishment is not to increase the number of parental prosecutions but to safeguard children and adopt a policy of zero tolerance towards any violence against them.

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Our role as health professionals should be in supporting and educating parents, including those from a different cultural background, in becoming authoritative parents that are able to discipline their children in an effective and nurturing manner, away from using any form of violence. Successful evidence based parental intervention programmes exist that may help provide these necessary skills. Health professionals should also adopt a child centred approach whereby the child's views are considered and any allegation made taken seriously.

Training in safeguarding children is recommended for all professionals who come into contact with children and families.

Keywords

parental discipline; physical punishment; children's rights

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Background

Physical punishment can be defined as a parental act which aims to correct or control a child's behaviour by deliberately inflicting physical pain but not causing injury.[1] The use of physical punishment in children has been a common yet controversial research topic with some countries still widely supporting its use, others that defend 'reasonable chastisement' whilst others, including Malta, that have legally banned its use. A literature search on this topic was deemed relevant with the aim of understanding better the outcomes of physical punishment, with special reference to the United Nations Convention of the Rights of the Child (UNCRC) and the implications of this for clinical practice.

A structured literature search was conducted through PubMed, Psych-info and ASSIA using appropriate critical appraisal checklists.[2] Another source for identifying relevant articles was to retrieve studies from the reference section of the papers chosen from the

initial literature search. The main concepts used in the search strategy were corporal and physical punishment, children's rights, law and culture. The search was confined to English language papers which is a limitation to this review. Published research from the last 20 years was sought in order to present the latest evidence available and which also reflects the change in cultural attitudes over the recent years. The papers chosen for this review were from peer-reviewed journals and had to measure at least one outcome of physical punishment. Studies which grouped physical punishment with disciplinary techniques that are known to cause severe injury to the child (i.e. techniques that are in themselves abusive such as whipping, punching or shoving) were excluded in order to keep with Straus' definition of physical punishment.[1]

Physical punishment through the eyes of the child

Statutory UK guidance emphasizes the importance of adopting a child-centered approach and considering the child's view; a concept that is often neglected by professionals.[3] Qualitative studies in England and New Zealand have adopted this approach with children aged 5 to 14 years.[4-5] They reported that children did not view physical punishment as being something gentle or light but as a very negative and painful experience; *"it hurts and it's painful inside – it's like breaking your bones"*. A number of participants reported that they were hit around the face, head and back which are areas that may cause significant trauma. Although the number of children interviewed was small, the findings confirm how physical discipline is far from what many adults describe as being 'gentle'.[6] It is important to remember that certain vulnerable groups such as infants and disabled children are difficult to include in these studies. A meta-analysis of 17 studies report that children with disabilities are 3.6 times more likely to experience physical violence, including physical punishment, than children without disabilities.[7]

Children's rights and change to the Maltese law

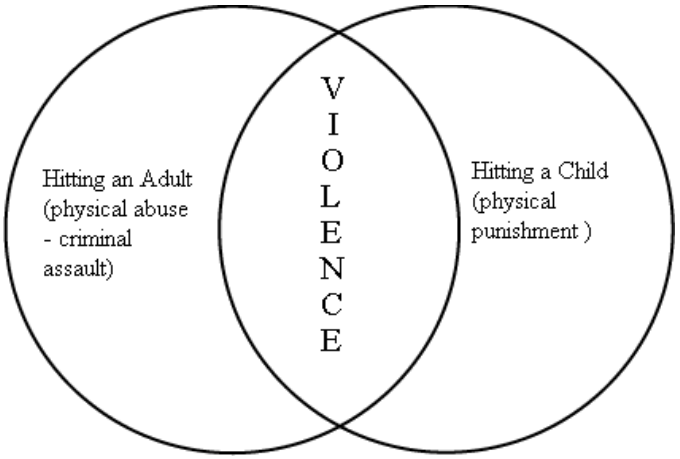
The UNCRC was established in 1989 to ensure that children have human rights and are protected. Of the 192 member nations that signed the convention only Somalia and the United States of America have not ratified it. Article 19 of the convention states that every state should ensure that children are protected 'from all form of physical and mental violence'.[8] The Committee on the Rights of the Child (CRC), reported that countries supporting physical punishment are breaching the UNCRC. Adopting a child's right approach has been put forward by scholars as a measure to prevent child maltreatment.[9] In February 2014, Malta has become one of the 39 countries that outlawed physical punishment of children, with Sweden being the first country to do so in 1979.[10] This was done through an amendment to Article 339 of the Criminal Code which previously allowed for the use of physical punishment, as long as it did not exceed 'the bounds of moderation'. The Criminal Code (Amendment No. 3) Act 2014 now provides legal clarity in stating: "…physical punishment of any kind shall always be deemed to exceed the bounds of moderation."[11]

Arguments against physical punishment

Physical punishment and physical abuse

Many societies justify physical punishment in children but do not accept violence against adults.[6] Violence is however the common theme between physical punishment and physical assault (Figure 1).

Figure 1*: Violence is the common theme for any form of physical assault*



Many speak of physical punishment and physical abuse as two separate entities. In reality there is no fine line that delineates the one from the other as reflected in many serious case reviews published in the UK.[12] One of the strongest findings of a meta-analysis of 88 studies reviewing physical punishment and associated behaviours in children found that its use was significantly associated with the risk of parents physically abusing their children.[13] Since then, a number of other studies have confirmed that the majority of cases of physical abuse occurred as a consequence of the child being physically punished in a way that was retrospectively deemed inappropriate.[14-15] A major UNICEF study of child discipline in more than 30 low- and middle-income countries found that on average 75% of children experienced violent discipline, with 17% experiencing severe physical punishment including being hit with an implement.[16]

Many of those who advocate for the use of physical punishment argue that despite them being physically chastised as children, they do not consider themselves to be negatively affected by it'. In a study of 11, 600 adults, 74% of those who were severely physically punished (e.g. kicked, choked or punched) failed to

recognise these acts as being physically abusive which questions the mode of discipline they would use on their own children.[17]

Physical punishment as an outlet of parental frustration

Research shows that physical punishment is linked with parental anger and frustration.[5,18-19] This makes physical punishment very subjective to what the parent is going through during the time the child is misbehaving. Graziano (1996) reports that 85% of a cohort of parents expressed moderate to high anger, remorse and/or agitation during or after physical punishment. Although the majority of parents seemed to justify their actions, 85% of them reported that they would consider an alternative method of discipline.[15]

Negative outcomes associated with physical punishment

Gershoff's meta-analysis reported that, although immediate obedience is usually obtained as a result of physical punishment, the child does not learn the desired behaviour and thus it has to be repeated, at times at greater intensity, in order to achieve similar results. Physical punishment has also been associated with a number of other negative outcomes including an increased risk of anti-social behaviour and mental health problems as adults as well as an increased risk of physical abuse to one's partner and/or children.[1,13,20] The methodological weaknesses in these studies include the fact that researches had to rely on reports from parents rather than from observations. Moreover, there are a number of confounding factors that are not controlled for in these studies. These include the child's initial temperament and other contextual variables such as whether the child is hit repeatedly by a rejecting parent or whether the parent is a loving one who only uses physical punishment occasionally and with reasoning. These factors make it difficult to conclude that physical punishment on its own is a cause of these negative outcomes.

Culture and physical punishment

Culture and religion also play an important role in the use of physical punishment. In America, physical punishment is prevalent amongst 90% of parents especially in the African-American population.[21] Culture should never be an excuse to under-investigate cases of children who might be victims of physical abuse. This echoes the concern of Lord Laming in his report on the death of Victoria Climbié in 2003 in the UK.[22] Many professionals involved failed to act as they attributed her suspicious behaviour and physical evidence to the fact that she came from an Afro-Caribbean culture.

A challenge for many Western countries today, including Malta, is the integration of migrant families who come from diverse cultural backgrounds and who may have an alternative method of child rearing. Some of these migrants come from war torn countries and may be traumatised in a way that can affect their ability to parent effectively (e.g. being previously tortured or witnessing the death of close relatives) unless provided with adequate support. Thus, a cultural competent approach should be adopted in these situations by trying to understand the family's background and avoid making false assumptions or stereotypes that are not in the child's best interest.[23] One should aim at engaging and educating vulnerable ethnic minority groups. This includes making them aware of what is accepted or not by the legislation of the country they are residing in.

Arguments in favour of physical punishment

Most of the studies that argue in favour of physical punishment report sharp contradictions to the findings of those who advocate against it. A meta-analysis of child outcomes of customary physical punishment showed that non-abusive spanking enhances child outcomes if used within certain boundaries and that the apparent detrimental outcomes of physical punishment have been found for every alternative disciplinary tactic when investigated with similar analyses.[24-25] A meta-analysis of 70 studies involving over 47,000 participants who were disciplined by physical punishment, did not appear to be at statistically significant risk of developing cognitive, affective and behavioural problems yet the researcher still concludes that as professionals we are ethically obliged to raise the concern of escalation to physical abuse with parents.[26] Researchers who advocate that physical punishment can be an effective and needed disciplinary tool, make it clear that in order to do so, it should not reach levels of abuse or neglect which in practice is difficult for parents to understand if not given clear guidance.[27]

Implications for clinical practice

The results from the published research on outcomes of physical punishment is contradicting, making it difficult to arrive to definitive evidence based conclusions. Some still argue that "no amount of research can undermine parents' right to act on their instincts".[28] On the other hand the American Academy of Paediatrics, the Canadian Paediatric Society and the Royal College of Paediatrics and Child Health have all issued recommendations against the use of physical punishment (especially in the younger age group) due to the risk of escalation to physical abuse and instead emphasise on promoting other modes of discipline that are equally effective.[29-31]

In a similar manner to how the majority of countries that today do not tolerate any form of violence amongst adults, the 39 countries that have banned the use of physical punishment through the use of necessary

legislation are sending a strong message of zero tolerance towards violence against children. The initiative that started in Sweden back in 1979 has today decreased the incidence of physical abuse and has created a change in mentality.[1] In Malta, this change in law has been a very positive step towards taking a child's right approach against violence in children. However the next challenge will lie in effective implementation of this law whilst also bearing in mind that other modes of discipline can amount to equally damaging forms of abuse such as emotional abuse or neglect if not used appropriately. The ultimate aim in changing the law is not to increase prosecution of parents for minor assaults but to create more awareness towards children's rights and to create a society which does not tolerate any form of violence.[6]

One of our roles as health professionals has to be supporting and engaging all parents, including those from a different cultural background, by educating them on what to expect at different childhood developmental stages and how to use discipline and boundary setting in an effective and nurturing manner. Baumrind's research on the dimensions of parenting has provided evidence in supporting the authoritative parenting model where the child's basic needs are met through care and control. This model aims at achieving the child's maximal potential through high parental affection and expectations in a developmentally appropriate manner.[32] Evidence based interventional programmes can help parents achieve this aim. Amongst these one finds individual/group training programmes, self-administrative and multilevel programmes. A successful example of the latter is the Triple P-Positive Parenting Programme that has been established with success in a number of countries that aims to equip parents with the necessary skills to become independent problem solvers with realistic expectations.[33] Through positive parenting, one is promoting the child's overall development within an environment that is non-threatening.

Another key role we have as professionals is to listen carefully to what the child is really trying to tell us. The child making an allegation of being hit must be taken seriously not only from the physical health aspect but also from the safeguarding point of view. This involves delving deeper into what is happening in the context of the home setting, whether other siblings are effected and whether there are any other safeguarding concerns include exposure to domestic violence or other concerning parental factors.

Training in safeguarding children is essential for all professionals who come in contact with children and families and should not be limited only to paediatricians who usually have a leading role. This is especially relevant in Malta where mandatory reporting for child maltreatment has been put forward in a recent Bill entitled the Child Protection Act, 2014 (out of home care) making safeguarding children everyone's responsibility.

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Review Article

The Great Pretender: Autoimmune Pancreatitis

Neville Azzopardi

Abstract

Autoimmune pancreatitis is a benign disorder which frequently presents with symptoms and imaging suggestive of pancreatic malignancy. Up to 21% of pancreatoduodenectomies performed for suspected pancreatic cancer are found to have benign disease. Autoimmune pancreatitis responds rapidly to corticosteroids and may be associated with extra-pancreatic manifestations. Type 1 forms part of the IgG4-related disease while type 2 autoimmune pancreatitis is less likely to have elevated levels of IgG4. This review discusses the characteristics of the two types of autoimmune pancreatitis and highlights the management and prognosis of this condition.

Keywords

Autoimmune pancreatitis; IgG4-related disease; pancreatoduodenectomy; lymphoplasmacytic sclerosing pancreatitis, idiopathic duct centric pancreatitis.

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Autoimmune pancreatitis (AIP) is a benign, infrequently recognised disorder which typically presents with symptoms and imaging suggestive of pancreatic cancer. It was first classified as a disease entity in 1995 and accounts for approximately 2% of cases of chronic pancreatitis. AIP is a great "pretender" of pancreatic carcinoma, being found in 2.4% of pancreas resection specimens.[1] Peak age of onset is in the seventh decade with the vast majority of patients being older than 45 years.[2]

AIP is divided into two types: type 1 or lymphoplasmocytic sclerosing pancreatitis and type 2 or idiopathic duct centric pancreatitis. AIP type 1 typically affects older patients, is characterised by positivity to IgG4 and forms part of the IgG4-related diseases.[1] IgG4-related disease is a rare systemic fibro-inflammatory disorder which may involve various abdominal organs and can lead to autoimmune pancreatitis, retroperitoneal fibrosis, sclerosing cholangitis, gallbladder pseudotumors, multifocal renal abnormalities and sclerosing mesenteritis. It is characterised by abundant infiltration of IgG4+ plasmacytes and lymphocytes.[3] Extra-pancreatic manifestations of IgG4-related disease are common in AIP type 1, with 68% of patients having extra-pancreatic (usually biliary) involvement.[4]

An IgG4 level >210 mg/dl has been shown to have the greatest sensitivity (83.8%) and specificity (89.5%) for AIP though up to 35.5% of patients with pancreatic adenocarcinoma and 25.4% of patients with chronic pancreatitis have values >140 mg/dl. Therefore, elevated IgG4 levels alone are not enough to differentiate between pancreatic cancer and AIP.[5] Serum IgG4 levels also have a poor positive predictive value in the diagnosis of IgG4-related disease with only 15% of patients with IgG4 levels >130 mg/dl having IgG4-related disease.[6] A number of cases of type 1 AIP without IgG4 tissue infiltration or serum IgG4 elevation have also been described, suggesting that AIP should also be suspected in patients with normal IgG4 levels.[7]

Type 2 AIP typically affects younger patients, is confined only to the pancreas and is not associated with elevated levels of IgG4.[8] Pancreatic histology is characterised by granulocytic epithelial infiltration.[3] Patients with type 2 AIP typically present with abdominal pain and a tumor-like mass in the pancreas. Serum levels of IgG4 are less frequently elevated than in type 1 AIP (12% in type 2 versus 55% in type 1), so distinguishing from pancreatic cancer is even more difficult.[9]

AIP typically presents with clinical features which are very suspicious for pancreatic malignancy, including obstructive jaundice (50%), abdominal pain (44%), fatigue and weight loss (13%). These symptoms frequently prompt surgical intervention.[10] Benign lesions are found in 5-21% of pancreatoduodenectomies performed for suspected neoplasms.[11] A study on pathological samples in Mainz, Germany showed that 8.8% of patients (33 patients from a total of 373 patients) undergoing pancreatoduodenectomy had benign disease and 11 patients (33%) with benign disease were found to have AIP.[11]

Work-up for patients with suspected AIP

Laboratory investigations frequently show deranged liver function tests (with a typical obstructive picture). Serum immunoglobulin and IgG4 levels are typically increased. Initial imaging (CT scan) and ultrasound abdomen will reveal a focally enlarged pancreas (in 38% - this increases the suspicion of pancreatic adenocarcinoma) or a diffusely enlarged pancreas (in 62%). Unfortunately, a good number of these patients undergo surgical resection for a condition which can be managed medically. Histological analysis typically reveals pancreatic interstitial fibrosis with infiltration of lymphocytes and plasma cells.[10] Pancreatic parenchyma is usually infiltrated by immune cells, particularly CD4 or CD8 T lymphocytes and IgG4-bearing plasma cells.[12] While radiological and clinical findings frequently raise the suspicion of pancreatic cancer in patients with AIP, specific findings on CT and MRI may help distinguish between the two. Diffuse pancreatic enlargement, capsule-like rim and delayed homogenous enhancement are more suggestive of AIP. Main pancreatic duct narrowing by >1/3 of the pancreatic length, skipped narrowing in the main pancreatic duct and smooth and straight intra-pancreatic common bile duct stenosis on MRCP are more in keeping with AIP.[13] Another common finding at MRCP is the presence of multiple, long stenoses of the main pancreatic duct without dilatation in the remaining portions of the pancreatic duct.[14]

There is typically a rapid clinical and radiological response to treatment with corticosteroids in patients with AIP. Pancreatic swelling improves in 83% while pancreatic duct irregularities improve in 75% within 2 weeks of starting corticosteroid therapy.[15]

Endoscopic tools in the diagnosis of AIP include endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS). Endoscopic ultrasound images the main pancreatic and common bile ducts and also allows sampling of pancreatic tissue for histological analysis. Diffuse, irregular narrowing of the main pancreatic duct in the absence of upstream dilatation from the stricture (<5mm) is a typical finding at ERCP, though localized narrowing may be difficult to differentiate from stenosis secondary to pancreatic cancer. The main pancreatic duct and common bile duct immediately adjacent to the papilla (up to 1.5cms from the ampullary orifice) are frequently maintained with no narrowing seen in the initial portion of these two ducts.[16] Transpapillary biopsy with IgG4 immunostaining of biliary strictures may be necessary to rule out cholangiocarcinoma and to reach a diagnosis of IgG4-sclerosing cholangitis. IgG4 immunostaining of histological specimens from the major papilla may also be helpful in diagnosing AIP.[17] Biliary stent placement during ERCP is important in the initial management of AIP with biliary stenting being useful in relieving jaundice in 71% of type 1 and 77% of type 2 AIP.[18]

EUS allows operators to obtain cytological and histological samples by fine needle aspiration. EUS typically shows diffuse hypoechoic pancreatic enlargement. Novel EUS techniques including EUS-elastography and contrast-enhanced harmonic EUS are also able to differentiate between AIP and pancreatic cancer, though histological sampling of the pancreas is by far considered the gold standard diagnostic technique.[19]

Classification

Several different classification criteria have been devised to diagnose AIP. The most recent classification system (the International Consensus Diagnostic Criteria - ICDC) has been shown to have higher sensitivity, specificity and accuracy than the older HISORt and Asian criteria.[20] The ICDC criteria include:

1. imaging of the pancreatic duct and parenchyma
2. serology
3. other organ involvement
4. pancreatic histology
5. the optional criterion of response to steroid therapy

Diagnosis of type 1 or type 2 AIP may be definitive or probable depending on the strength of the findings and in some cases, one may not be able to distinguish between the subtypes (AIP *not otherwise specified*). Imaging and response to steroids is not able to distinguish between type 1 and type 2 AIP. Typical serological abnormalities as well as other organ involvement are seen only in type 1; however inflammatory bowel disease seems to be associated with both types. Absence of serological abnormalities and other organ involvement does not necessarily imply a diagnosis of type 2 AIP since type 1 may also be seronegative and without other organ involvement.[21] Therefore, even with the use of the ICDC criteria, it is not always possible to confirm AIP subtype without histological analysis of pancreatic tissue.[22]

These diagnostic criteria are bound to change further. A recent international symposium on the diagnosis of AIP held in Seoul has concluded that there is room for improvement in the ICDC and that further

modifications might be required in the future.[23]

Management and Prognosis

Treatment for AIP should be considered if patients develop jaundice, systemic manifestations or persistent pain. Initial treatment is with corticosteroids though azathioprine may be necessary if patients relapse on tailing down steroids.[1] Clinical remission is achieved in 99% of type 1 and 92% of type 2 AIP with corticosteroid therapy.[18] The recommended dose of prednisolone for induction of remission is 30-40 mg/day tailing down over 2-3 months to a maintenance dose of 5-7.5 mg/day for a period of 3 years.[24]

However, different countries use different tailing down regimes of steroids. In the United States, the initial induction dose is of 40 mg prednisolone for 4 weeks with the steroids being tailed down by 5 mg per week until the steroids are stopped completely.[25] In Japan, the initial induction dose is given for 2-4 weeks, after which steroids are tailed down by 5 mg every 1-2 weeks until a prednisolone dose of 15 mg is reached. At this point, the steroid dose is reduced more slowly (by 2.5 – 5 mg every 2-8 weeks) until a maintenance dose of 2.5-5 mg per day is reached. Researchers from Holland have shown that response to low-dose (10-20mg/day), medium-dose (30 mg/day) and high-dose (40-60 mg/day) prednisolone as induction therapy for AIP was comparable.[26] However, while resolution of pancreatic abnormalities is relatively quick, extra-pancreatic lesions (retroperitoneal fibrosis, bile duct strictures and ductal wall thickening) take more time to resolve and tailing down of steroids should therefore be tailored to each patient according to the disease activity of all organs involved.

Risk of relapse is high in type 1 (up to 30-50% relapse within 6-12 months) while risk of relapse in type 2 AIP is much less frequent.[27] The largest study on AIP carried out so far (1064 patients from 23 institutions in 10 different countries) showed that relapse occurs in 31% of type 1 and 9% of type 2 AIP. Remission is rapidly achieved on re-introducing corticosteroid therapy.[18]

Since the sensitivity and specificity of serological tests (IgG4 and Ca19.9) and imaging (CT and MRI) in distinguishing between AIP and pancreatic cancer is low, an important tool in differentiating between the two conditions involves the empirical treatment with corticosteroids. AIP exhibits a quick and dramatic response to corticosteroids while pancreatic cancer does not exhibit such a response.[28]

Management of AIP is important not only to manage the symptoms associated with this condition but also to avoid the development of chronic pancreatitis. While acute phase AIP responds immediately to corticosteroids, the long-term prognosis and outcome of AIP are still unknown. Up to 20% of patients progress to chronic pancreatitis and AIP is suspected to lead to the development of pancreatic duct stones, probably secondary to narrowing of the pancreatic ducts.[29]

Smoking appears to increase the risk of pancreatic damage and increase the risk of diabetes in AIP. Smoking cessation should be encouraged in all patients.[30]

Initial analysis on cancer risk in patients with AIP and IgG4 related disorders has revealed no increased risk of malignancy in these patients with the cancer risk being similar to that of age-and gender-matched controls.[31-32] However, prospective follow-up of 115 patients from two large tertiary referral centres in the UK showed that both type 1 AIP and IgG4-related sclerosing cholangitis are associated with significant morbidity and mortality owing to extra-pancreatic organ failure and malignancy.[33] The largest study on AIP carried out to date has shown that pancreatic calculi and cancer are rare in type 1 and absent in type 2 AIP.[18]

Since AIP is frequently mistaken for pancreatic malignancy, it is important to consider whether a biopsy of a pancreatic mass lesion should be carried out before undertaking major surgery. With 5-21% of resected pancreatic specimens being benign, an international panel of pancreatic surgeons working in well-known, high-volume centres reviewed the literature and worked together to establish a consensus on when to perform a pancreatoduodenectomy in the absence of positive histology. Consensus was reached that histological proof is not required before surgical resection in the presence of a solid mass suspicious for malignancy. However, malignancy should always be confirmed histologically (preferably by EUS-guided FNA or biopsy) for patients with borderline resectable disease who need treatment with neoadjuvant therapy before exploration for resection. A biopsy is also recommended when a diagnosis of AIP is highly suspected and a short course of steroids considered if the biopsy does not suggest malignancy.[34]

Conclusion

AIP is the great "pretender" of pancreatic malignancy. Increasing awareness of the clinical, radiological, serological and extra-pancreatic involvement associated with this disorder may allow early recognition and avoid unnecessary surgery for this benign condition. Better classification criteria and a standardised therapeutic plan with corticosteroids and other immune-suppressants are needed in AIP.

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Orations relating to the conferment of Doctor of Science honoris causa to Professor William Bannister

Godfrey LaFerla

We are gathered here today to recognise a distinguished international scientist and alumnus of this University and it is indeed my honour and privilege to present Professor William Bannister for the award of the degree of Doctor of Science *honoris causa*. His career spans almost six decades and during this time he has helped shape numerous individual careers, whole Departments and our understanding of several branches of Physiology.

William Bannister was born in Senglea in 1935. He was educated at Lyceum and subsequently at the Royal University of Malta. Precisely 59 years ago to this day there was a student sitting in the front rows here in this Church, about to graduate in Science and Pharmacy. Both degrees were conferred on William Bannister as he was placed first and being always first academically was to remain with him all his life. Three years on, in 1958 he was placed first in Medicine and a further three years on after proceeding as a Rhodes Scholar to Oxford University he obtained a first in Animal Physiology. He remained at Oxford as a Junior Research Fellow to carry out high quality research work opting to work on disproving the current thinking at the time, that acid secreted by the stomach came from the dissociation of carbonic acid after hydration of carbon dioxide by carbonic anhydrase. He developed the experimental model necessary to prove that the generated ATP drives the pump that secretes acid from the gastric mucosa. He was awarded the Doctorate in Philosophy for his work.

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Today, William Bannister, stands before you, about to receive his sixth degree, the fourth from his first Alma Mater. But this degree has been earned in a different way, without (he will be pleased to know) any examination; rather, we are here to honour William Bannister as a distinguished international scientist and alumnus of this University.

For those of us who learned from him, it was not difficult to mark William Bannister out as an exceptionally talented and highly motivated person whose love was teaching and carrying out research. Unfortunately those who taught him are no longer with us but he had the distinction of serving as a young Houseman to the late Professors Alfred Craig and Walter Ganado at St Luke's Hospital. It was however the great clinician Walter Ganado who instilled in young William for the first time the idea of doing research. A study on Brucellosis earned him his first paper in the acclaimed British Medical Journal and this introduction to research was the first step on a long distinguished academic journey. At Oxford, he was tutored by the two formidable fellows; JRP (Percy) O'Brien, the Reader in Clinical Biochemistry, who became a determinant factor in his career and a life-long family friend, and the great Neuroscientist Max Cowan who tutored him extensively in Neuroanatomy and Neurophysiology.

Despite being offered a Fellowship at Oxford on the completion of studies, William Bannister decided to return to Malta in 1964 and a year later became Professor and Head of Department of Physiology and Biochemistry until his retirement in 1999. Subsequently, in the year 2000, Council of the University of Malta honoured him with the title of Professor Emeritus and created him a Senior Fellow of the University. I should say that his retirement was from the payroll but not from active scientific research which continues today through various collaborators in Malta and abroad carrying out advanced computing in biological data analysis. He had also a brief interlude back at Oxford University between 1978 and 1982 as a Welcome Trust Senior Research Fellow.

When William Bannister became Professor and Head of Department His industry, his tenaciousness, his capabilities and his keen sense of direction was recognised by all even in his early days in the Chair. I remember Professor William Bannister very well

between the period 1972-1977, as I was a medical student at the time. I remember very clearly his lectures about the excitation of the Purkinje cells of the cerebellum and ion transfer across the axon in neurophysiology lectures. He was deeply passionate about tissue fluids and the perfusion pressures in the hind limb of animals as described by Pappenheimer. Of course, as 18-year-olds we hardly understood the significance of all these fundamental physiological principles because we were probably more interested in his drawings rather than the actual deep physiological meaning these concepts had and which many of us had to revisit many a time during our further postgraduate studies in the various disciplines.

By nature, Professor Bannister is the epitome of kindness and gentlemanly conduct. He was always prepared to listen to us students with whatever problems we presented him. He was very keen on hands-on teaching during our physiological practicals and took great pains to clearly explain the fundamental concept to each individual student as he paced incessantly up and down the corridors of the laboratory. He was certainly a welcome sight during the Physiology practical examinations as he would go around asking each individual student how he was performing during the exam and if the student had any problems he would just turn round and mutter in his soft voice "this is a serious shortcoming, but I'll tell you what to do."

However, apart from his qualities as a teacher, William Bannister on becoming Professor of Physiology, soon realised the importance of high quality research for the University to gain an international standing. In his Foundation Day Oration in October 1969 entitled "How much research?" he emphasised the pursuit of excellence in research. This created quite a stir as his ideas on far going research were unheard of at the time. The University actually published the oration to instigate support for research which was non-existent at the time. Instead, rather than facing the reality of the time, William Bannister sought external funding and was able to obtain significant funding over a period of time from the Nuffield foundation and the Welcome Trust in the United Kingdom. This funding enabled William Bannister to establish international research at the University. Collaboration through consanquinity played a major role in this development as William was joined by his brother Joe Bannister following the latter's return from Oxford in 1974. The work on copper proteins established an international reputation for our University and this collaboration continued at Oxford in 1978 with the work being extended to free radicals. Unfortunately the link was cut when William returned to Malta in 1982 to write a number of publications and Joe moved to become Professor of Biological Chemistry at Cranfield University. William was recalled to the University in 1987 but Joe did not return until 1994 and by then he had decided to pursue other pastures but not before they produced a paper on the discovery of superoxide dismutase which has a chromosome linkage with Downs Syndrome. This paper became famously known internationally as the Bannister and Bannister paper.

However, William continued with his work particularly in computational biology. William has published 156 publications of all kinds in international peer reviewed journals and for many years acted as a referee for these journals. His scientific visibility is well known internationally. Recently, Research Gate which analysis scientific visibility gave him a score of 95%. William's scientific work was not only on acid secretion, copper proteins and free radicals but extended to other areas particularly hemoglobin. Although William has a proclivity for going into a wide range of subjects, this has not gone into his head. He is the same modest person that we have always known. His great love was always the medical school and medical profession. Few people know that when an adult hemoglobin variant was discovered in his Department in 1970, he decided to name it hemoglobin St Luke's in memory of his introduction to scientific research at St Luke's hospital.

The University is proud to recognise William Bannister's many achievements since he first graduated. He is a scientist of distinction, as well as being respected and admired for his ability to get on with everyone, regardless of their status or background.

Chancellor, it is my honour to present Professor William Bannister, for the award of the degree of Doctor of Science, *honoris causa*.

Professor William Bannister
What is a university?

Distinguished and honourable guests, I am deeply moved by this occasion. The University has already honoured me by according me the title of Professor Emeritus and Senior Fellow, and I was not expecting today's added honour.

It is customary to make an oration on these occasions. I propose to be brief and put before you some questions that have bothered me all my university life. My teaching vocation has been in Human Physiology and my research vocation has been in Biochemistry at this university and here I come to my first and primary question, 'What is a university?' The consensus of opinion is that a university is a centre of teaching and research concerned with the pursuit of excellence in both areas. To some extent that definition is idealistic. Furthermore, I have problems with the idea of excellence, which I find exceedingly subjective. I prefer to define a university as an institution of intensive teaching and research. The conjunction of teaching and research is very important. Teaching and research are mutually beneficial. I hope you will not find me making dogmatic or ex-cathedra statements. In any case, such

statements are not as bad as they may seem to be because they stimulate criticism and new thinking. I have no doubt this university is a teaching-intensive institution, which is its primary purpose, but I doubt how it can maintain that position in the long run with an ever increasing number of students and a stationary number of full-time teachers. On this point it is prudent for me to stop here because I am not qualified to speak on education policies and whereof one cannot speak thereof one must be silent. That, of course, is a little gem from Wittgenstein.

I wish to make a point here about teaching. I think our primary function as teachers is to point the way to students, which may make them think that we teach nothing. If that happens it is our fault. It means we have not encouraged them sufficiently to cultivate their minds. In plain language, we have not encouraged them enough to use their minds. If we train them to use their minds, a task that is by no means easy, they will find inexhaustible sources of interest in the subjects that we teach them and will not think that we teach them nothing. There is more to this. With a properly cultivated mind they will be more likely to succeed in their second-life after university, as they will be more likely to adapt effectively to rapid change. I have a thought from Stuart Mill that I rather like. Applying that thought to a university, we need to ensure that we do not create what he calls small men. What small men can do is obvious. They can do nothing.

A teaching- and research-intensive university is among the best assets that we can have and invest in. It essentially means that we are good in research and education and delivering the service to the nation that follows. Furthermore, co-existence of research and education is essential for technology transfer flow from a university. From what I observe, the university has started to create a critical mass of researchers and research students, appropriate infrastructure, and innovative spirit. This brings me to my second question here, which is 'How much research?'. First of all we need to agree on what we mean by research. It is commonplace to define research as systematic, critical and self-critical enquiry, which aims to contribute towards the advancement of knowledge. That is typical academic thinking which, however strange it may seem, I do not find very fruitful as such. To my way of thinking, there are two kinds of research, basic research and applied research, whether inside or outside academia. Basic research informs applied research. It is the bedrock on which applied research is built. This is strikingly evident in current medical science and biotechnology. A strong case can be made for basic research as indispensable for an institution of higher education with research students as it educates the minds of the future. It is minds enlightened by basic research that makes possible the advance of technology.

Now my question, 'How much research?'. I have been preoccupied with that question all my working life in experimental science, and I am returning to it again here in an oration after no less than 45 years. All scientific research depends on having ideas that work. Productive research ideas that extend existing scientific knowledge are not difficult to come by. They come surprisingly easily from knowledge of current science, sifting of that knowledge, and imaginative thinking. Unfortunately experimental scientific research is plagued by the problem of adequate funding. We cannot expect the university to provide us by itself all our requirements in what we undertake to do. We have to face reality and seek extramural funds which are by no means easy to obtain, but they are vital if we wish to attain visibility in the highly competitive international field of science. From what I observe the university is making strenuous efforts to obtain extramural funds from all sources available to it. Once we have funds for scientific research we need to make certain that we make proper use of those funds for productive work. I can only speak for the biomedical sciences and I have to say I have high respect for the admirable work of present members of the university currently making inroads into the area of internationally acknowledged biomedical science and achieving a reputation for themselves and enhancing that of the university.

Another aspect that I wish to mention in connection with facing reality is our need to collaborate with powerful research groups at other universities and research institutions to do broad ranging and deep scientific research. Fortunately, unlike extramural funds, this materializes almost by itself once we have made a valid start and achieved a respectable scientific position with what we have at our disposal. That can be done and should be done unless we want to resign ourselves to doing nothing. It is not in my nature to elaborate on the obvious, and I propose to stop at this point and thank you for bearing up with me.

Review Article

Food for thought: Palatable eponyms from Pediatrics

Lisa Kipersztok, Gwinyai Masukume

Abstract

Food-related medical terms are frequently used in the field of pediatrics for the definition, recognition and diagnosis of disease. Almost 40 food-related medical eponyms used in Pediatrics have been 'cherry picked' and described by the authors. Two of these terms have been illustrated. Culinary medical analogies allow healthcare providers to easily interpret the variety of sensations experienced during medical decision-making, providing a better taste for interpreting pathology discovered on physical exam. Despite some misgivings, food-related medical terms make medical education more appetizing and allow for rapid diagnosis of classic presentations.

Key words

Pediatrics, medicine, food, analogy, metaphor

Food for thought

Investigations in obstetrics and gynecology stirred up a wide variety of food-related medical metaphors.[1] Following conception, pregnancy and delivery, the culinary medical journey can continue in the field of pediatrics. As children grow from infancy to childhood, so grows the list of food-related metaphors used by healthcare providers.

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With each clinical encounter, there exists a menu of possible medical maladies from which to diagnose. Metaphors, analogies and mnemonics are blended into the endless courses of information provided during medical training. Comparing symptoms and signs of disease to food can make recalling data much more palatable and may allow for rapid diagnosis upon recognition of 'classic' presentations.[2]

Historically, diabetes mellitus was distinguished from diabetes insipidus by carefully inspecting for 'honey urine' by color and even a sweet taste.[3] While healthcare providers (hopefully) no longer use taste for diagnosis, they continue to interpret all data available. In Pediatrics, one can hear the 'cracked-pot sound' of hydrocephalus, feel the 'palpable olive' of hypertrophic pyloric stenosis, smell the 'cheesy odor' of isovaleric acidemia, and see the 'strawberry tongue' of diseases involving superantigens (see Figure 1 and Table 1).

***Figure 1**: Strawberry tongue, also less commonly known as raspberry tongue (See Table 1)*

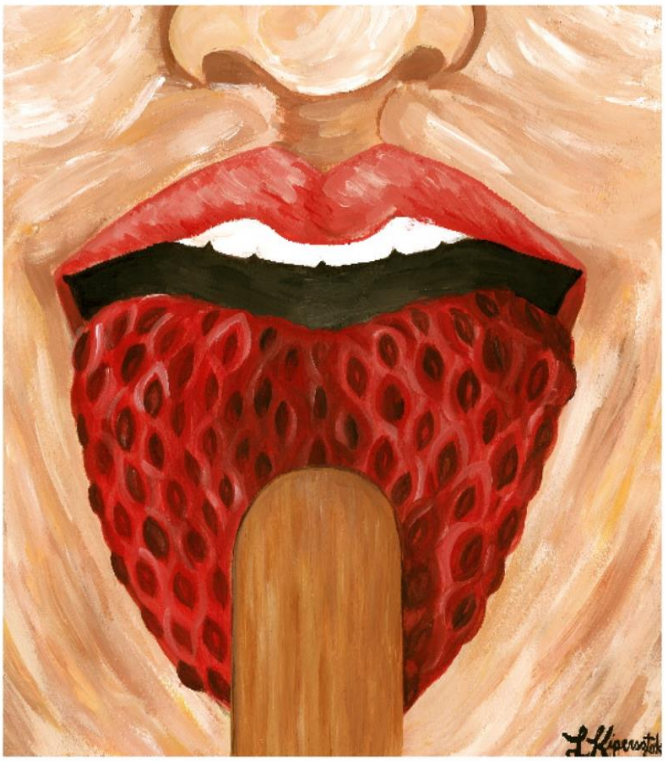


***Table 1**: 'Cherry picked' food-related medical metaphors in Pediatrics*

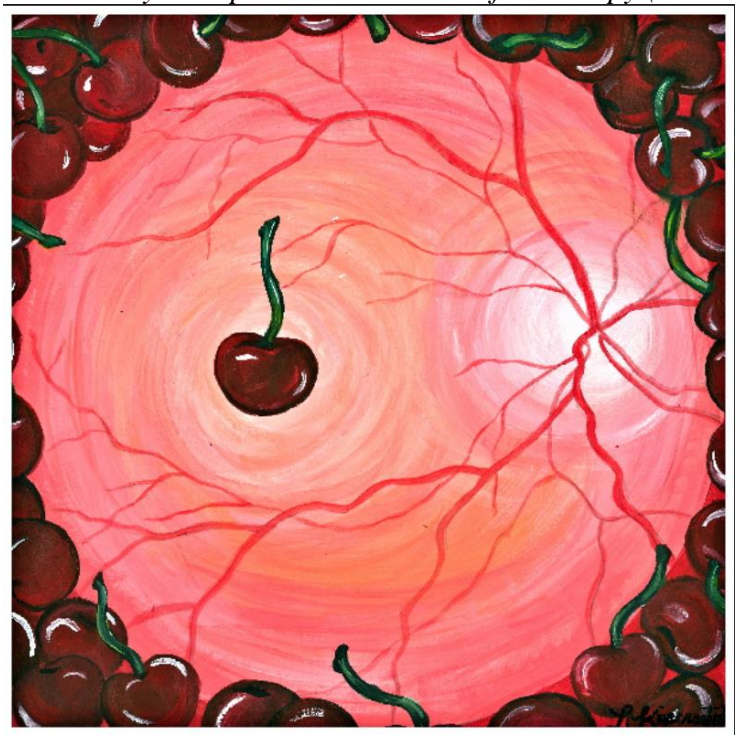
Analogy	Brief description
Blueberry muffin baby/rash/syndrome	cutaneous extramedullary hematopoiesis secondary to congenital infections, certain cancers or hematologic abnormalities[4]
Bread and butter appearance	the two layers of pericardium and intervening fibrin in cases of fibrinous pericarditis and sometimes rheumatic fever[5]
Cabbage-like odor*, Rancid butter odor	urinary odor due in tyrosinemia type 1 and Oasthouse syndrome, in tyrosinemia type 1 a rancid butter odor can occur[6]
Carrot-shaped nuclei	microscopic appearance of nuclei in medulloblastoma[7]
Celery stalk appearance	alternating bands of lucent and sclerotic metaphyseal bone of the femur and tibia on X-ray in patients with congenital rubella and other conditions[8]
Cheesy odor*	breath and body fluid odor in isovaleric acidemia[9]
Cherry red epiglottis	swollen epiglottis upon visualization by laryngoscopy, secondary to *Haemophilus influenzae* type b and other bacterial infections[10]
Cherry-red spot*	appearance of the vascular choroid under the macula on a whitened retina on fundoscopic exam in disorders of lipid metabolism[11] – See Figure 2
Cottage-loaf sign	chest X-ray appearance in patients with total anomalous pulmonary venous connection/drainage/return[12]
Cracked-pot sign	sound heard upon percussing the head of an infant affected by hydrocephalus[13]
Dish-face anomaly	congenital midface hypoplasia resulting in flattened features, seen in Larsen syndrome and Binder syndrome (maxillonasal dysplasia)[14,15]
Doughnut sign, Sandwich sign	doughnut shape seen on transverse sonography or computed tomography in intussusception; on longitudinal imaging intussusception resembles a sandwich[16]
Egg on a string sign	cardio-mediastinal silhouette seen on chest X-ray in transposition of the great arteries/vessels[17]
Fish odor syndrome*	body odor of rotten fish secondary to an accumulation of trimethylamine in flavin-containing monooxygenase 2 deficiency[18]
Honey-colored crusts	crusts overlying the healing blisters in cases of impetigo, a superficial skin infection caused by *Staphylococcus aureus* or *Streptococcus pyogenes*[19]
Hot cross bun head/skull	rare radiographic manifestation in which the skull looks like a hot cross bun due to abnormal bone deposition in congenital syphilis[20]
Ice cream sliding off the cone	hip X-ray appearance seen in slipped capital femoral epiphysis[21]
Maple syrup urine disease*	caramel-like urine odor in individuals with branched-chain alpha-keto acid dehydrogenase complex deficiency[22]
Milk anemia	iron deficiency anemia caused by the substitution of breast milk with cow's milk in early childhood[23]
Mulberry molars	abnormally increased number of cusps in the first permanent molars which occurs in congenital syphilis[24]
Oasthouse syndrome*	urine odor of an oasthouse, a building used for drying hops, in disordered methionine metabolism[25]
Olive-shaped mass	palpable abdominal mass the shape of an olive found in infants with hypertrophic pyloric stenosis (HPS)[26]
Onion skin reaction	periosteal reaction resulting in the layering of periosteum, seen on X-ray in Ewing sarcoma and sometimes in osteomyelitis or osteosarcoma[27]
Pancake brain	brain's shape seen on pathologic and radiographic examination in alobar holoprosencephaly[28]
Pea soup stool	consistency and appearance meconium or diarrhea secondary to typhoid[29]
Port-wine stains	birthmarks the color of port wine typically affecting the face and neck, caused by malformed capillaries in syndromes such as Sturge-Weber[30]
Potato chip scales	weeping, crusted scales typically on the face in staphylococcal scalded skin syndrome[31]

***Table 1**: 'Cherry picked' food-related medical metaphors in Pediatrics Cont.*

Analogy	Brief description
Prune belly syndrome	wrinkled abdominal skin caused by the absence of abdominal musculature[32]
Red-currant jelly stool	stool consisting of blood and mucus in cases of intussusception, dysentery or other diseases[33]
Rotten eggs odor*	urine odor in cystinuria[34]
Salmon patches	retinal hemorrhage visualized on fundoscopy in sickle cell retinopathy;[35] also used to describe the pink-red 'stork bite' of the nape of the neck in infants[36]
Salt-pepper retinopathy	focal areas of increased and decreased pigmentation seen on fundoscopy in rubella retinopathy, congenital syphilis or other congenital infections[37]
Salt grains	also known as Koplik spots, lesions that resemble grains of white or blue salt splattered on a red buccal mucosa in measles[38]
Sausage-shaped mass	right upper quadrant or epigastric mass that feels like a sausage on abdominal palpation in some patients with intussusceptions[39]
Strawberry hemangioma	also known as a capillary hemangioma, a benign red-blue tumor of blood vessels which regress by age 10[40-41]
Strawberry tongue, Raspberry tongue	bright red tongue with prominent papillae found in diseases likely mediated by superantigens including toxic shock syndrome, scarlet fever and Kawasaki disease[42-43] – see Figure 1
Sunflower cataracts*	sunflower appearance of the lens of the eye caused by copper deposition in Wilson's disease, a disorder of copper metabolism[44]
Tumbler test aka glass test	controversial clinical sign elicited when a transparent tumbler is pressed against a skin rash, positive for meningococcemia if the rash does not blanch[45]

*Underlying disease is usually inherited in an autosomal recessive manner, Some cutaneous food-related medical terms may not be applicable in those with pigmented skin
Please see the Supplementary appendix for a more detailed table

***Figure 2**: Cherry-red spot as visualized on fundoscopy (See Table 1)*



Discussion

Although food-related eponyms vary across cultures and specialties, they contribute to the medical knowledgebase used by all healthcare providers.[2] In some instances, the same culinary term has described more than one medical condition. For example, the cottage loaf appearance has been used to refer to radiographic studies of children with total anomalous pulmonary venous connection, but has also been used to describe the appearance of a herniated choroidal melanoma, or a liver protruding through a ruptured diaphragm. Some eponyms have widespread use, found frequently in medical literature. Some are used colloquially, mentioned in operating rooms and pathology laboratories but rarely documented.

It is not possible to classify food-related medical terms into discreet medical specialties because there is substantial overlap between areas of expertise. For example, we covered previously the grape-like appearance of the malignant tumor, sarcoma botryoides,[1-2] found in young girls that others may classify as being pediatric and others gynecologic.

Food-related medical analogies have rarely been validated in terms of sensitivity, specificity and predictive values, and are not always found in cases of the medical conditions that they describe. [46] Intussusception, for example, only results in the triad of a sausage-shaped mass, red currant jelly stool and pain in about 15% of cases.[39] Additionally, as technology progresses, students and healthcare providers focus less on perfecting their skills of inspection, palpation, percussion and auscultation, and instead rely on easily available imaging studies.[47] Palpating an olive-shaped mass in children with hypertrophic pyloric stenosis, for example, has decreasing utility in a medical system that promotes early imaging when the disease is suspected.[26]

Nevertheless, these terms have utility in broadening differential diagnoses when confronted with symptoms and signs of disease, and are easily memorable for rapid recognition in classic cases. Food-related eponyms continue to be taught in medical school classrooms and physical diagnosis courses, and are likely to be retained in the 'visual specialties' of radiology and pathology.[48] Culinary medical eponyms will continue to spice up the melting pot of medical jargon, particularly in the field of Pediatrics.

While the eponyms described are primarily encountered in Pediatrics, many continue to be discovered as children grow into adulthood, where the list of delicious medical findings will continue. These pediatric culinary terms certainly do not represent the final course in the medical food analogy feast.

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Author contributions

GM conceived the article. Both authors contributed to the writing and editing of the article and approved the final version. LK designed and painted figures 1 and 2.

Competing interests

LK and GM have no financial relationship with any food company or any other organization that may have an interest in the submitted work. GM is the author of the blog http://foodmedicaleponyms.blogspot.com, he also blogs at http://www.improbable.com/ on food-related medical terms.

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