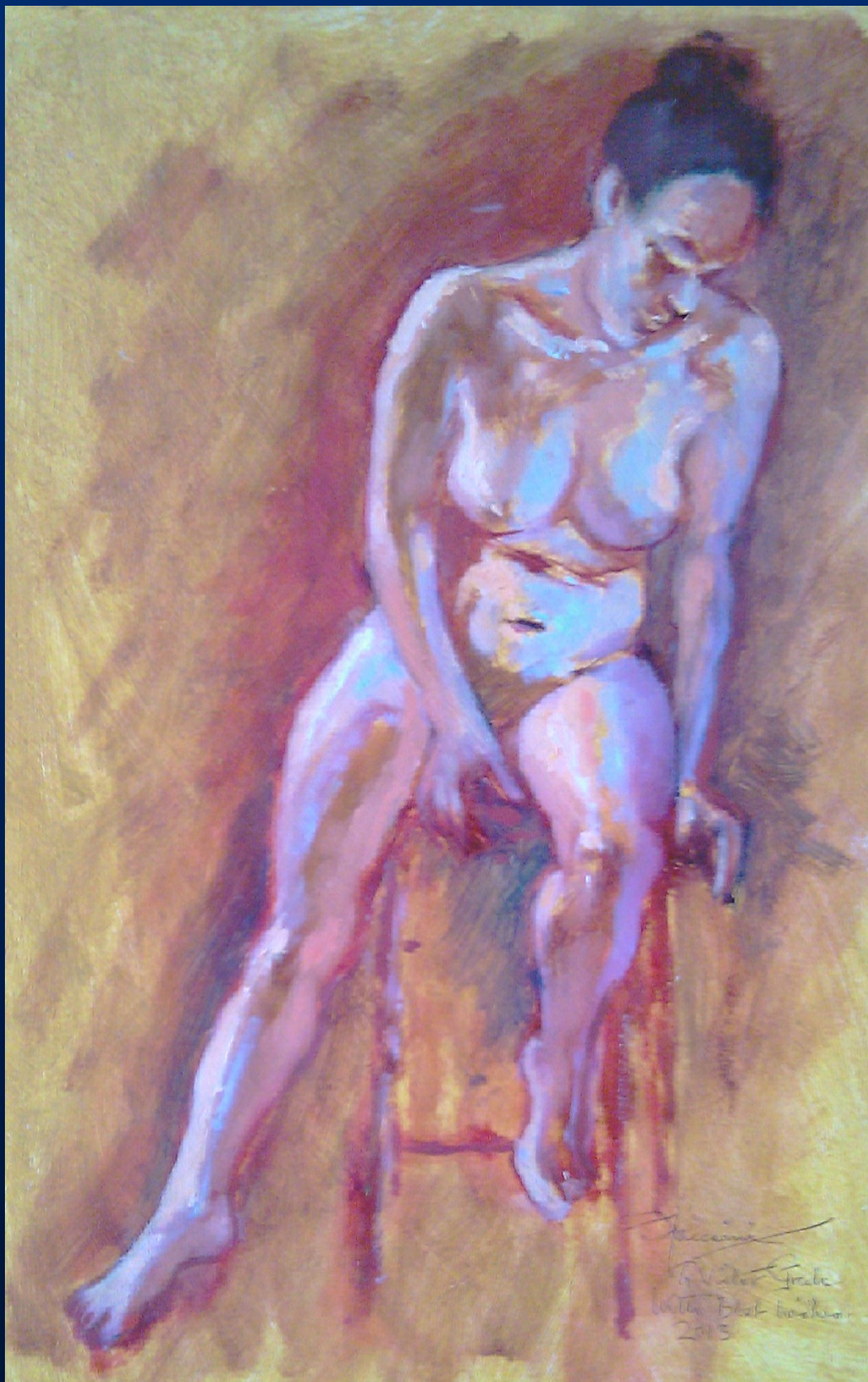


# Malta Medical Journal



# The Malta Medical School Conference

Carmel Mallia

The next Malta Medical School Conference, the ninth one in the series, is being held towards the end of 2015.

The original idea of a regular medical conference started in the early 1970s when the then “Association of Surgeons and Physicians of Malta” used to organize a yearly meeting – quite a modest affair - held in the Conference Room of the Medical School in Pietá, attracting about 40-50 doctors, mainly consultants and other hospital doctors and some general practitioners. After 1977 this activity was disrupted for several years and the concept of a Medical School Conference was born about 25 years ago, the idea being the brainchild of Prof. Frederick Fenech, then Dean of the Faculty of Medicine and Surgery, and of Dr. Joseph Pace then Chairman of the Postgraduate Medical Education Committee. The aim was to establish a triennial multi-disciplinary conference with material presented by graduates of the Medical School of Malta, practising both locally and overseas. Representatives of the various Royal Colleges and Postgraduate Medical Centres of Excellence were also invited. The First Malta Medical School Conference was held at the Suncrest Hotel, Qawra, on 15-16<sup>th</sup> December 1989: it was an unqualified success. It is worth recalling comments that were sent to the local organizers by some of the foreign visitors:

*“.... A two days’ scientific meeting exclusively conducted by Maltese doctors. I have seldom been to a wide-ranging symposium of such sustained excellence. I was left marvelling at so much medical distinction deriving from such a small population.” (the late Prof. J. Richmond, then President of the Royal College of Physicians of Edinburgh)*

*“....I thoroughly enjoyed the Conference which was brilliantly organized and a magnificent success” (Prof. R.B. Cole School of Postgraduate Medicine, University of Keele)*

*“....It was a most rewarding experience; the organization of such a large and complex meeting was beyond criticism and I felt that the presentations were of a consistently high standard.” (Prof. J. Anderson, Dean, Postgraduate Institute for Medicine and Dentistry, Newcastle upon Tyne)*

It may have seemed that the first Malta Medical School Conference set a standard that would be difficult to emulate. However the success of this first conference was reproduced in all successive ones - thanks, in no small measure, to the hard work of the different organizing committees of the various conferences, as well as the scientific contributions and overall participation. I feel privileged to have been a member of the committees of the first four and Chairman of the seventh Malta Medical School Conference. It was a pleasure working with so many different colleagues whose sole purpose was to ensure the success of the conference. One characteristic quality that was present throughout was the enthusiasm displayed by all who were involved in the meeting – starting with the support of the respective Deans of the Faculty of Medicine and Surgery, committee members, secretarial staff, sponsors, pharmaceutical exhibitors, medical student helpers and many others. If I had to single out one particular person for a special word of recognition it would be Mr. Charles Borg Galea who was in charge of the (one-man) audio-visual department at the Medical School for many years. In the days before Power-Point, Mr. Borg Galea would prepare all the 35 mm transparencies for all presentations: despite the ‘strict’ deadlines he used to impose, many would still hand in their work very late, and several of us would go back having noticed some mistakes in our original material. We must have tried his patience to the limit – but he always delivered on time. He was also responsible for the audio-visual services during the conference, initially practically

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single-handed.

All editions of the conference attracted Maltese Medical/Dental School graduates who achieved high standards in their countries of adoption. They included, among others, Professor Sir Alfred Cuschieri, one of the pioneers of keyhole surgery, Professor George Zarb, (Professor of Dentistry, University of Toronto), Professor Michael Camilleri, (Professor of Medicine and Physiology, Mayo Clinic, Rochester, Minnesota), Professor Anthony Busuttil, (Emeritus Professor of Forensic Medicine, University of Edinburgh), Dr. Joseph DeGiovanni, (Consultant Cardiologist University Hospital, Birmingham), and Dr. Joseph Coleiro, (Consultant Ophthalmologist Ninewells Hospital, Dundee, Scotland).

The Malta Medical School Conference has retained its original format namely, that of a multi-disciplinary meeting which covers a wide spectrum of the various medical/surgical specialties. Papers submitted by Maltese medical graduates practising locally or overseas complement keynote speeches by experienced clinicians and academicians, both local and foreign. This way doctors working in different disciplines are exposed to other branches of medicine that are not their main area of interest. There has always been an excellent response in terms of scientific contributions to the conference, with the number of submitted papers increasing with every conference, the latest two conferences receiving over 450 papers. This confirms the continuing and, indeed, the ever-growing popularity of the conference. The request for oral – as opposed to poster – presentations is much higher than can be accommodated. This always renders the task of the adjudicating Scientific sub-Committee very difficult. Short of having more parallel sessions (which partly defeats the scope of the conference) or a longer conference (which poses major logistical problems) the various committees constantly try to find ways of giving posters a more prominent place in the conference. The Scientific Committee tries to encourage participants by accepting most of the abstracts that are submitted, but the time has come when more effective pruning has become necessary so as to ensure the high standards that the Conference has achieved.

The number of delegates at the conference continues to increase – numbers now reaching about 700. While this is partly due to the generous support of the Faculty of Medicine in subsidizing the attendance of clinical students, the number of doctors attending the meeting is also increasing. The organizing committees always do their utmost to draw up a programme that is of interest to all who attend the meeting.

Like its predecessors, the 8<sup>th</sup> Malta Medical School Conference was a major success. The Chairman of the Conference was Dr. Raymond Galea, who has, once again, been entrusted with the next edition of the

Conference. I am sure that Dr. Galea, with his energy and infectious enthusiasm, together with his organizing committee, will maintain the tradition of staging a very successful conference that is generally looked upon as a showpiece of our Medical School. I augur Dr. Galea and his co-workers every success.

### **Cover Picture:**

‘Nude’

Acrylics on board.

**By Carol J. Jaccarini**

*Carol J. Jaccarini graduated MD from the Royal University of Malta in 1961. Trained in Paediatrics in the United Kingdom, qualified DCH Lond (1966), MRCP UK (1969), FRCP Lond (1985), and was Consultant Paediatrician at St Luke's Hospital between 1975 and 1978. Since then he has carried on with private practice in Paediatrics. Tutored for 8 years by artist Anton Calleja, he paints mainly in acrylics and is a regular contributor in collective art exhibitions.*

# Changing clinical activity in Paediatrics in Malta, 1996-2011

Simon Attard Montalto, Miriam Gatt

## Abstract

**Aim:** This study reviews the clinical workload in paediatrics in Malta over a 16-year period.

**Methods:** National statistics for live birth rates were obtained from the Directorate of Health Information and Research. Data for paediatric (birth to 14 completed years) and neonatal admissions, day cases, outpatient visits, attendance at Paediatric Accident and Emergency and the Community-based Developmental Unit were obtained from the Annual Reports, Department of Paediatrics, for the period 1996-2011.

**Results:** During the study period, live births fell by 11% from 4,349 in 1996 to 3,857 in 2005, and recovered to 4,283 in 2011. Whereas neonatal admissions to NPICU remained constant at around 340( $\pm$ 22) per annum, inpatient admissions to the general Paediatric wards decreased by 19% (from 3,151 to 2,550), and casualty reviews dropped by 35% (11,831 to 7,773). In contrast, day care reviews increased by 66% (1,347 to 3,928), the total outpatient workload increased by 70% (13,500 to 22,998), and cases reviewed in the Community-based Child Developmental Unit increased by 184% from 413 to 1174. Changes observed in the clinical activity in Gozo General Hospital were similar but less marked.

**Conclusion:** Over a 16 year period, there has been a significant shift in the paediatric workload in Malta from an in-patient bias in 1996 to increased day care and outpatient reviews in 2011. This shift is largely the result of improved hospital and community day health care services, and can be increased further with augmented community care. Health resources and future paediatric health care programmes will need to take heed of these trends.

## Key words

changing clinical activity, Paediatrics

## Introduction

Several factors, both within the hospital setting and in the community, may influence the clinical workload in paediatrics and, in turn, may impact the Healthcare needs and planning requirements for this important service. Malta, the smallest island state within the European Union with a total population of 415,654 (August 2013), has a single Clinical Department of Paediatrics based within the main 825-bedded State Hospital. All hospital services are catered for in three paediatric wards (36 beds), a combined Paediatric and Neonatal Intensive Care Unit (NPICU, 33 cots), Day Care (12 beds), Emergency and Outpatient Departments, whilst Community care is based in a Child Development Unit and Health Centres, off-site from the main hospital. A small 7-bedded Paediatric Unit, in the 159-bedded state General Hospital on the sister island of Gozo, caters for approximately 6-10% of paediatric consultations, and a few children are born and/or admitted to privately run hospitals. Hospital admissions are more likely in children under 4 years of age. Infants (below 1 year of age) make up 28( $\pm$ 2)% of all hospital paediatric admissions, whilst 30( $\pm$ 1)% of hospital paediatric admissions include children between the age of 1-3 years. Hence, a change in number of births, with a subsequent change in the prevalence of infants and children below school age, would be expected to impact the clinical workload. Additionally, changing population demographics affected by immigration could affect clinical workload. The latter would include legal adoptions and irregular migration, in these cases both

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the total number and country of origin of adoptees/migrants may vary considerably over a period of a few years, thereby creating new health problems with different requirements on existing healthcare services. Finally, changing standards of health care, in-hospital sub-specialisation as well as improved community-based services and education are all potentially contributing factors that may alter the paediatric workload.

This study reviews the clinical workload in the Department of Paediatrics at a National level in the light of a changing birth rate, changing national demographics, and improved in-hospital and community services for children, over a 16-year period.

**Running title:** changing workload, paediatrics

## Methods

During the study period, paediatric cases were defined as all children from birth to 14 completed years (subsequently increased to 16 years in 2012). National statistics for livebirths were obtained from the Directorate of Health Information and Research, whereas figures for paediatric and neonatal admissions, day cases, outpatient visits and reviews in Paediatric Accident and Emergency were obtained from the Annual Reports, Department of Paediatrics, for the period 1996-2011. Chi squared test was used to compare changes in numbers of births to indigenous or non maltese mothers, assuming  $p \leq 0.05$  to achieve significance.

## Results

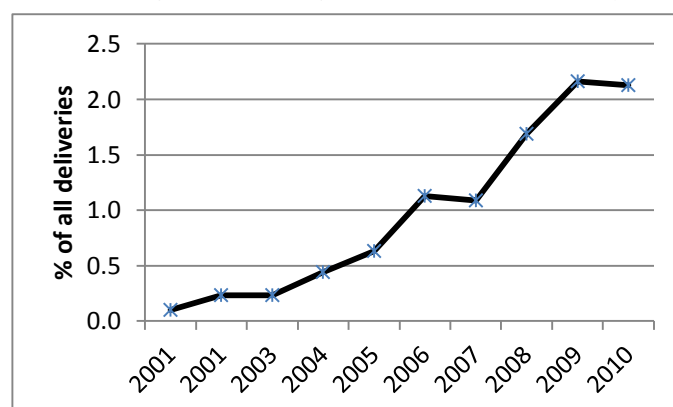
### *Changes in births, demographics*

The client base for paediatric services in Malta has been shrinking for more than half a century. Births in Malta and Gozo have been falling even before the study period from the peak of 11,304 in 1946 to a nadir of 3,536 in 2007 with some recovery since.<sup>1</sup> During the study period 1996-2011, the live births fell by 19% from 4,349 in 1996 to 3,536 in 2007, and recovered to 4,283 in 2011 (down 1.5% from 1996).<sup>1</sup> These rates have contributed to a reduction in the paediatric population (below the age of 14 years) recorded in the national census of 71,848 in 2000, to 59,414 in 2011.<sup>1</sup> Almost all of the births registered during the study period included those to indigenous maltese parents, and non maltese children below 14 years only amounted to 2,091 (3.5%) from the total of 59,414 in 2011.<sup>2</sup> Hence, relatively few non-Maltese children were added to the official population, and these included legal adoptions and irregular migrants.<sup>1-4</sup>

Prior to 1997, an average of 44 children were legally adopted every year, with  $12 \pm 1$  (28%) from Malta and  $32 \pm 7$  overseas, mostly from Romania (50%) and

Pakistan (13%). During the study period a mean of 65 children were legally adopted every year with  $16 \pm 7$  (25%) locally, and  $49 \pm 8$  from overseas, mainly from Russia (36%), Ethiopia (25%) and Cambodia (14%).<sup>2-4</sup> Concomitantly, approximately  $174 (\pm 83)$  children enter the country through irregular immigration per year, mostly from sub-Saharan Africa.<sup>3</sup> Furthermore, deliveries to mothers of Sub-Saharan African nationality have increased steadily and significantly from 0.1% (4) of all deliveries in 2001 to 2.13% (84 deliveries) in 2010,  $p < 0.001$  (Figure 1).<sup>5</sup>

**Figure 1:** Percentage of all deliveries in Malta occurring to mothers of Sub-Saharan nationality.



### *Changes in workload*

Over the 16 year study period 1996-2011, the total number of clinical events covering all areas of paediatric care in Malta increased by 27% from 30,582 to 38,763 per annum.<sup>6</sup> Whereas neonatal admissions to NPICU remained constant at around 340 ( $\pm 22$ ) per annum, in-patient admissions to the general paediatric wards decreased by 19% (from 3,151 to 2,550, Figure 2), and casualty reviews dropped by 35% (from 11,831 to 7,773, Figure 3).<sup>6</sup>

**Figure 2:** General admissions, 1995-2011.

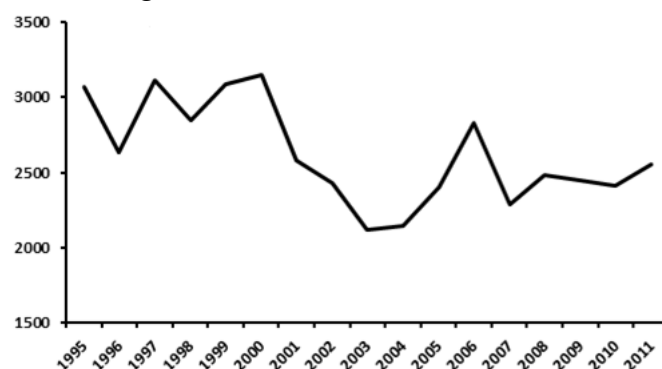
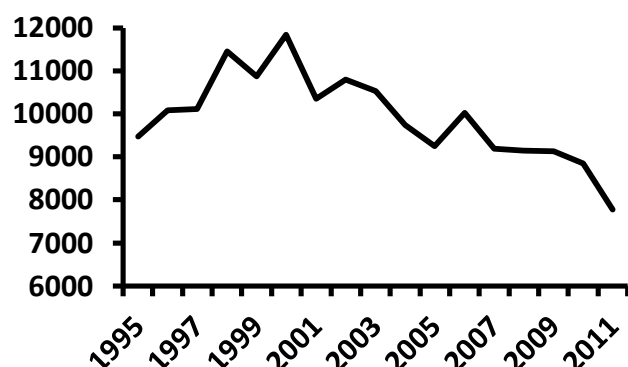
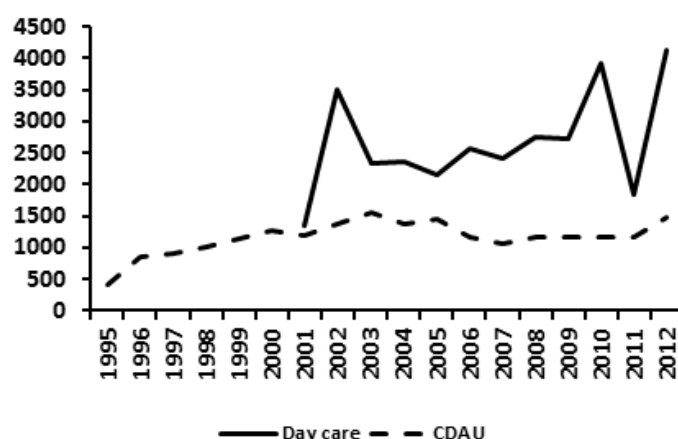


Figure 3: Casualty reviews, 1995-2011.



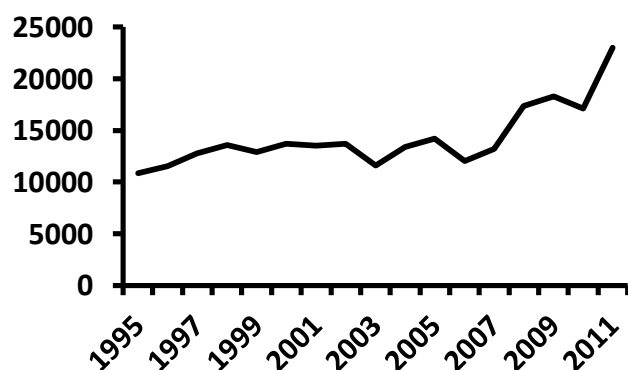
In contrast, day care reviews increased by 66% (1,347 to 3,928, Figure 4), cases reviewed in the Community-based Child Developmental Unit increased by 184% (from 413 to 1,174, Figure 4), and the total outpatient workload increased by 70% (13,500 to 22,998, Figure 5).<sup>6</sup>

Figure 4: Changes in Day and Community workload, 1995-2012.



\* Dip in 2011 reflects prolonged periods when day care unit was not available for use.

Figure 5: Changes in outpatient visits, 1995-2011.



Over the same 16-year period, the total number of clinical events covering all areas of paediatric care in Gozo General Hospital decreased from 4,098 to 3,385 per annum.<sup>6</sup> Although, over the same time period, live births in the sister island of Gozo decreased by 23% from 363 to 279,<sup>1,6</sup> the inpatient workload was unchanged from 664 to 676 cases, outpatient cases decreased 25% from 1852 to 1391 and casualty reviews decreased by 17% from 1,582 to 1,318.<sup>1,6</sup>

## Discussion

This study clearly shows that the paediatric workload in Malta, at a national level, has changed considerably over the past decade and a half. Overall, there has been an increase of 27% in the total number of 'all comer' clinical events recorded each year, despite a concomitant reduction in the national crude birth rate ranging from 13.1/1000 population in 1996 to 9.6/1000 population in 2010.<sup>1,6</sup> This increase is largely the result of a significant increase in day care (66%), outpatient (70%) and community (184%) workload, and is partially offset by a steady decrease in inpatient and casualty-based activity of 19 and 35% respectively, over the same time period.

Several factors are likely to have contributed to the changing trend from in- to out-patient based work, including the expansion and improvements in existing services within the primary care setting, in line with similar trends overseas.<sup>7</sup> During the study period, the community-based Child Developmental and Assessment Unit was firmly established as a service provider and augmented by an increase of community-based consultant posts from one incumbent in 1996 to four in 2011. This, together with a general improvement in primary care services and an increasing number of paediatric-trained personnel working in primary care within both government and private sectors, have diverted a significant proportion of care away from the hospital setting. Improved care and disease prevention in children with, for example the achievement of >96% vaccine coverage against *haemophilus influenzae type b* (Hib) within the National Immunisation Programme<sup>8</sup> and an estimated figure of >75% for *Streptococcus pneumoniae* administered in the private sector, are likely to have had a significant impact on the health burden that these infections create. Indeed, in the UK, US and elsewhere, widespread and effective immunisation programmes for these two infections alone have resulted in far fewer cases requiring hospital admission.<sup>9-12</sup>

Simultaneously, there has been a steady trend toward in-hospital sub-specialisation, and the hospital-based consultant pool increased from five generalists in Malta and Gozo in 1996 to four generalists and six

subspecialists in 2011 (and seven in 2013). These have expanded existing and/or introduced several new services many of which include day care work such as endoscopy, endocrine testing, echocardiography, and gastro/cardiac/neuro-interventional procedures, amongst others. Invariably all these services, in turn, generate additional work mainly relating to imaging and investigations most of which are carried out as day cases. Other subspecialties, although not yet consultant-based, have also expanded along the same format, in turn creating their own demand on existing services whilst creating new services including focused outpatient clinics. Invariably these services are more complex and demanding than what was in existence beforehand. Indeed, these changes would, to some extent, explain the observed increase in children outpatient-based services in Malta compared with a corresponding drop of 25% in Gozo where subspecialisation has not occurred.

The rationale and benefits of visiting consultant clinics (VCCs) has been well documented,<sup>13,14</sup> and the introduction and expansion of the VCCs in paediatric specialties in Malta has continued to add to the outpatient workload.<sup>4</sup> In 1996, 7 visiting consultants carried out 8 clinics annually and, in 2011, this had increased to 9 consultants attending 22 clinics. This would translate into an increase in patient attendance from an average of 160 to 450 in all VCCs per annum, but would also have had a knock-on effect for subsequent day care work (e.g. for investigations) as instructed by the visiting consultant. Whilst providing a review service at a local level and helping to train local personnel, VCCs reduce the need for referrals for some groups of patients overseas, but also flag up other 'new' patients (and any accompanying health requirements including investigation and treatment), that were previously unrecognised. In many cases, for a given subspecialty, the overall number of patients reviewed and those referred abroad remains generally constant before and after the establishment of a VCC, albeit with the level of clinical excellence being raised.

Over the study period, increasing staff expertise, achieved through improved training carried out locally and overseas along well defined training programmes, better links with tertiary and quaternary service providers (including the VCCs), and well established training initiatives such ongoing continued medical education, symposia, travel for conferences, etc., are all likely to introduce more 'modern', time efficient and out-patient based practices.

Clearly, workload as perceived by number of patients alone is of limited value, and the actual burden on health services may be considerably greater if the increasing numbers also present with different and more complex diseases.<sup>15,16</sup> Hence, for example, in 2011 the

number of international adoptions and irregular migrant children entering the country per year had increased to a mean of 49 and 174, respectively.<sup>1-4</sup> Although arriving in relatively small cohorts, these children are more likely to have medical problems requiring attention and, although the impact in Malta is unknown, they have been estimated to add a significant burden to healthcare budgets in other countries.<sup>17-21</sup> Similarly, although outpatient care is generally cost effective compared with hospital admissions, new treatment modalities and 'modern' medicine particularly with regard to newer drugs remain, in many cases, very expensive regardless of whether these can be administered in an outpatient setting. For this reason, the clear shift from in- to outpatient care over a 16-year period has not been associated with a parallel reduction in the cost of care within Paediatrics in Malta.

## Conclusion

This 16 year review clearly demonstrates a significant shift in the paediatric hospital workload in Malta from an in-patient bias in 1996 to increased day care and outpatient reviews in 2011. This shift is largely the result of improved hospital day-care and community health services and can be increased further with augmented community care. Health resources and future Paediatric health care programmes will need to take heed of these trends and must be planned accordingly.

## Acknowledgements

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# Gendercide – a review of the missing women

Victor Grech, Julian Mamo

The term gendercide was first coined in 1985 and refers to the deliberate extermination of persons of a particular sex.<sup>1</sup> The notion and its potential consequences had been conceived as far back as 1793, when the Marquis Nicolas de Condorcet had speculated “what might be [the effect] on humankind [of] the discovery of a means of producing a male or female child according to the will of the parents [...]. Supposing that this is likely to become a common practice, [...] would it [not] lead to [changes] in the social relations of human beings, whose consequences could be harmful to the peaceable development of that indefinite perfectibility with expectations of which we have flattered humankind?”<sup>2</sup>

Due to the patriarchal nature of most human societies, the extermination of females is a far commoner occurrence than the extermination of males. Male preference resulting in a higher proportion of males at all ages, particularly in Asia, has been attributed to the Confucian patriarchal tradition that is characterised by strong son preference and female subordination.<sup>3</sup>

**Key words:** Sex Ratio, Infant, Newborn, Birth Rate/\*trends

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Patriarchy thus becomes an “explicit or implicit notion [...] an overarching concept to signify a fundamental power differential between men and women in which women are invariably the victims and men the unnamed perpetrators of gender wrongs”.<sup>4</sup> Indeed, it has been calculated that more girls have been killed in the last half century, simply because they are females, than the sum total of all males killed in all the wars in the 20<sup>th</sup> century.<sup>5</sup> This has led to the phenomenon of “rampant demographic masculinization”,<sup>6</sup> with the looming phantom of a “world without women” attracting profound interest from the media.<sup>4</sup>

Female infanticide has a long tradition in countries such as China. For example, as far back as two centuries ago, the practice of exposing female babies to the elements was done openly. Jesuit missionaries documented that thousands of these infants were abandoned in the streets of Beijing to be eventually buried in a common grave outside the city.<sup>1</sup> Femicide is widespread in certain parts of the world and its antenatal application greatly affects the male to female (M/F-male births divided by total births), leading to a dearth of females.<sup>6</sup>

Modern and scientifically accurate methods for antenatally determining gender have been available as early as 1975 in China with the use of chorionic villous sampling.<sup>1,7</sup> Antenatal sexing was later facilitated, worldwide, by ultrasound technology.<sup>8,9</sup>

The efforts to erase female babies and children from society due to son preference has led to a significant number of missing women, particularly in Asia. This was first noted in 1990,<sup>10</sup> and is due to a combination of infanticide, child abuse or neglect (such as inadequate nutrition or medical care), sex-selective abortion and the non-registration of unpermitted children.<sup>8</sup> The original estimate claimed that over a hundred million women were “missing”.<sup>10</sup>

Since then, it has been estimated that in Asia alone, the number of missing women is in the region of 163 million.<sup>11</sup> The European Commissioner responsible for Employment and Social Affairs has quoted unofficial United Nations calculations that “estimate that 200 million females are missing in the world; women who should have been born or grown up, but were killed by infanticide or selective abortion”.<sup>12</sup> The countries with the highest percentage of missing women were calculated as being Pakistan, India and Bangladesh with

11, 9.4 and 8.9% of all missing females respectively.

This paradigm is prompted by social, cultural, political and economic factors.<sup>13,14</sup> These are predominantly caused by the tendency for patrilineal inheritance in patriarchal societies coupled with a reliance on male children to provide economic support indefinitely. This is especially so when sons are higher wage earners than daughters, by far the commoner situation.

For example, in India, female children are considered less desirable as they require a dowry to be married off (while a marrying male brings in a dowry), and male children along with their wives and families are expected to care for the husband's (and not the wife's) parents.<sup>15</sup> For this reason, in this country alone, it was calculated in 2006 that half a million female fetuses had been aborted annually, resulting in a deficit (up to that time) of approximately 10 million female fetuses over the previous two and a half decades.<sup>16</sup>

Neglect also kills. For example, in India, a form of discriminatory behaviour may commence before birth. It has been shown that when it is known that the foetus is female, failure to attend antenatal clinics and take the tetanus vaccine accounts for 4-10.5% of the excess female neonatal mortality.<sup>17</sup> Thus, even when female pregnancies are carried to term, neglect can still lead to death.

Women in such countries may experience tremendous social pressure to produce sons, becoming repeatedly pregnant until they do so, since failure may incur violence, rejection or even death.<sup>18</sup>

This attitude is also prevalent, albeit less strongly, in more developed countries and it has been stated, based on a United States National fertility study, that "the most lasting implication of the introduction of sex-control technologies would appear to be a significant increase in the probability of the firstborn being a male, and the second child being a female".<sup>19</sup>

This mind-set prevails in all social classes, such that even in the United States, a large sample of university students revealed that 85% preferred a firstborn male and 73% desired a second child to be female.<sup>20</sup>

Gender-selective abortion is the commonest form of femicide, and remains in widespread use in Asia and in countries with a high population of Asian immigrants.<sup>21</sup> There is also evidence of its use even among particular ethnic groups in more developed countries, such as the United States, where it has been shown that for third and higher order births, M/F was significantly elevated in Chinese, Asian Indians and Koreans.<sup>22</sup> Similarly, in Canada, it has been shown that M/F in multiparous women who had been born in India was significantly higher than that of multiparous women born in Canada.<sup>23</sup>

In countries with reduced fertility, the M/F skew is very high, as experienced in China with its one-family, one-child policy. This had been enforced in China in 1979 following a government attempt to overcome the economic stagnation engendered by the so-called "Cultural Revolution." At this time, China contained a quarter of all of humanity on seven percent of the planet's arable land, with two thirds of its population aged under thirty years. The Communist government perceived this policy as essential to an improvement in living standards by economic reform. And in a society which prizes males, the parents will desire that the single child will be male at any cost. The policy was enforced by discretionary rewards and punishments which included large fines, confiscations of belongings, obligatory abortions and dismissal from work. In rural areas, a second child was generally permitted only if the first child was female, a clear acknowledgment of the traditional son preference.<sup>24</sup> The widespread non-reporting of unwanted or abandoned female babies was also common in China, often with the collusion of local authorities.<sup>25</sup>

Asian governments, cognizant of the problems of M/F distortion, have sought to outlaw all forms of femicide, with limited effect,<sup>24</sup> and it seems that change can only come about slowly with increased population education.

For example, South Korea was in the forefront in the utilisation of sex-selective technology, greatly distorting the country's M/F.<sup>26</sup> However, by 2007, M/F in this country had dropped to conventionally accepted values, probably due to rapid economic growth and development, with a reduced son preference.<sup>27</sup>

It is also theoretically possible for couples to deliberately influence M/F without resorting to abortion, such as by timing coitus within the menstrual cycle or even by choosing the time of conception within the calendar year.<sup>28</sup>

In the interim, until M/F normalises, the social consequences are expected to be catastrophic. For example, it is estimated that in parts of China and India, there will be an excess of 12-15% young men, to their great detriment, since in these regions, marriage is highly desirable and a crucial factor on which social status and acceptance depends.<sup>29</sup>

It was estimated that the global sex ratio for 2012 was 0.5169.30 The global effects on the sex ratio assuming a current ratio of 0.5169 and a world population of 7 billion are shown in Table 1 using quadratic equations for exact calculation of 95% confidence intervals for ratios.<sup>31</sup> This table factors in female deficits ranging from 100 to 200 million (assuming that all such females have survived).

**Table 1:** Effects of missing women on global M/F assuming a current global sex ratio of 0.5169<sup>30</sup>

Assumed female deficit	None (observed)	100000000	150000000	200000000
Missing females %	-	1.43	2.14	2.86
Calculated male population	3618357488	3618357488	3618357488	3618357488
Calculated female population	3381642512	3481642512	3531642512	3581642512
Total	7000000000	7100000000	7150000000	7200000000
Upper confidence interval	0.51692	0.50964	0.50608	0.50256
M/F	0.51691	0.50963	0.50606	0.50255
Lower confidence interval	0.51690	0.50962	0.50605	0.50254

Missing females displayed as a percentage of current total global population

The large number of missing women has led to speculation that there will be increased levels of antisocial behaviour and violence in such regions.<sup>32</sup> For example, in China, unmarried men are known as *guanggun* (bare sticks), with implications of being outcast and somehow threatening to the public order. In popular lore, moreover, *guanggun* were associated with bullying and banditry.<sup>4</sup> Such individuals are likely to be drawn toward military organizations, potentially threatening global security, especially since this demographic imbalance will occur in global political hotspots.<sup>29</sup>

There is historical precedent for this as it has been noted that male population youth bulges appeared to precipitate Europe's imperial expansion after 1500, Japan's imperial expansion after 1914, the Cold War civil uprisings in Algeria, El Salvador, and Lebanon, and the recent rise of Islamist extremism in Muslim countries such as Afghanistan, Iraq and Pakistan. It has been argued that "third and fourth sons" frequently fail to find prestigious or meaningful positions in their societies and channel their energies into religious and/or political ideologies.<sup>33</sup>

Developed countries are not immune to these effects. It has been shown that a male-biased secondary sex ratio (the sex ratio in mature and fertile adults) influences men such that they forego considerations about the future and attempt to access immediate rewards, along with a willingness to incur debt for immediate expenditures. Such men are willing to spend more money on courtship behaviour (such as engagement rings), even if this means leaving them indebted.<sup>34</sup>

The situation has been compared with Ernest Hemingway's collection of short stories, *Men Without*

*Women*<sup>35</sup> which features gangsters, bullfighters, wounded soldiers, and killers.<sup>36</sup> This scenario has also been extensively explored in science fiction.<sup>37</sup>

These negative outcomes may well occur despite the fact that one of the few positive consequences of selective abortion should be a reduction in the number of unwanted children.

The situation could eventually be self-limiting since any gender imbalance will lead to a reduction in birth rates. In addition, as the number of girls decreases, their social status should increase due to their rarity, leading to a decline in son preference.<sup>38</sup> Furthermore if, due to scarcity, a significant proportion of men marry older women, there should be fewer single, lonely individuals in old age since women have a greater life expectancy than men.<sup>32</sup>

Fortunately, the younger generations already show signs of self-remedying this state of affairs in that the traditional preference for boys may be changing.<sup>39</sup> The Chinese National Family Planning and Reproductive Health Survey of 2001 showed that 37% of women claimed to have no offspring gender preference, 45% stated that the ideal family consisted of one boy and one girl, and in the case of one offspring, women were slightly more in favour of having one girl than one boy.<sup>40</sup>

There is thus yet hope that the man-made imbalance in M/F may be alleviated by improved levels of education and better standards of living.

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# The optimal treatment of multivessel coronary artery disease

Alexander Manché

*"The time of ad hoc angioplasty for the patient with multivessel coronary artery disease has passed."* James Wilson, Texas Heart Institute.

## Abstract

The practice of percutaneous coronary intervention has overtaken coronary bypass surgery in the treatment of ischaemic heart disease. Several randomized controlled as well as registry and observational trials have addressed the issue of patient selection and outcomes in order to provide the cardiologist with data enabling optimal treatment selection. This article reviews the major trials performed over the past 25 years, underscoring their strengths and limitations and draws on lessons and guidelines that are relevant to our local practice.

## Introduction

Coronary artery bypass grafting (CABG) was popularised in the 1970's. Within a decade this operation became the commonest and most comprehensively studied major surgical procedure in the Western world. Randomised trials proved that, in certain subsets of patients, it was superior to medical treatment. A third treatment modality, that of percutaneous coronary intervention (PCI), initially with balloon angioplasty and later with stent implantation, has captured an increasing share of the market over the past 25 years, such that the current volume of PCI has far outstripped surgery. This situation has fuelled intense debate as to which treatment best serves the patient with severe coronary artery disease. Numerous trials have been conducted, comparing PCI with CABG, and these have resulted in guidelines, reached by consensus amongst the European Societies of interventional cardiologists and cardiac surgeons, defining the optimal treatment for these patients.

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This paper describes these developments, analyses the local situation, and asks whether guidelines are being adhered to in the interest of best practice.

## Key Words

Ischaemic heart disease, multivessel disease, coronary surgery, percutaneous intervention

## CABG versus medical therapy

In 1994 the Lancet published a meta-analysis of seven randomised trials of CABG versus medical treatment, analysing 2650 patients with a follow-up of ten years.<sup>1</sup> The authors showed there was a survival advantage and marked symptom improvement with CABG as compared with medical therapy in left main stem (LMS) disease, triple vessel disease (3VD) and proximal left anterior descending (LAD) disease. These benefits were enhanced with severe symptoms, a positive stress test and impaired ejection fraction (EF). The results were analysed on an intention-to-treat basis although 40% of patients assigned to medical treatment crossed over to surgery. Only 10% of patients received a left internal thoracic artery (LITA) graft, known to be an important component of surgery. There was no survival value in CABG for single or double vessel disease and normal LV function. The authors concluded that future trials comparing CABG with another treatment should include a high proportion of patients in whom surgery is known to be beneficial. However this never happened.

## CABG versus PCI

### Randomised controlled trials

From 1994 to 2002 five major randomised controlled trials of CABG versus PCI were conducted, namely the Randomised Intervention Treatment of Angina (RITA),<sup>2</sup> the Coronary Angioplasty versus Bypass Revascularisation Investigation (CABRI),<sup>3</sup> the German Angioplasty Bypass Surgery Investigation (GABI),<sup>4</sup> the Bypass Angioplasty Revascularisation Investigation (BARI),<sup>5</sup> and the Stent or Surgery trial (SoS).<sup>6</sup> None of the patients selected in these trials had LMS disease and EF was either normal or not specified. From an initial combined population exceeding 100,000, patient selection resulted in only 5% entering these trials (range 3-12% for individual trials). The resultant

samples were unrepresentative of the real world CABG population where LMS disease is present in over 20% and low EF in over 35%. The incidence of 3VD in the studies was a mean of 31%, that of proximal LAD disease was either low or unspecified and LITA usage was 75% (all parameters over 90% in the real CABG world).<sup>7</sup> In summary the vast majority of these patients had single or double vessel disease and normal LV function, a population in whom there was no expected prognostic benefit from surgery. Conversely these trials largely excluded those patients who are known to benefit prognostically from surgery, namely those with LMS disease and 3VD, those with proximal LAD disease and impaired EF.

A meta-analysis of 5 trials comparing CABG and PCI also excluded patients with LMS disease and impaired EF. Patients selected in these trials represented 2 to 5% (depending on the particular trial) of the initial population. The overall incidence of 3VD was 42%.<sup>8</sup> The Arterial Revascularisation Therapy Study, ARTS, one of these five trials, included 68% of patients with single or double vessel disease, and all patients had normal LV function. The authors reported similar one and five-year survival rates for surgery and PCI. However, reintervention rates were 30% for PCI versus 9% for CABG and mortality in a subset of 208 diabetics was 13% for PCI and 8% for CABG.<sup>9</sup> The SoS trial, also included in this meta-analysis, reported a significantly higher one-year mortality in the PCI group (2.5 versus 0.8%).<sup>6</sup> The 6-year median follow-up confirmed a sustained significantly higher mortality of 10.9% for PCI versus 6.8% with CABG.

David Taggart, a cardiac surgeon from Oxford, UK, highlighted the inherent prejudice of these papers against surgery in that they included highly selected patient populations unrepresentative of multi-vessel disease in the real CABG world. Moreover editorials disregarded this basic flaw.<sup>10</sup>

### Registry and observational trials

A study by Hannan reported on long-term outcomes in almost 60,000 patients undergoing surgery or stenting.<sup>11</sup> Data was derived from the New York Registry during a 3-year period 1997 to 2000 and reflected a real world situation. One-year mortality for all groups was 6% after CABG versus 9% after PCI. The mortality at 3 years in patients with 3VD was 10.7% after CABG and 15.6% after PCI. The hazard ratio for death at 3 years with CABG versus PCI was 0.76 for 2-vessel disease and 0.65 for 3VD. The incidence of repeat revascularisation was 5% for CABG versus 35% for PCI.

The Syntax trial is another landmark study comparing bypass and stenting in the real world.<sup>12</sup> 1800 patients, in whom the cardiologist and surgeon

determined to offer equivalent revascularisation, were randomised to receive CABG or PCI. From the original 4337 patients 1262 were deemed ineligible, and a further 1275, deemed only suitable for one treatment modality, were entered into the registry (1077 in the CABG arm and 198 in the PCI arm). At one year the two groups had similar rates of death from any cause. The rate of repeat revascularisation was significantly increased in the PCI group (13.5 versus 5.9%), as was the overall rate of major adverse cardiac and cerebrovascular events (MACCE) (17.8 versus 12.4%). The Syntax trial provided insight into the subgroups benefiting most from surgery by way of the Syntax score, an indicator of coronary disease severity and complexity. Thus the greatest difference in the MACCE rates was seen in the high Syntax score patients ( $\geq 32$ ). At five years the overall rates of cardiac death (5.3 versus 9.0%), myocardial infarction (3.8 versus 9.7%), and reintervention (13.7 versus 25.9%), were significantly lower with CABG. The cumulative MACCE rate (25.8 versus 36.0%) was also significantly lower after CABG in intermediate score (23-32) patients. At 5 years the registry patients showed an even larger divergence in the incidence of major events with 23% after CABG versus 49% after PCI. The authors suggest that 71% of all patients, including 25% of patients of the original total in the CABG arm of the registry together with 46% of patients with Syntax scores above 22, are still best treated with CABG. For the remaining 29% of patients PCI is an alternative to surgery.

The ASCERT trial, published in 2012, analyses the comparative-effectiveness of CABG and PCI and is not a randomised trial like the Syntax trial.<sup>13</sup> Patients selected were over 65, without LMS disease, and requiring their first revascularisation. ASCERT represents over ten times as many patients as the total enrolment of all randomized trials comparing CABG and PCI (86,244 CABG and 103,549 PCI patients enrolled). This became possible because the Society of Thoracic Surgeons, the American College of Cardiology, and the Centres for Medicare and Medicaid Services pooled their data, sourced from the National Cardiovascular Data Registry and from the Society of Thoracic Surgeons Registry. This peri-procedural data, which was adjusted for risk, was combined with administrative data from the Medicare and Medicaid registries, providing records on long-term survival. The median follow-up was 2.7 years. Triple vessel disease was present in 80% of patients who underwent CABG and in 32% of patients undergoing PCI, confirming that treatment strategies were based on clinical grounds. The results at one year were similar, but over time the progressive survival advantage of CABG became significant. Survival at four years was 83.6% with CABG and 79.2% with PCI, the hazard ratio for death



was 0.79 and for combined stroke, death or MI was 0.81 for CABG compared with PCI. The benefit from CABG was seen in all subgroups studied. The sheer numbers of patients in this study lend weight to the findings that survival was significantly better with CABG at four years, the results were consistent across all subgroups, and were consistent with the Syntax results, another large real world trial.

### Will stent revascularisation replace CABG?

#### Lessons learnt from landmark trials

Revascularization outcomes include three major endpoints, namely death, myocardial infarction, and symptom control (often requiring reintervention). With respect to death, surgical revascularization benefits patients who have severe multivessel disease and left ventricular dysfunction or other physiologic indicators of high risk. This evidence comes from three seminal trials performed in the 1970s and 1980s, namely the CASS randomised<sup>14</sup> and registry<sup>15</sup> trials and the Veterans trial,<sup>16</sup> and from many observational studies. When angioplasty was introduced the hope was for a method of revascularization that would rival coronary artery bypass grafting.<sup>17</sup> Angioplasty worked well in patients with no major risk factors, but failed in diabetic patients. The BARI trial demonstrated that the use of PCI in diabetics is potentially harmful when compared with a LITA to the LAD.<sup>5</sup> In stable coronary disease the Courage trial, published in 2007, showed that the addition of PCI was unsuccessful in proving a positive impact over optimal medical therapy alone.<sup>18</sup> The bare-metal stent was developed as a metallic buttress to overcome restenosis after angioplasty. The use of stents drastically reduced the probability of emergent surgery after attempted PCI from 1 to 0.3%, increased angiographic success from 89 to 97%, increased freedom from six-month major events, from 77 to 85%, and drastically lowered six-month reintervention rate, from 20 to 8%.<sup>19</sup>

The drug-eluting stent was developed to cure restenosis. However the probability of new lesion formation or late restenosis after intervention did not decrease. This figure was quoted as 10.1% restenosis requiring revascularisation during a three-year follow-up in the J-Cypher registry trial.<sup>20</sup> Stent-in-stent repeat revascularisation was better than balloon angioplasty at preventing further revascularisation, with a hazard ratio of 0.44 favouring stenting, but two-year mortality was similar, at 10.4% after stent-in-stent and 10.8% after balloon angioplasty. Drug-eluting stents with their promise of no restenosis failed to deliver.

#### Guidelines and local trends

The current European Society of Cardiology/ European Association for Cardio-Thoracic Surgery

(ESC/EACTS) guidelines are for a 1A recommendation for CABG in all patients with low predicted surgical mortality in all but one scenario, that of single or double vessel disease, not involving the proximal LAD. The other recommendation, at class 1C, is that, in patients with multivessel disease, the appropriate revascularization strategy should be discussed by the Heart Team.<sup>21</sup>

CABG trends in the US showed a decline of 38% from a peak in the year 2001 to 2008. During the same period PCI decreased by 4%.<sup>22</sup> During a corresponding 7-year period locally, this time starting from peak CABG rates in 2004, the decline in CABG equates to 49%. Local PCI rates increased by 63% during this same period and 26.5% of these were ad hoc procedures, where an investigational angiogram led directly to a PCI. In 2004, 463 patients were referred for CABG, of which 347 (75%) received 3 or more grafts for multivessel disease. In 2011 although the number of angiograms increased by 23% over the 2004 figure, only 150 operations were performed for multivessel disease. Had referral patterns remained unchanged this figure would have reached 427. The real decline in referral of patients with multivessel disease for surgery over this period was of 277 patients in 2011, or 65% of the projected figure. Local PCI numbers increased from 520 in 2004 to 845 in 2011, an increase of 62.5%.

The SYNTAX score is a recognised, computer-based tool for evaluating the risk of complications or failure after PCI. There are other risk stratification systems for estimating mortality after surgery. These estimates enable cardiologists to objectively advise patients regarding the revascularization method that has the best short- and long-term probability of success. In patients with non-life-threatening disease, those without significant LV dysfunction, 3VD or LMS disease, stent revascularization has become an alternative to surgery. However, this is true only if stenting is confined to patients whose anatomy is suited to it, a consideration that is well quantified in the SYNTAX score. With regard to the choice of revascularization, in a patient with multivessel disease, a reasoned approach must be taken, using these predictive tools and considering the patient's wishes. Treatment decisions should include all parties, the patient and the heart team, including the cardiologist and the cardiac surgeon. Thus the ESC/EACTS guidelines recommend that patients be adequately informed about the potential benefits and short- and long-term risks of a revascularization procedure and enough time should be allowed for informed decision making. This is a class 1C recommendation. In this setting there is virtually no recommendation for ad hoc angioplasty.

### Inappropriate stenting

Inappropriate stenting is a term that includes the placement of a coronary stent in a vessel when the lesion is not clinically important, as well as the placement of stents in patients who would benefit more from surgery. In a recent multicentre, prospective study the appropriateness of PCI was assessed in the acute and non-acute clinical scenario.<sup>23</sup> 500,154 PCI patients were recruited from 1091 US hospitals and these were classified as acute (71.1%) (ST-segment elevation MI 20.6%, non-ST-segment MI 21.1% or unstable angina 29.3%) or non-acute (28.9%). In the acute group 98.6% were deemed appropriate. In the non-acute group 50.4% were deemed appropriate, 38% uncertain due to lack of adequate data, and 11.6% inappropriate. Appropriate PCI in the non-acute situation was defined as that performed in the presence of angina, high-risk ischaemia on stress testing, or optimal medical treatment. 95.8% of inappropriate PCI's were performed in the absence of optimal medical treatment. Lack of adequate data in the patient's file may be interpreted as a corresponding deficiency during the decision-making process leading to PCI, in which case the uncertain/inappropriate cohort reached a disturbing level of 49.6%. This study poses important implications on our local practice where non-acute PCI's represent 59.1% of the total program, more than twice that in the study by Chan. Moreover, because of long local PCI waiting times the patient's clinical state may be unknown or may have changed from the time of referral to intervention.

### Conclusions

Local referral patterns for multivessel disease have changed drastically over the years 2004-2011. During this period surgery for multivessel disease decreased by 65% and PCI increased by 62.5%. Syntax scoring is not performed and treatment plans for patients with multivessel disease are not discussed in a multidisciplinary heart team, as proposed by ECS/EACTS guidelines. Ad hoc procedures, which allow little opportunity for informed consent, reached 26.5%. The incidence of non-acute PCI is very high, a cohort in which the incidence of inappropriate stenting is increased. Clearly much can be improved.

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# Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

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## Abstract

ME/CFS is a debilitating condition hardly discussed in the Maltese Islands, and was only recognized in 2009 as a neurological disease in our archipelago despite it being recognized by WHO in 1969. The authors discuss the origin of the combined terminology ME/CFS, the importance of recognizing the condition at an early stage, the appropriate treatment and the potential role of the health services. The authors also highlight the lack of official statistical data available in the Maltese archipelago.

## Keywords

Malta, ME/CFS, terminology, treatment, health service.

## Introduction

ME/CFS is a debilitating, chronic, acquired disease characterized by a range of disturbances effecting all body systems, but predominantly the neurological, endocrine and immune systems. Following normal physical or mental activity, ME/CFS sufferers experience profound fatigue, exhaustion, loss of muscle power, pain, joint tenderness and cognitive dysfunction.

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Other conditions should be excluded such as sleep apnea, anemia, unresolved infections such as hepatitis B or C, side effects of medications and other major depressive disorders. (ICD-9-CM, 2011).

## The Terminology Crisis

Since 1969, ME/CFS has been classified as a neurological disorder in the World Health Organisation (WHO) International Classification of Diseases (ICD 10 G93.3).

The combined terminology: ME/CFS has in-depth history and is still a grey area as many doctors are unsure which terminology to use.

However, in October 2011, Carruthers rejected the term CFS and stated that:<sup>5</sup>

*'In view of more recent research and clinical experience that strongly point to widespread inflammation and multisystemic neuropathology, it is more appropriate and correct to use the term 'myalgic encephalomyelitis' (ME) because it indicates an underlying pathophysiology. It is also consistent with the neurological classification of ME in the World Health Organization's International Classification of Diseases (ICD G93.3).'*

Despite this, many practitioners opt to make do with the combined terminology, to prevent misunderstandings within the medical, research and patient community, avoiding confusion within medical health care.

## Epidemiology

Carruthers reported that the prevalence ranges from 0.4% to 2.5% worldwide, around 235-700 per 100,000 individuals, more prevalent than AIDS, lung or breast cancer.<sup>2</sup>

There is no current epidemiological data for the local Maltese Islands, despite the 800 sufferers living in the archipelago according to a local newspaper published in 2009. This was found to be confirmed by Dr. John Greensmith, representing 'ME Free For All' U.K based organization who obtained this calculation through foreign statistics in 2009.

Until 2011, Malta did not recognize ME/CFS as a disability despite the syndrome enlisted as a neurological disorder by WHO.<sup>10</sup>

## The Aetiology of ME/CFS and the relevant risk factors

The aetiological causes of ME/CFS are topics of vigorous research and debate due to the multi-factorial pathogenesis (Figure 1). The scientific community has not yet identified the cause but suggest a variety of factors which can be classified into two:

- a. Predisposing factors
- b. Events that stress the immune system and prompt onset

### A. Predisposing factors

According to Shepherd genetics, gender, age and psychological factors are the crucial predisposing factors.<sup>20</sup> The psychological factors are mainly excessive stress, a study carried out by Bentall indicate the presence of a stressful event experienced by one-third of the patients prior to the onset of disease.<sup>37</sup> The study conducted by Bell has shown that women are more vulnerable to ME/CFS and three-fourths of the sufferers develop the condition in the mid-40 age group.<sup>10</sup>

### B. Events that stress the immune system and prompt onset

ME/CFS frequently follows an acute infection such as an upper respiratory infection, amongst others. However, there is no conclusive evidence for the latter with no specific pathogen. Carruthers argues that the following are thought to related:<sup>2</sup>

- Epstein-Barr Virus
- Human Herpesvirus-6 and 7
- Enterovirus
- Cytomegalovirus
- Lentivirus
- Chlamydia
- Mycoplasma

### Clinical Features

Physical and emotional fatigue is the main clinical symptom, which lasts for more than 24 hours and is not treated with sleep. This causes loss of concentration, short term memory loss and muscle pain. Headaches and sore throats are frequent accompanying symptoms and usually persist for 6 months or more (Figure 1).

## Investigations

There is no single diagnostic test for ME/CFS, and testing is done to exclude other organic causes for the clinical features. Blood test may include checking the levels of creatinine kinase to exclude a myopathy. This may further be supported with an electromyogram. EEG studies have revealed particular characteristics pertinent to ME/CFS in children even though such evidence has yet to be further evaluated.<sup>29</sup>

## Treatment

‘In my experience, CFS is one of the most disabling diseases that I care for, far exceeding HIV disease except for the terminal stages.’<sup>15</sup>

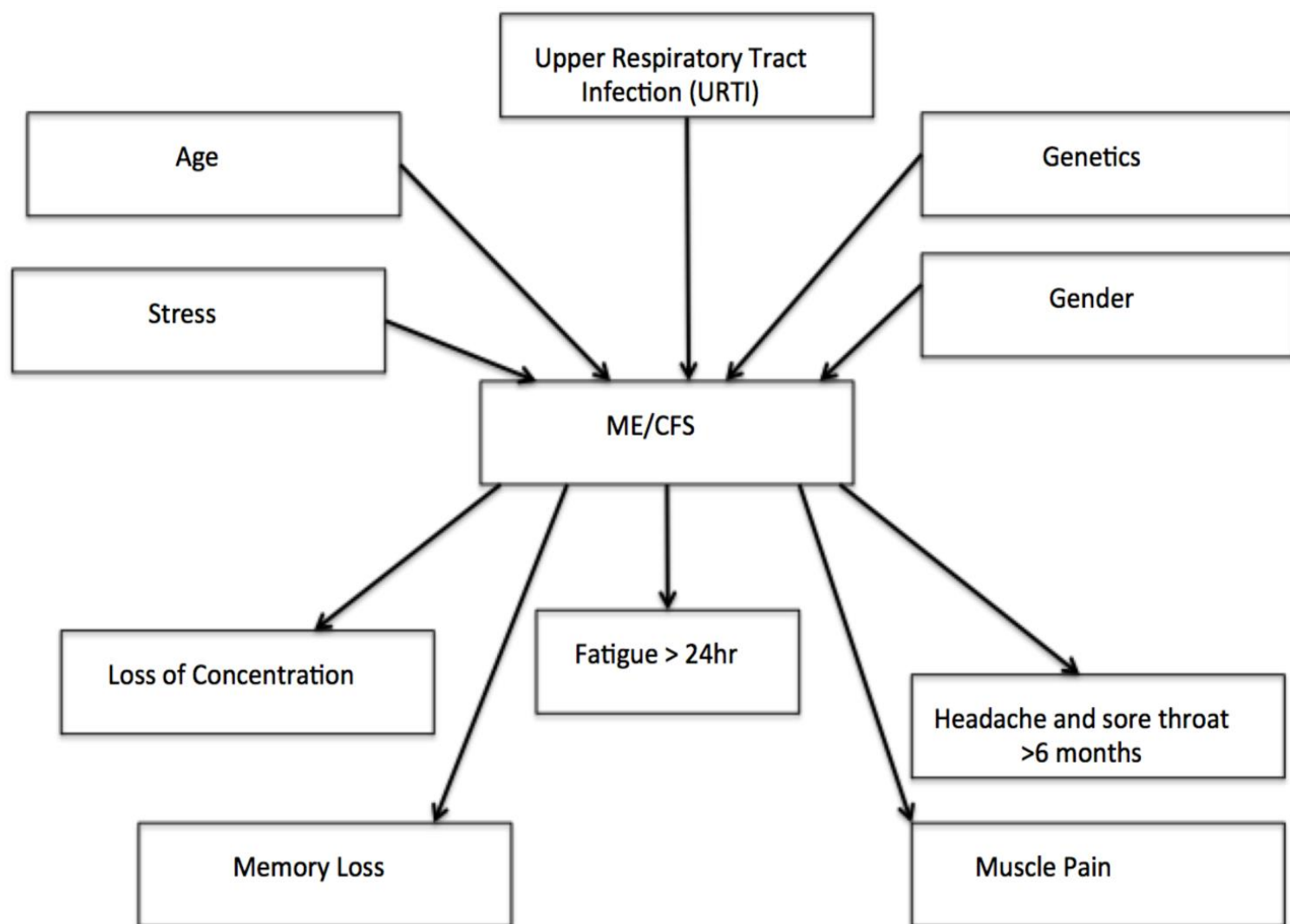
Muscle symptoms are common in ME/CFS patients, prompting research regarding the disturbance of carnitine homeostasis. According to Evans *et al.* this may possibly be due to a decreased carnitine palmitoyltransferase-I (CPT-I) activity and accumulation of omega-6 fatty acids.<sup>30</sup> Hence, possibly an increase intake of omega-3 fatty acids and L-carnitine will increase CPT-I activity, improving symptoms.

Perrin *et al.* suggests that ‘Perrin Technique’, an osteopathic intervention may be the key to future treatment whereby findings suggest that many of the symptoms experienced by ME/CFS patients are due to a lymphatic drainage disturbance.<sup>29</sup> The ‘Perrin Technique’ stimulates toxin drainage out of lymphatic system into the blood, which are then detoxified by the liver (Figure 2). This results in a decrease toxin level within the cerebrospinal fluid and hence improved symptoms.

Holtorf reported that ME/CFS patients have a reduced cortisol output and hypothalamic-pituitary-adrenal axis hypofunction which causes the fatigue.<sup>15</sup> Cortisol treatment should be part of the multi-system treatment program for ME/CFS individuals.

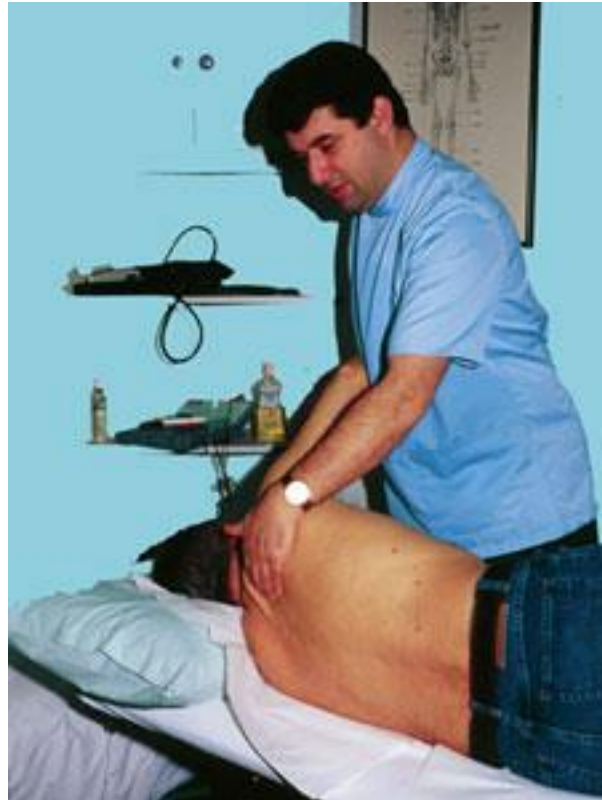
Further research is required to locate the site of abnormality in brainstem perfusion which Costa *et al.* reported a decrease in ME/CFS patients.<sup>3</sup> This may explain why patients experience cognitive dysfunction, the typical ‘brain fog’.

**Figure 1:** Summary of factors contributing to ME/CFS and the clinical features of the condition.





**Figure 2:** The 'Perrin Technique'. A therapy recommended by Perrin *et al.* which causes toxin drainage from the lymphatic system.<sup>35</sup>



### The Role of Health Services

In Malta, issues relating to ME/CFS are hardly discussed, with very few individuals within the community aware about the condition.

To date there is no specific treatment for ME/CFS apart from pharmacological therapy to alleviate symptoms. However, a CFS/ME Multidisciplinary team should be set up and available to all individuals suffering from the disorder on the island, rather than patients seeking treatment regimens internationally.

This group will increase the awareness of CMS/ME and develop group and individualized therapeutic options for sufferers by:

- Offering a rehabilitation program which advises patients on energy and anxiety management.
  - Advising patients how to overcome psychological obstacles, how to maintain a well balanced diet despite their numerous sensitivities
  - Setting up a lifestyle management program designed by occupational therapists, which advises patients on work simplification techniques.
  - Adequate pharmacological treatments to alleviate the numerous symptoms patients experience.
  - Providing professional Adaptive Pacing Therapy (APT), Graded exercise therapy programs (GET) and Cognition Behaviour therapy (CBT).
- According to McCrone *et al.* the PACE trial

compared the four main treatments: general advice about management, APT, CBT and GET available for ME/CFS patients, and found CBT as the most cost-effective from a health care perspective.<sup>8</sup>

The lack of CFS/ME services will pose a problem to individuals who suffer from this disorder who without appropriate local services, will increase the incidence of the disease within the Maltese islands.

Thus, with adequate awareness, knowledge and health services, ME/CFS individuals may become productive citizens within the community. This will benefit themselves and society.

### Conclusion

ME/CFS is a disorder characterized by numerous systemic symptoms which severely impacts the quality of life, equivalent to late stage AIDS.<sup>19</sup> A few patients recover whilst others are left permanently debilitated.<sup>32</sup> Although CBT was found to be the most cost-effect therapy for ME/CFS, there is no specific cure and hence is a disorder which is being thoroughly researched. Regarding the local status in the Maltese islands, a multi-disciplinary team should be developed, for adequate treatment and management. More educational awareness within the medical community should be provided as this prevents late and incorrect diagnoses. This will prevent any possible sources of error in future epidemiological studies.

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# Femoroacetabular Impingement (FAI) Syndrome - the Medical Imaging perspective

Anthony Zammit

## Abstract

**Introduction:** Sports persons, physicians, orthopods and radiologists have become increasingly aware of the extra stress that is imposed on the hip joints with excessive activity particularly when superadded weight bearing and asymmetrical variations from the normal hip joint anatomy are present leading to Femoroacetabular Impingement.

**Subject:** Presentation of the abnormalities within the ball and socket areas of the hip joint and the resultant types of impingements, the predominant cam, the predominant pincer or mixed types femoroacetabular impingement (FAI) are discussed and illustrated. The different kind of sportspersons that are prone to FAI and the risk factors involved are discussed.

**Method:** The main methods of investigation: The radiological techniques and radiological signs of the disease entity utilizing plain radiography and computerised transverse scanning techniques are elaborated and graphically depicted. Within the ball part of the hip joint, measurements for femoral head asphericity, that is, the Alpha ( $\alpha$ ) angle and the offset distance between the femoral head and neck are presented. With regard to pincer type FAI affecting the socket part of the hip joint, the acetabular version angle and the depth (or shallowness) of the acetabulum with their methods of quantification are discussed.

**Conclusion:** Femoroacetabular Impingement is a syndrome which is currently more appreciated within the sports medicine field and various approaches to assessment have been devised regarding how to diagnose and quantify congenital anomalies and developmental abnormalities within both the ball and the socket regions of the hip joint.

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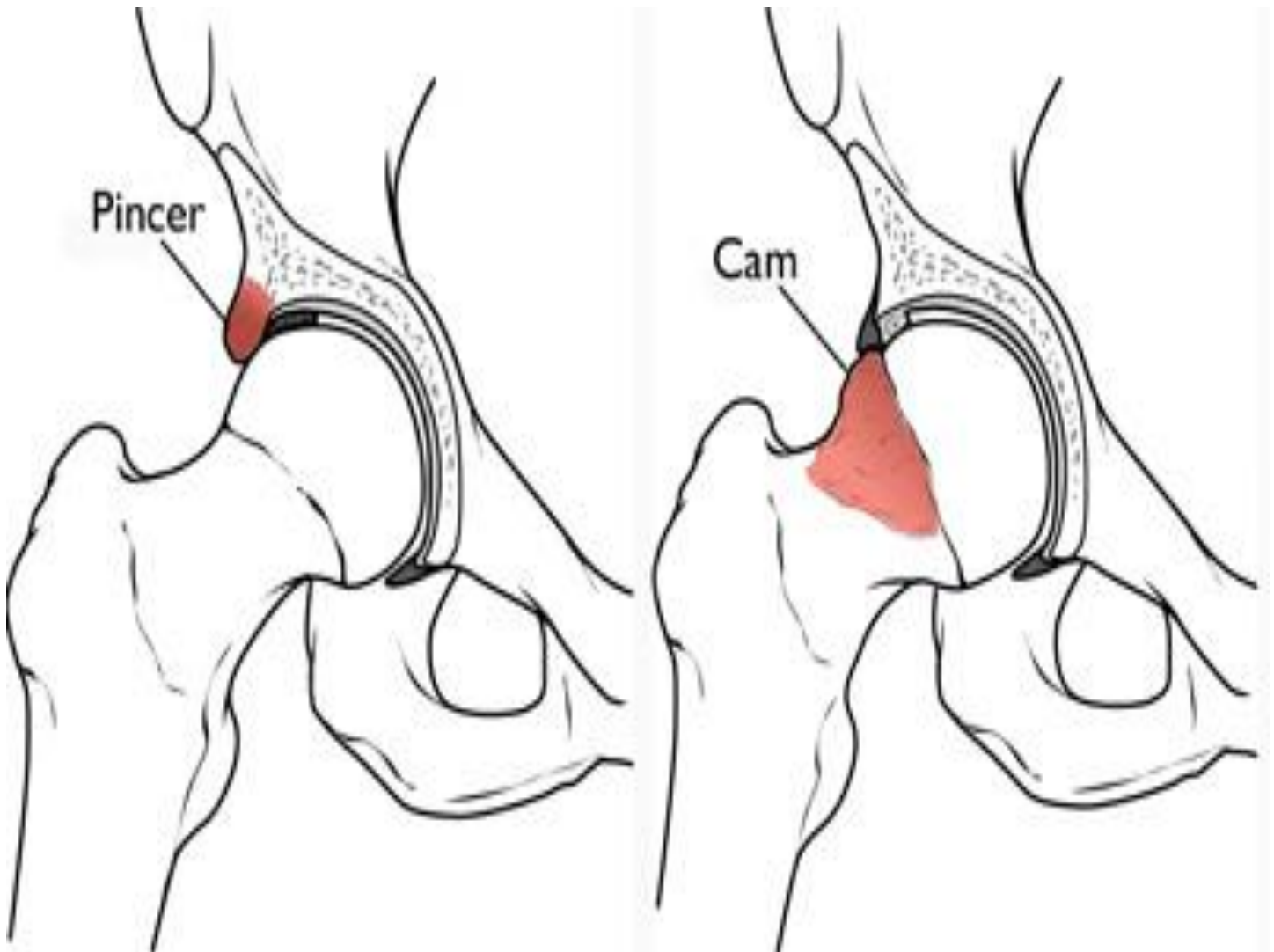
## Introduction

The hip joint is a ball and socket type joint, both aspects of which are prone to congenital anomalies and developmental anatomical variations thereby resulting in impingement with increased activity within several practiced sports. Sometimes anatomically normal hips develop femoro-acetabular impingement (FAI) with extremes of movement.<sup>1-2</sup> There are two main types of FAI first described by Mayer et al in 1999.<sup>3</sup> Abnormalities of the ball, that is the femoral head to femoral neck relationship, which leads to cam type of impingement and abnormalities of the socket or acetabulum which leads to the pincer type of impingement.<sup>2,4</sup> In the cam type FAI, abnormally eccentric femoral head on femoral neck resembling the cam shaft of a car engine impinges on a normal acetabulum. With the pincer type FAI, normally shaped femoral head to neck hinges on abnormally angled or shaped acetabulum resulting in a pincer tight grip on the cartilaginous labrae and the femoral head to neck junction. In 86% of cases subjects have components of both forms of impingement, therefore it is best to talk about mixed type FAI<sup>5</sup> possibly with the predominant cam FAI or the predominant pincer FAI in such patients. The subjects are mostly 20 to 40 year young<sup>6</sup> and are prone to early osteoarthritis.<sup>7-10</sup> The mechanism of each type of FAI is depicted graphically on Figure 1.<sup>11</sup>

## The cam type FAI

With the cam type of FAI, the eccentricly placed femoral head on femoral neck (Asphericity) impinge as it is mismatched to the normal acetabulum. Allen et al reported approximately 78% of cases are bilateral.<sup>12</sup> There is controversy as to whether the presence of the osseous bulge (or bump) at the femoral neck, which is due to hypertrophy of bone, impinges on the acetabulum (commonly on the supero-anterior aspect) is a primary or secondary presentation. Cam type FAI is commoner in physically active males,<sup>13</sup> heavy labourers and sportspersons, with the afflicted groups being dancers, athletes, golfers, runners, ballet dancers, martial arts and yoga participants. The medical history of affected persons usually reveals risk factors such as post-traumatic deformities, post-septic hips, developmental dysplasia of the hip, Perthe's disease, slipped upper femoral epiphysis, coxa vara and avascular necrosis commonly secondary to steroids, barotrauma or the hypercoagulable states.

**Figure 1:** Taken from “Orthoinfo web site” about FAI demonstrates the mechanism of each type of impingement.



### The Pincer type FAI

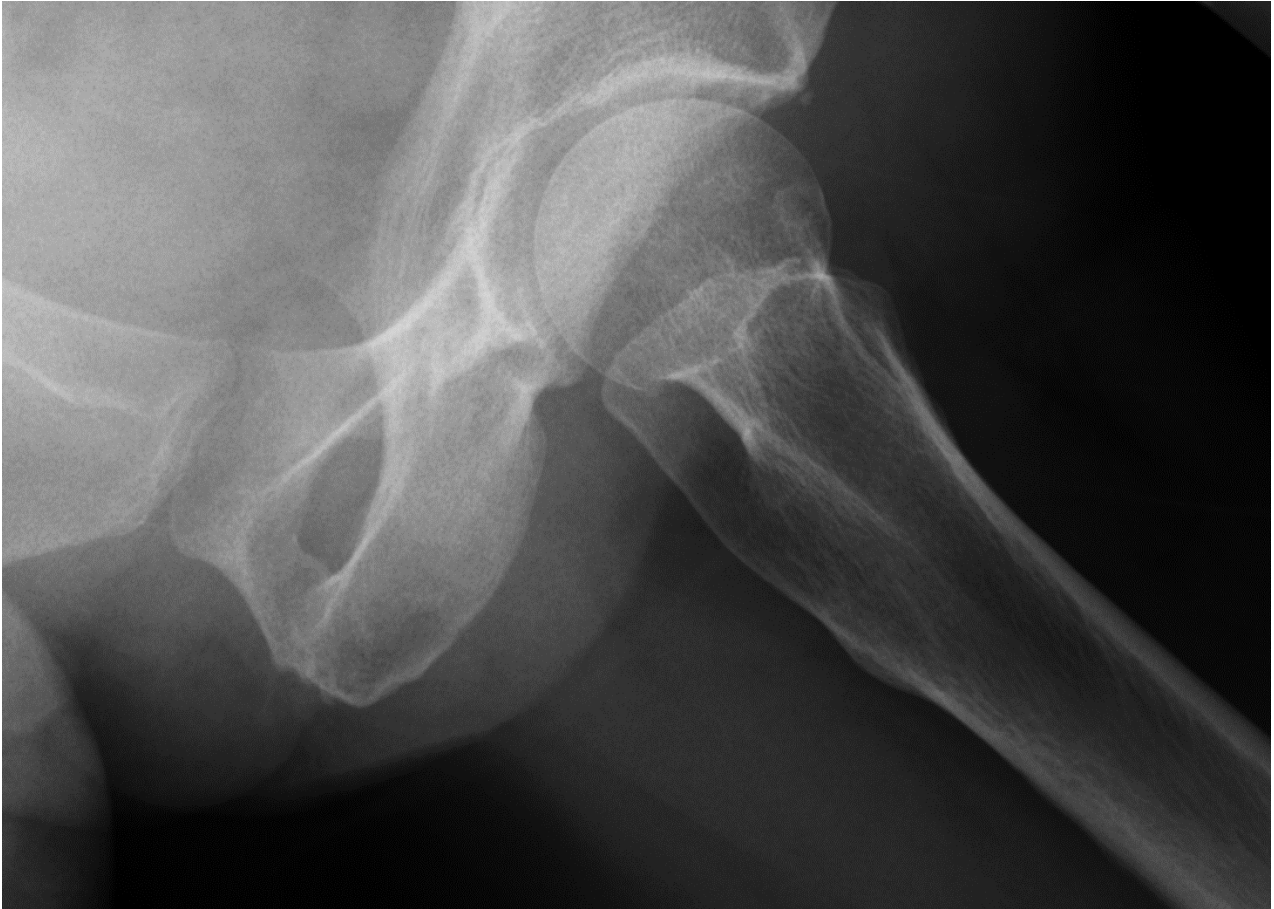
With the pincer type FAI the normally shaped femoral head contacts the abnormally angled or shaped acetabulum. Causes of this type of FAI include acetabular retroversion, acetabular overcoverage (coxa profunda or protrusio acetabuli) and femoral retroversion. This type is commoner in middle aged females<sup>13</sup> engaging in activities requiring extreme ranges of motion such as with ballet dancing or yoga.

### Investigation of FAI

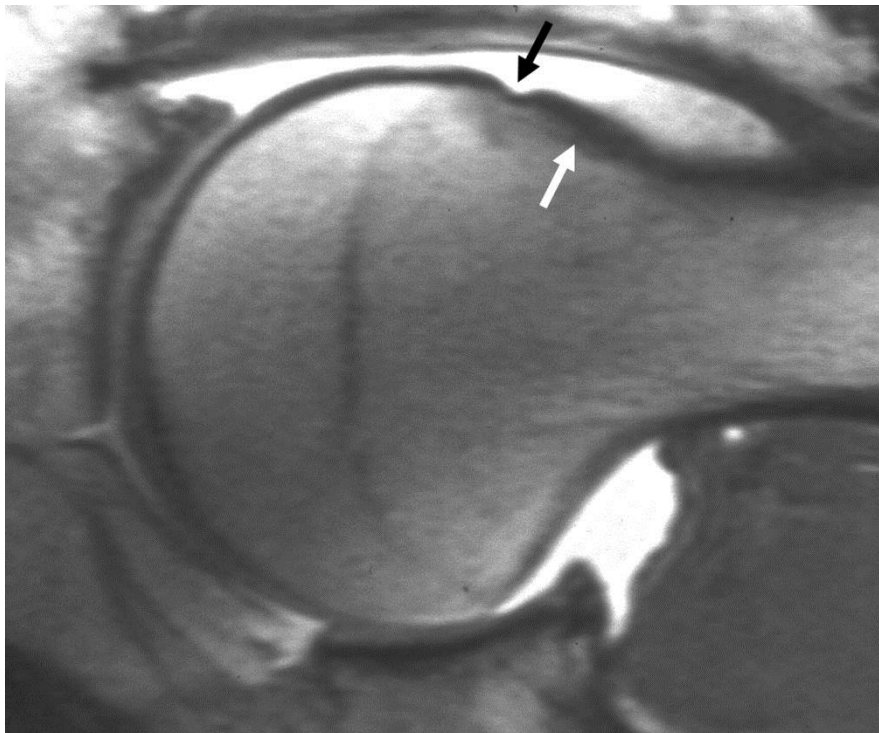
The investigation of FAI with plain radiography involves both conventional and specialised views such as AP Pelvis View,<sup>14-16</sup> Frog Leg Lateral, Cross Table Lateral,<sup>17</sup> False Profile View<sup>18</sup> and Dunn view.<sup>19</sup> Spiral Multidetector CT scan currently has the option of 3D and axial sectioning can be reformatted into axial obliques and coronal planes for diagnostic and quantification purposes. Lately MR techniques are becoming further utilised with suspected FAI in view of their resolution of soft tissue components and because of

the safety aspect as magnetic resonance is not an electromagnetic radiation like Xrays and CT Scan and to visualise the cartilaginous labra. In Cam type FAI, acetabular rim ossicles(or Os Acetabuli), impingement cyst and osteophyte (from early secondary osteoarthritis) are common findings on x-rays, Image 1. Care is indicated not to diagnose these bony fragments as excessory ossicles in symptomatic presenting patients as congenital supernumerary ossicles are usually asymptomatic. The Pistol Grip Deformity described by Stulberg et al<sup>7</sup> is another sign of FAI due to femoral head eccentricity (asphericity) on the femoral neck. One can depict the femoral head to neck eccentricity on axial oblique CT Scan with reformed (computer manipulated) images from scanned axial sections. This can also be assessed on plain x-rays such as with Dunn View or Crosstable Lateral best with internal rotation.<sup>19</sup> Femoral focal osseous bumps or bulges are also well assessed with plain radiography as Crosstable Lateral View. Another approach to this involves CT Scan and if one wishes to avoid radiation and with more invasiveness and complexity by carrying out an MR Arthrogram, Image 2.

**Image 1:** Plain Xray of the left hip (EuroMedic Clinic Cork on a 30 year old patient showing Cam type FAI with ossicle in supero-lateral aspect of the acetabulum, impingement Cyst on lateral aspect of the femoral head and osteophyte on the medial aspect of the femoral head to neck junction.



**Image 2:** MR Arthrography demonstrates: Herniation Pit as black arrow and Osseous Bulge as white arrow. The labrae and articular cartilages are intact and well depicted on 18 year old patient investigated at EuroMedic Clinic, Cork.





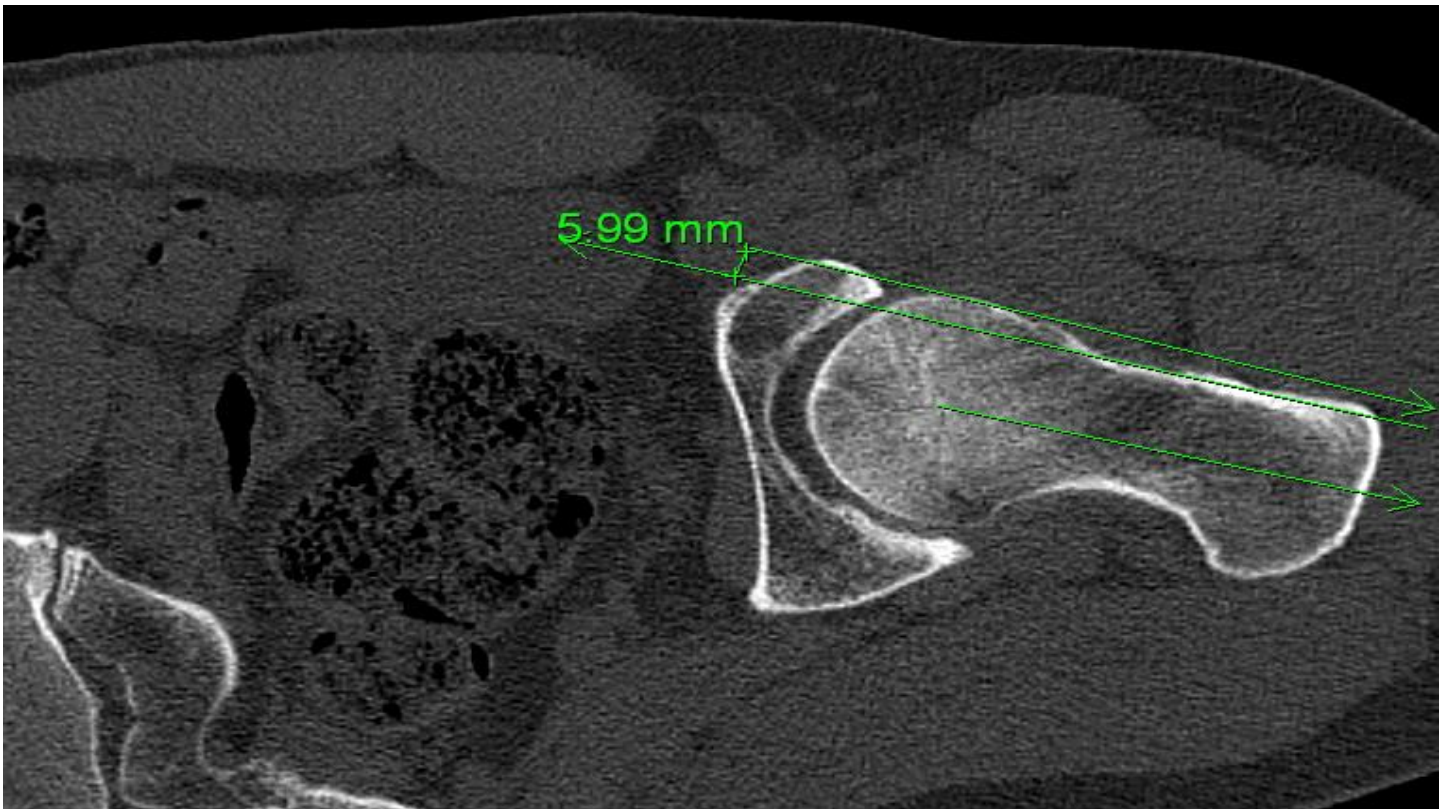
In cam type FAI assessment may also be performed by measuring the femoral head to neck Offset Distance which is the thickness of bony hypertrophy resulting in an osseous bulge and is also proportional to the extent of eccentricity of the femoral head to neck relationship, Image 3 (Normally 9mm or greater).<sup>2,4</sup> The Alpha Angle which is a measurement of femoral head eccentricity,<sup>17</sup> Image 4 (Normal less than 55 degrees) requires CT Scan ideally utilising an axial oblique plane for adequate assessment. Normal acetabular version (Angle of inclination) on simple plain AP Pelvic Xray results in an Inverted V sign arising from the anterior and posterior margins of the acetabulum which projectionally meet at the superior aspect, Image 5. With the pincer type FAI, this sign transforms to a crossover or figure of 8 sign (as the acetabular wall margins cross at three points) depicting acetabular retroversion, Image 6. Acetabular retroversion is also assessed well with crosssectional imaging. The acetabular version angle is more accurately quantified on axial CT Scan, being normally greater than 15 degrees, Image 7. That is the acetabular hollow space is directed anteriorly and downwards.

Measurement of the Center Edge Angle (the line joining the femoral center to superior acetabular margin and the angulation to the vertical line) is also another method of quantifying FAI as a sign of acetabular depth, Image 8. Coxa Profunda is well diagnosed subjectively on plain x-ray and more objectively quantified with Coronal CT Scan utilising the Center Edge Angle and by measuring the depth of the center of the femoral head to the acetabular margin line, Image 9. Acetabular overcoverage is assessed also with plain Xray such as with the False Profile View, Image 10. Microsurgery for FAI is available as Arthroplasty with trimming on the femoral osseous bulges and acetabular rims while the labrum is excised when torn.

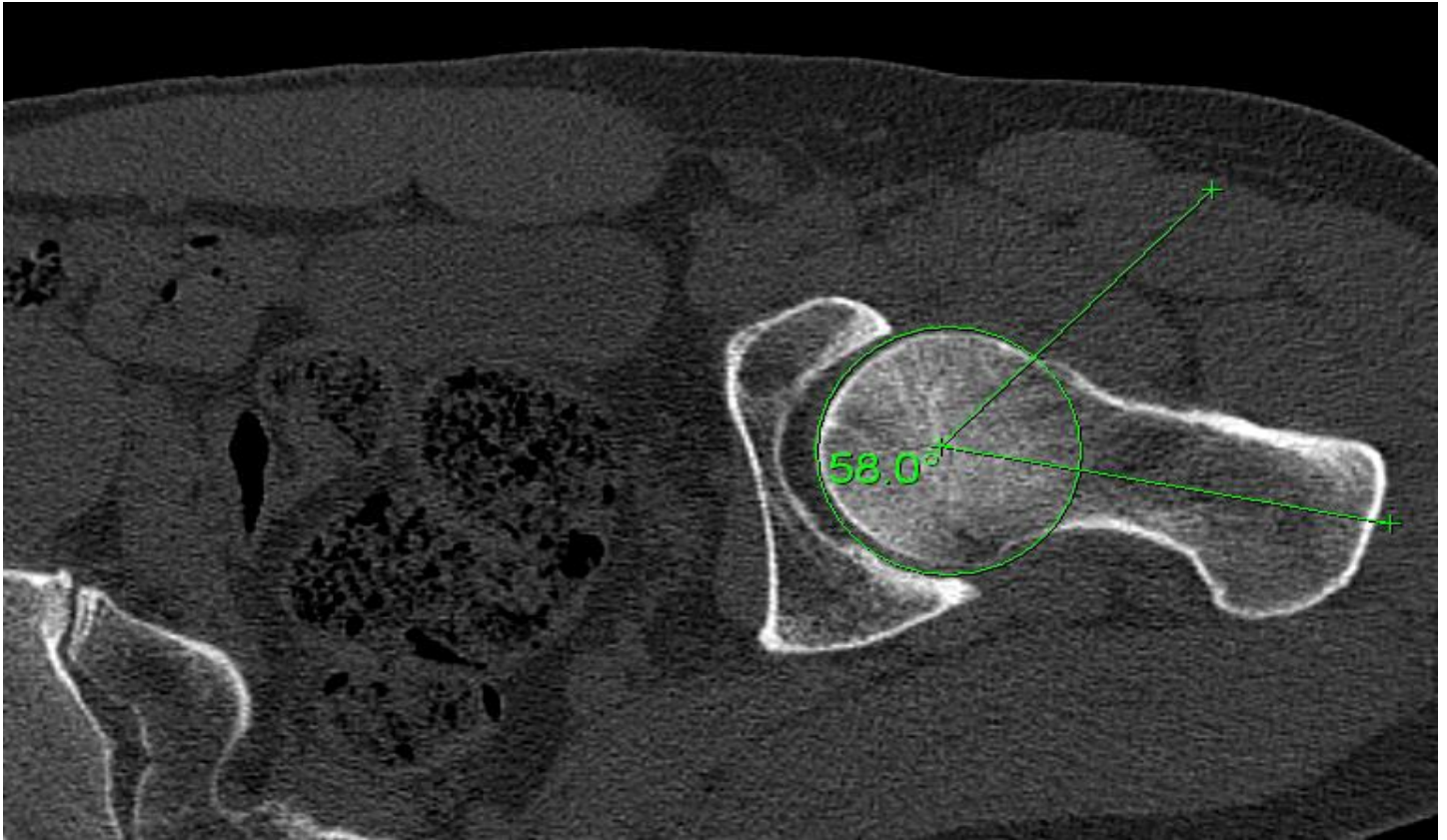
## Conclusion

The Cam and Pincer type of Femoro-Acetabular Impingement is a syndrome with current various modality approaches to assessment regarding how to diagnose and quantify the grade of the congenital or developmental anomalies which create mismatch between the ball and the socket regions of the hip joint. This mainly includes asphericity of the femoral head, acetabular retroversion, Image 6 and acetabular overcoverage, Image 10.

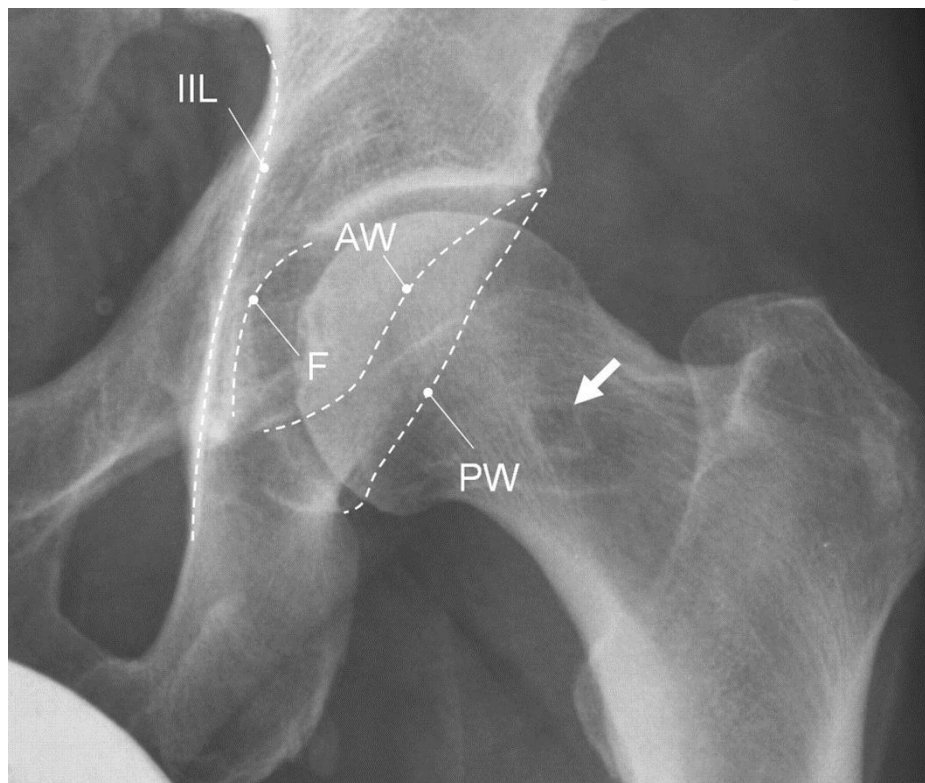
**Image 3:** CT Axial Oblique 0.5 mm collimation from EuroMedic Clinic Cork on a 17 year old patient with the Offset Distance being abnormal at 5.99mms (Normal is 9 or greater mms).



**Image 4:** The Alpha Angle on axial oblique CT Scan (reformatted image from 0.5 mm collimation taken in EuroMedic Clinic Cork) in 25 year old patient is 58 degrees. Subjectively the femoral head eccentricity on femoral neck is well shown. An abnormal Alpha Angle would be greater than 55°.

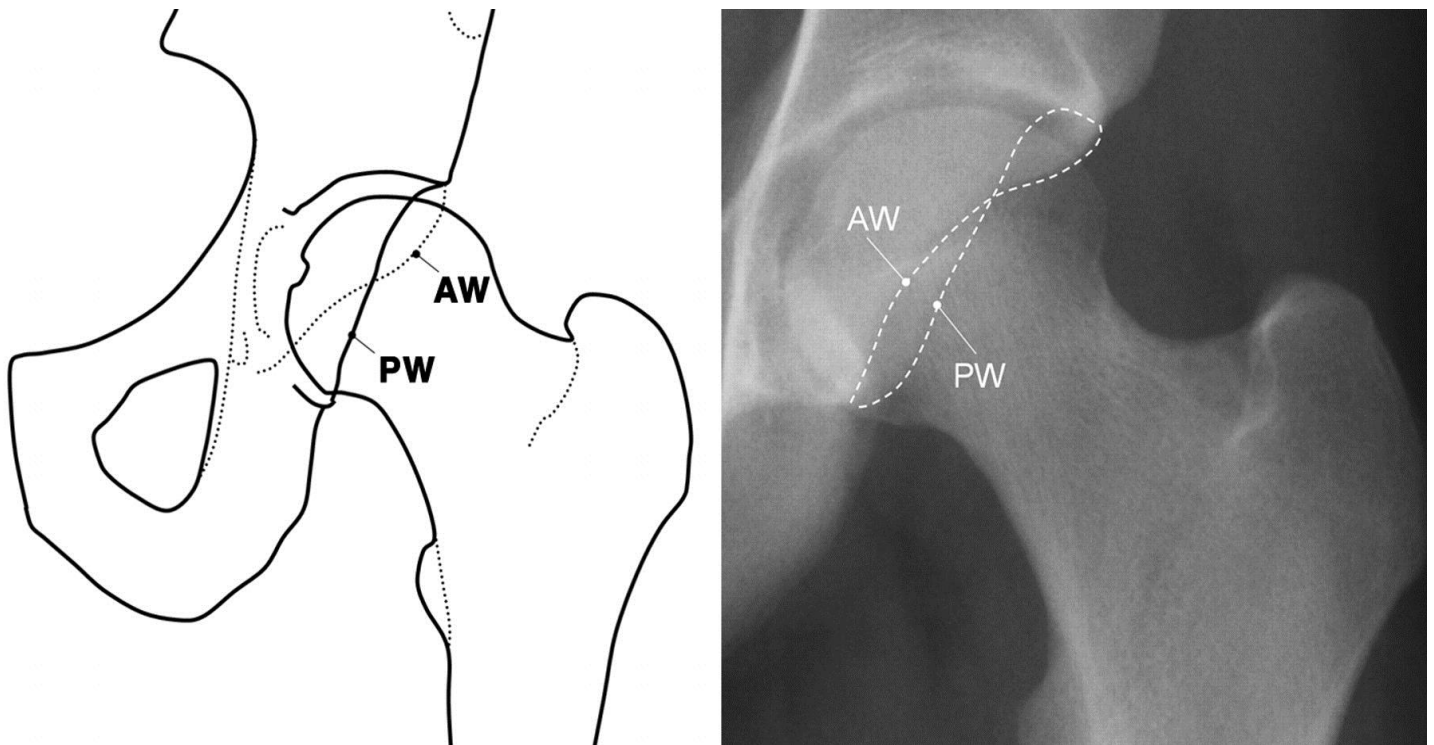


**Image 5:** Plain Xray demonstrates Inverted V Sign. AW-Anterior acetabular wall, PW-Posterior acetabular wall, F-Fovea IIL-Ileo Ischial Line. Arrow depicts herniation pit.

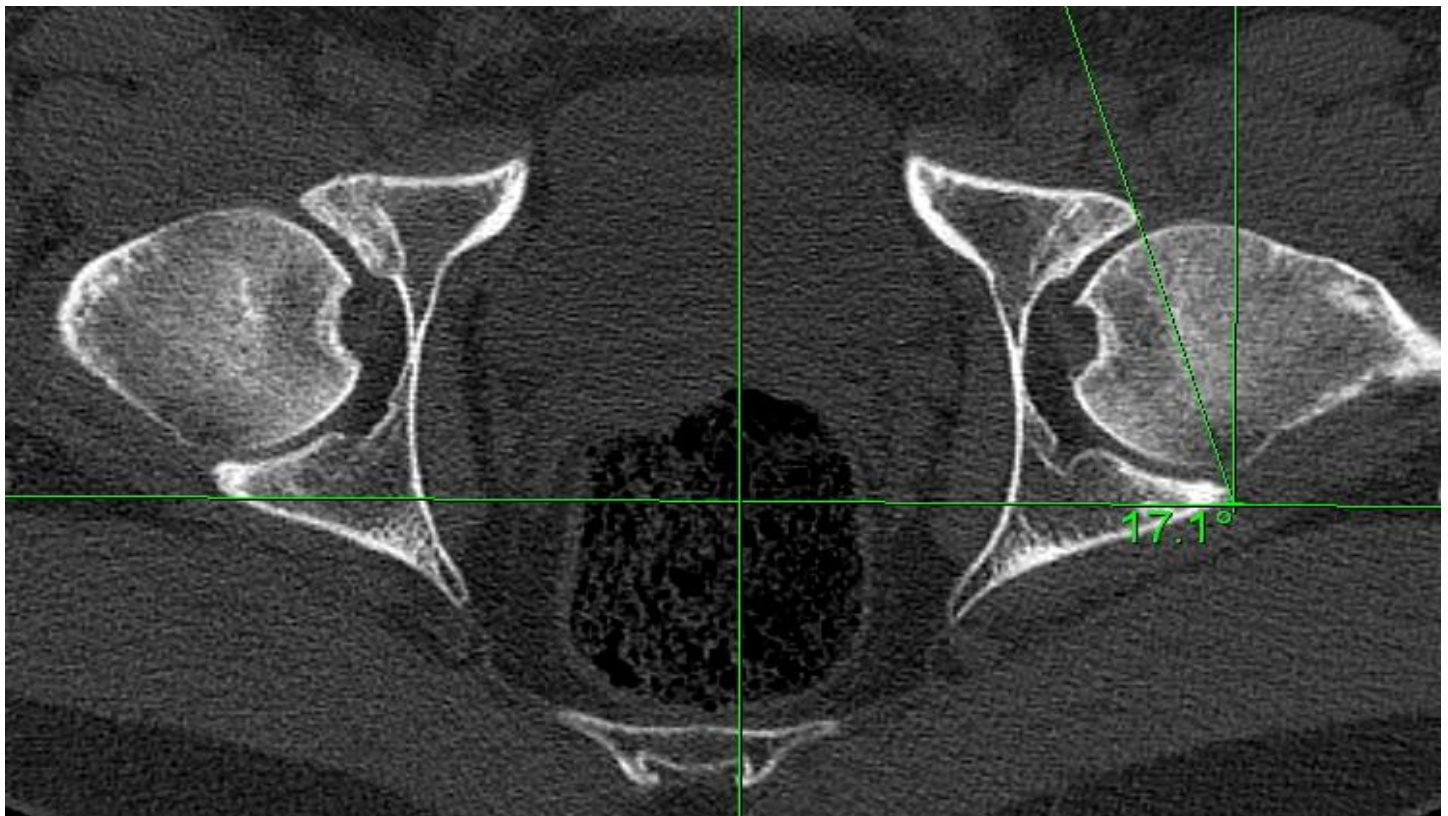




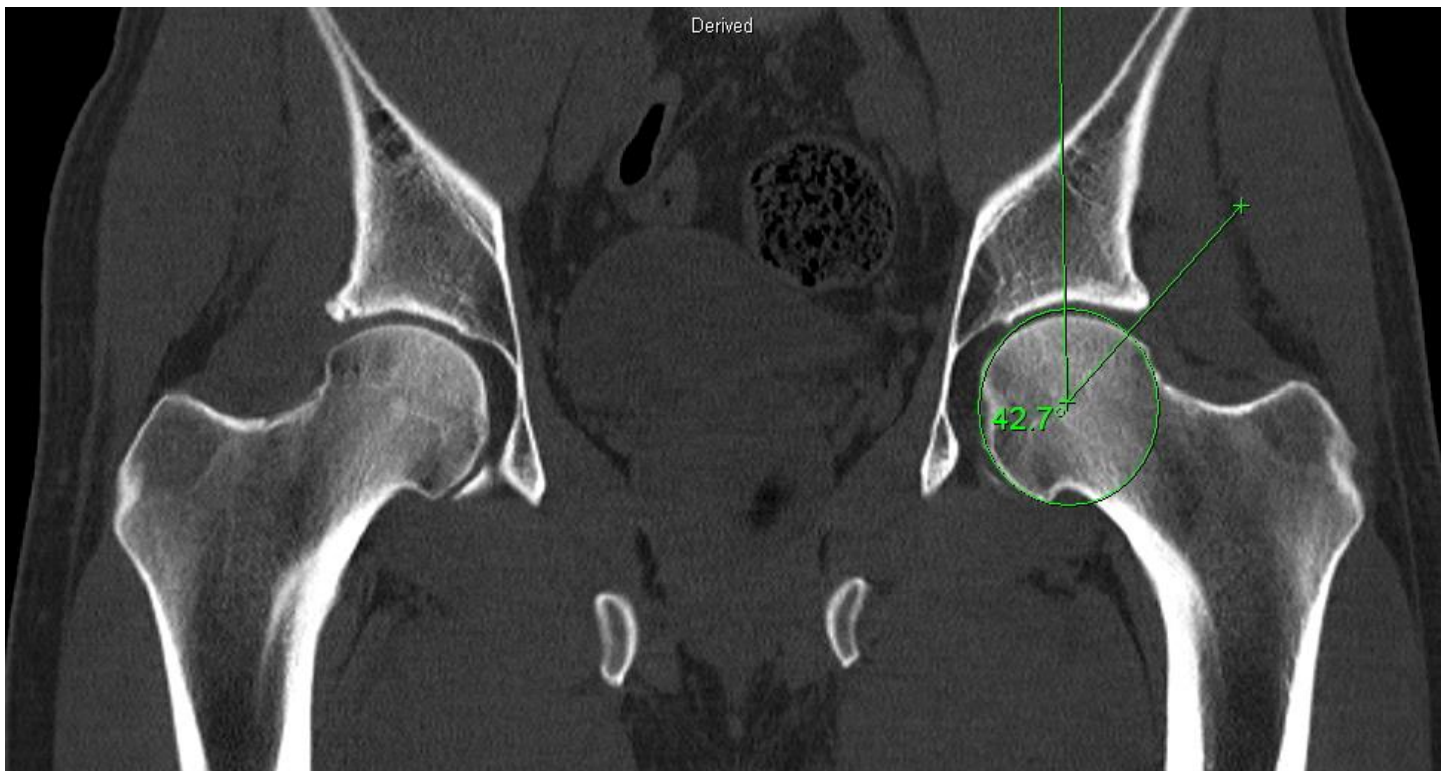
**Image 6:** Diagram and Plain Xray of the left hip with the Crossover or Figure of Eight Sign of the anterior and posterior walls of the acetabulum in a 23 year old patient with Acetabular Retroversion.



**Image 7:** Acetabular Version Angle is  $17.1^{\circ}$  which has a normal inclination. An abnormal Version Angle is less than  $15^{\circ}$ .



**Image 8:** Coronal reformatted CT Scan 0.5 mm section in 25 year old patient investigated at EuroMedic Clinic Cork. Center Edge Angle (CEA)  $42.7^\circ$  is abnormal as CEA in Coxa Profunda is greater than  $40^\circ$ .

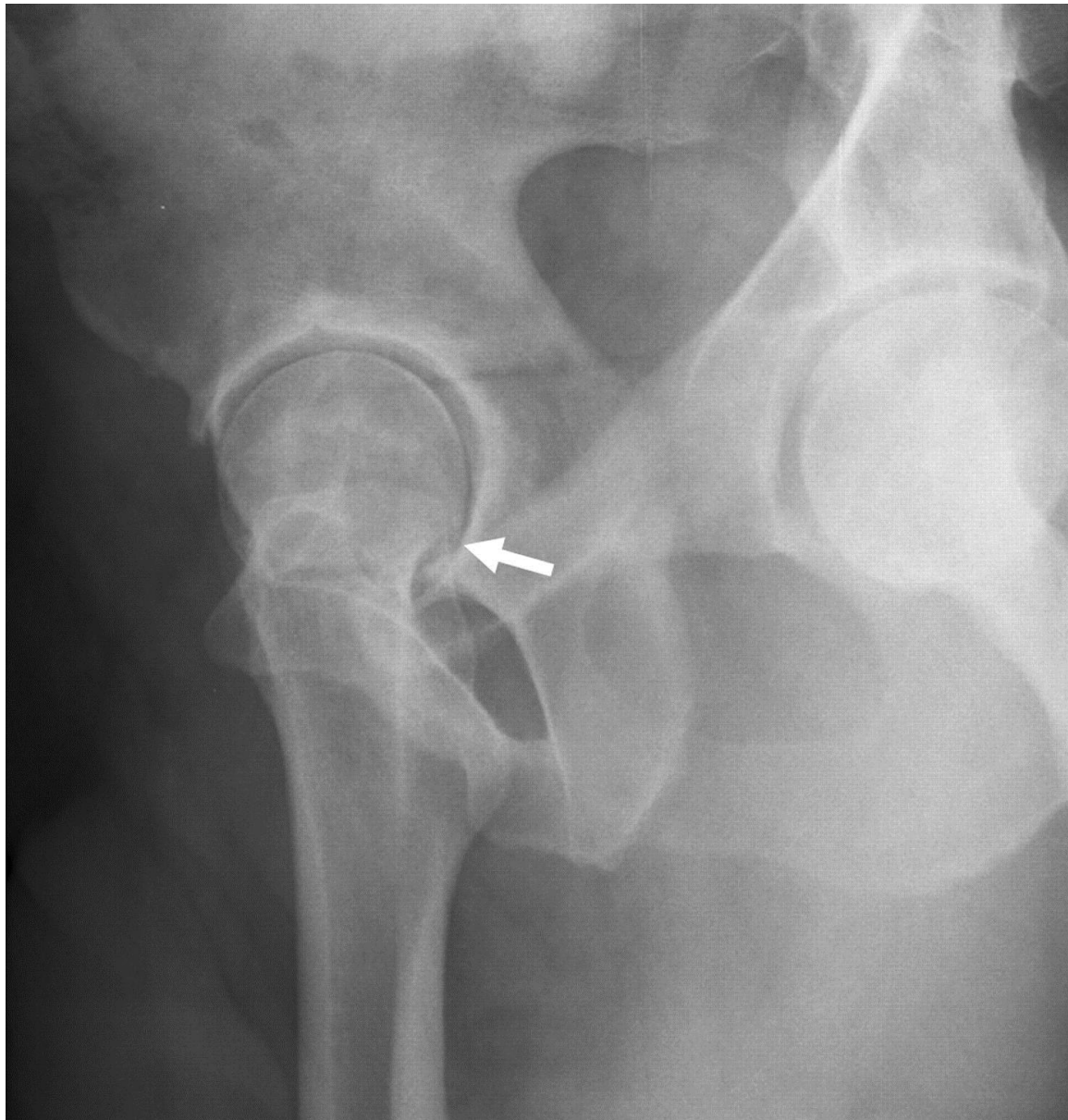


**Image 9:** On CT Scan coronal plane (reformatted image at 0.5 mm slice – EuroMedic Clinic Cork) the Femoral Head Center on 25 year old patient is 4.89 mm deep to the acetabulum.





**Image 10:** False Profile View assesses (anterior) femoral head overcoverage leading to Pincer type FAI. Early hip degeneration in 27 year old and loss of posterior articular cartilage( arrow).



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# Identification of a novel regulatory mechanism for the disease associated protein, uPAR

Michael A. Portelli, Ian P. Hall, Ian Sayers

## Abstract

Expression quantitative trait loci (eQTLs), as determined through a series of statistical association studies collectively known as genome-wide association (GWA) studies, have provided us with a hypothesis free approach for the investigation into regulatory loci for disease and disease-associated proteins. This has led to the identification of multiple novel gene-disease interactions, especially in the field of respiratory medicine. This review describes the case study of a GWA approach in order to identify eQTLs for the soluble form of the urokinase plasminogen activator receptor (uPAR), a protein associated with obstructive respiratory disease. Molecular and cellular investigations based on the eQTLs identified for this GWA study has led to the identification of a novel regulatory mechanism with implications in the disease processes with which this protein is associated. This highlights the potential of eQTLs defined associations in the identification of novel mechanisms, with implications in disease.

## Key Words

*Genome-wide association, eQTLs, uPAR*

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## Introduction

Expression quantitative trait loci (eQTLs) are regions present in the human genome that are (i) able to regulate the expression of mRNA and/or protein of a related or unrelated gene or (ii) able to influence changes in the observed phenotype. EQTLs are driven by genetic variation including single nucleotide polymorphisms (SNPs). These SNPs may be located within, or are in linkage with, regions that contain a gene that either (i) drives changes in expression of the target mRNA or protein or (ii) are associated with a particular outcome, such as obesity<sup>1</sup> and lung function.<sup>2</sup> Investigations into eQTLs are carried out through a series of statistical associations collectively known as a genome-wide association (GWA) study. These GWA studies have allowed for investigation into regulatory loci for disease and disease-associated proteins, without the burden of having a pre-defined hypothesis. Indeed, this has led to the identification of multiple novel gene-disease interactions, especially in the field of respiratory medicine.<sup>2,3</sup> Our research has involved the implementation of a GWA approach in order to identify eQTLs for the urokinase plasminogen activator receptor (uPAR), which has been associated with the obstructive respiratory diseases asthma & chronic obstructive pulmonary disease (COPD).<sup>4-11</sup> Through our research, we have identified a novel mechanism of action derived from a genome-wide significant protein eQTL, which has significant regulatory effect on uPAR driven biological effects on primary human bronchial epithelial cells (HBECs) *in vitro*.

## *The plasminogen activator receptor – a respiratory disease associated molecule*

Multiple studies (see below), have identified a relationship between uPAR and respiratory disease. Initial work has identified the uPAR gene *PLAUR* as an asthma susceptibility gene in 587 asthma families.<sup>7</sup> In the same study, the authors also identify that SNPs across *PLAUR* and its five and three prime untranslated regions (5'UTR and 3'UTR) as being associated with asthma, bronchial hyper-responsiveness (BHR) susceptibility, baseline lung function and lung function decline in populations originating from multiple centres, as well as serum uPAR levels.<sup>7</sup> A follow up study on the same 25 SNPs in a population of 992 smokers, identified association with baseline lung function.<sup>8</sup> Association with an alternate

obstructive lung disease, i.e. COPD, was determined in an independent study, where through gene expression profiling and lung function studies in 43 COPD subjects, *PLAUR* was determined to be differentially expressed in the COPD lung when compared to controls.<sup>6</sup> Interestingly, the association of *PLAUR* with COPD was found to be independent of the smoking pack/year status.<sup>6</sup> Our own study has identified a strong association between circulating uPAR levels and obstructive lung disease. A further two studies identify elevated soluble cleaved uPAR (scuPAR) levels in the induced sputum of asthmatic and COPD patients<sup>4, 5</sup>, with levels associated with airflow limitation, health status and exercise tolerance in COPD patients.<sup>4</sup> Levels of circulating scuPAR were also found to be correlated with lung function in a separate study.<sup>7</sup> This suggests that identified uPAR dependant effects may be at least partially driven by the soluble cleaved form of the receptor, a situation previously hypothesised in a human bronchial epithelial cell population.<sup>9</sup>

Further evidence for the role of uPAR in obstructive lung disease has been published in a number of *in vitro* and *ex vivo* studies as described below. While membrane bound uPAR has been shown to be standardly expressed in the apical membrane of the airway epithelium<sup>12</sup>, levels were elevated in the inflamed asthmatic epithelium when compared to healthy controls<sup>9,13</sup> and in COPD subjects when compared to controls.<sup>6</sup> uPAR was also elevated in the lungs of patients who died of *status asthmaticus*, when these were compared to the airways obtained from 7 lung donors with no prior diagnosis of asthma.<sup>14</sup> In an *in vitro* study using normal HBECs, mechanical stimulation of cells in order to mimic the process that occurs in the lung during bronchoconstriction, an important event in both asthma and COPD, resulted in a 16.2 fold increase in the expression of *PLAUR* mRNA in conjunction with the elevation of other molecules involved in the fibrinolytic pathway, such as the uPAR ligand urokinase (uPA) and its inhibitor the plasminogen inhibitor type 1 (PAI-1).<sup>14</sup> A more recent study has also identified a role for the receptor in the epithelial-mesenchymal transition of bronchial epithelial cells.<sup>15</sup> Here data suggests that a uPAR-dependent signaling pathway is required for EMT induced through exposure of cigarette smoke, contributing to small airway fibrosis occurring in COPD.<sup>15</sup> Globally, this evidence suggests that uPAR may be involved in asthma and COPD pathogenesis, where elevated receptor levels could cause changes in the airways synonymous with both asthma and COPD, a hypothesis supported by a study which identifies uPAR as a potential marker of airway disease severity.<sup>16</sup>

Direct roles for uPAR in obstructive respiratory disease has in fact been suggested, where uPAR is

identified as being involved in lung tissue remodelling and repair in COPD subjects. This hypothesis that uPAR is involved in asthma and COPD pathophysiology through a direct role in airway remodelling, is further supported by a number of other studies.<sup>17-19</sup> In the first instance, elevated levels of uPA and PAI-1 in the airways post injury<sup>17</sup>, suggest involvement of uPAR in airway disease. Involvement of uPAR in airway disease was confirmed through the concomitant discovery that uPAR is not only critical for efficient bronchial wound repair *in vitro*, but that *in vivo*, inhalation of uPA protects against sub-epithelial fibrosis and airway hyper-responsiveness in an asthma mouse model.<sup>18</sup> Together, these data suggest that the uPAR pathway is likely important in airway injury. Indeed, a recent study has confirmed the role of uPAR in airway injury in uPAR-deficient mice, where the knockout mice spontaneously developed airway fibrosis.<sup>19</sup> Airway injury and the deregulation of repair are prevalent in asthma and COPD and are known to have a role in airway remodelling during disease development.

### Structure of the urokinase plasminogen activator receptor

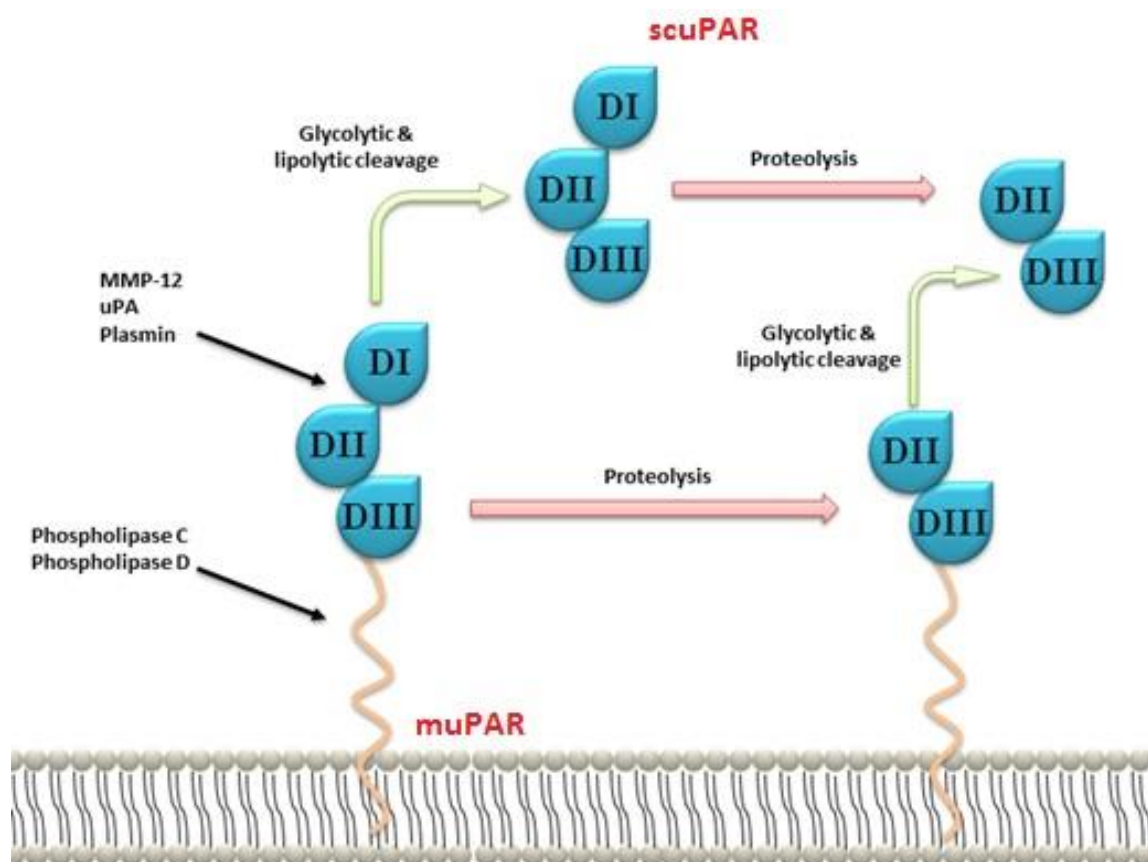
The plasminogen activator receptor is a three homologous domain protein<sup>20</sup>, where each domain (annotated as D<sub>I</sub>, D<sub>II</sub> and D<sub>III</sub> respectively) is separated by a 15 residue inter-domain linker sequence and which is attached to the outer leaflet of the phospholipid bilayer of the cellular membrane via a glycosylphosphatidylinositol (GPI) anchor.<sup>13, 21-23</sup> uPAR is encoded for by a gene located on chromosome 19q13 and is present on the anti-sense strand of the human genome.<sup>20</sup> The *PLAUR* gene in its full form consists of 7 exons; of these, exon 1 encodes the 5' UTR and a signal peptide, while exons 2-3, 4-5 and 6-7 respectively encode the homologous protein domains D<sub>I</sub>, D<sub>II</sub> and D<sub>III</sub>.<sup>20</sup> (see Fig. 1.)

The GPI anchor, which attaches the receptor to the cellular phospholipid bilayer, is susceptible to glycolytic and lipolytic cleavage, most significantly by the enzymes phospholipase C and D.<sup>25, 26</sup> This results in the release of the entire protein moiety from the cell surface forming scuPAR (Fig. 2). This soluble moiety has been detected in the periphery (serum levels) and has been shown to be elevated in asthmatic patients when compared to non-respiratory disease controls and in COPD patients when compared to asthmatics and non-respiratory disease controls, with elevated levels also identified in the induced sputum of these patients.<sup>11</sup> The scuPAR has also been identified to have a direct role in the modulation of disease, specifically in focal segmental glomerulosclerosis, which leads to proteinuric kidney disease, where scuPAR is directly involved in disease development through activation of the podocyte  $\beta(3)$  integrin.<sup>27</sup>

**Figure 1:** Gene structure for the PLAUR gene. PLAUR is located on chromosome 19q13 and in its full form consists of 7 exons when code for the full-length membrane-bound protein uPAR. Exon 1 encodes for the gene's 5'UTR and a signal peptide, while the exon pairs 2&3, 4&5 and 6&7 each code for the receptors three homologous domains, known as DI, DII and DIII. This gene has been identified to be expressed in the lung, in human airway smooth muscle cells and in human bronchial epithelial cells 24. Other splice variants exist in either form, namely Exon 3, Exons 4 & 5, Exon 5 and Exon 6 deletions and an alternate exon 7(b) located at a further distal region and encoding for an alternate DIII and 3'UTR.



**Figure 2:** PLAUR cleavage products. PLAUR is a 3 globular domain protein attached to the cellular membrane via a GPI anchor. Cleavage occurring on the membrane bound receptor can either be proteolytic or glyco/lipolytic. Glycolytic and lipolytic cleavage occurs at the GPI anchor by substances such as Phospholipase C & D, and results in the formation of a soluble form of the receptor which structurally mirrors the corresponding membrane bound receptor. Proteolytic cleavage occurs in the linker region between DI and DII and results in the loss of DI to form a DII/DIII fragment which has chemotactic activity.



### **Genome-wide association identifies a novel regulatory region for scuPAR**

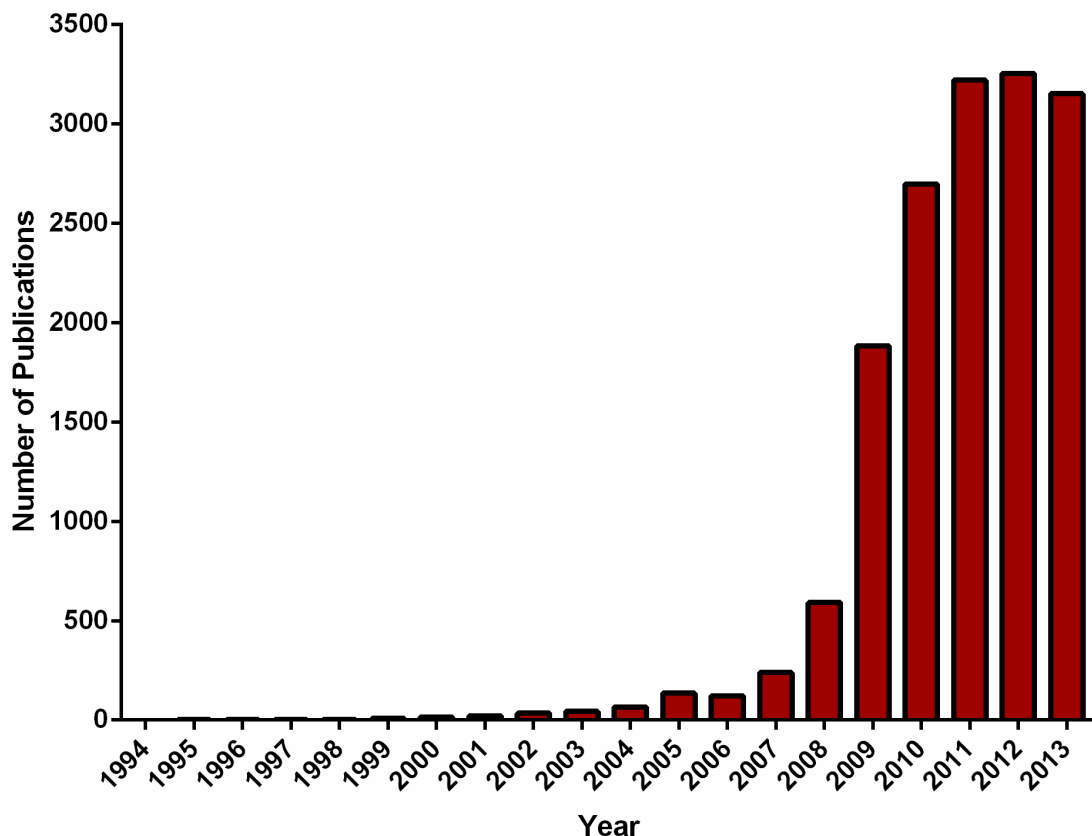
As part of our interest into uPAR and its role in obstructive lung disease, we were concerned about the regulation of circulating scuPAR. A 2009 genetics study had identified a link between uPAR polymorphisms associated with lung function and serum scuPAR levels, suggesting a link between the soluble molecule and respiratory disease. A better understanding of the regulatory mechanism of scuPAR would therefore theoretically allow for a more complete understanding of how this molecule regulates and is associated with disease. Also further determination of scuPAR regulation would provide potential novel therapeutic targets for scuPAR regulation. Using a hypothesis-free approach, i.e. a GWA study, we investigated eQTLs driving scuPAR levels in the serum of asthma patients and non-respiratory disease controls investigating a total of 295,196 SNPs.<sup>11</sup> This study identified a locus of interest at location 4q35 containing associations for SNPs rs4253238 and rs1912826 in a combined dataset of the control and asthma patient serum samples ( $n=584$ ,  $\lambda=1.009$ ), which achieved genome-wide significance as defined by the Bonferroni method ( $p<1.69\times10^{-7}$ ).<sup>11</sup> These SNPs were found to be in near complete linkage

disequilibrium (LD) ( $D'=0.99$ ;  $R^2=0.94$ ) in the study population and so were considered as a single region of variation. The location of this region of association was identified to lie in the promoter/5' coding region of the gene for human plasma kallikrein (*KLKB1*; previously known as *KLK3*). Confirmation of the association in a secondary genotyped in a COPD cohort ( $n=219$ ), further defined this region as an eQTL for serum scuPAR levels ( $p=5.34\times10^{-7}$ ;  $B=0.16812$  for log10-transformed uPAR levels and additive allele coding)<sup>11</sup>, as did a meta-analysis including all three populations ( $n=803$ ) ( $p=5.037\times10^{-12}$ ;  $B=0.0879$ ).<sup>11</sup>

### **Molecular Biology techniques confirm a GWA identified eQTL**

Although multiple GWA studies have been published over the past few years since the first publication identified in a PubMed search using the target word 'GWAS'<sup>28</sup>, with a large number of publications with the target word 'GWAS' being identified in the past few years (Fig. 3), very few studies have investigated in detail the mechanism driving the genetic association(s) described.

**Figure 3:** Publications listed on Pubmed returning when queried with the word 'GWAS'. Results identify the first publication originating in 1994, with a year on year increase culminating with over 3000 publications per year after 2011.



In our scuPAR GWA study, carried out to determine the regulation of serum scuPAR levels, we utilise a number of molecular and cell biology techniques to dissect the mechanism driving the eQTL highlighted by SNP rs4253238.<sup>11</sup> Investigation of KLKB1 activity in the same population of serum samples confirmed differences in KLKB1 activity based on rs4253238 genotype. However interestingly, analyses of uPAR mRNA levels by Taqman qPCR identified no change in uPAR mRNA expression in primary HBECs on stimulation with KLKB1.<sup>11</sup> With this, we highlight the importance of protein eQTLs. GWA studies have, to date, mainly considered changes in mRNA levels as outcomes for eQTL association. Our study suggests that analyses exclusively based on mRNA will not cover all mechanisms important in determining expression levels, including post-translational mechanisms. Indeed an *in silico* GWA study/mRNA eQTL carried out in parallel and the analyses of HBEC mRNA levels via Taqman qPCR<sup>11</sup> did not identify the locus at 4q35 as being associated with uPAR mRNA expression levels.<sup>11</sup>

Further investigations using cleavage of recombinant uPAR protein, and recombinant over-expression models using the pcDNA3 plasmid vector, allowed us to define with confidence the mechanism behind our protein eQTL result. We identified that the association between KLKB1 and scuPAR stemmed from a cleavage interaction between KLKB1 and scuPAR, cleaving the scuPAR molecule into multiple fragments. This would therefore inhibit scuPAR driven effects on the bronchial epithelium, such as proliferation.<sup>11</sup>

### Summary

In summary, in our study we have identified a novel regulatory mechanism for the asthma and COPD associated molecule scuPAR, through an in depth analyses of a protein eQTL study. We are among the first to have shown that an eQTL derived association defined through a GWA study can be followed through, through molecular and cell-based techniques, to define a mechanism to which the eQTL can be attributed to. Defining such mechanisms confirms that eQTL analysis provides us with the opportunity of determining novel regulatory and association pathways. This of course has important implications for those associations connected to a variety of disease states, allowing for a better understanding of disease processes and providing potential novel targets for future therapeutics.

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# An evaluation of the bariatric surgical patient

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Obesity continues to be one of the most common prevalent chronic diseases worldwide with recent data stating that it has now reached global pandemic proportions making it a major public health problem. In 2008 the World Health Organisation (WHO) stated that worldwide around 1.4 billion adults were overweight (body mass index [BMI] 25.0-29.9 kg/m<sup>2</sup>) and a further 500 million were obese (BMI  $\geq$ 30 kg/m<sup>2</sup>). Of note, the prevalence of obesity has tripled in Europe over the last 30 years with around 50% of the population in the majority of European countries being overweight or obese.<sup>1-4</sup> Locally, the situation is also alarming with data from the European Health Interview Survey (EHIS) in 2011 stating that Malta had the highest rate of obese males in Europe (24.7%) and when it comes to females, Maltese women were the second most obese after British women (21.1% and 23.9% respectively).<sup>5</sup> Even more worrisome is the fact that Malta also tops the charts for the highest prevalence of overweight and obesity in school-aged children thus accentuating the fact that urgent action needs to be taken in order to tackle effectively this world-wide epidemic.<sup>6</sup> Unfortunately obesity is strongly linked to several co-morbid conditions such as type 2 diabetes, hypertension, cardiovascular disease, dyslipidaemia, obstructive sleep apnoea, non-alcoholic steatohepatitis, osteoarthritis, as well as some cancers (including breast, ovary, prostate, endometrium and colon) and psychiatric illnesses and thus it stands to reason that an increase in prevalence of obesity has also led to an increase in prevalence of these co-morbidities resulting in an impaired overall quality of life and decreased life expectancy in these subjects.<sup>7-10</sup>

In view of the heavy burden obesity is posing on health-care systems worldwide, several medical and surgical societies have put forward guidelines on how one should best manage such patients.<sup>11-16</sup> Unfortunately, the non-surgical options available for the treatment of obesity (including dietary modification enhanced physical activity, behavioural modification and drug treatment) do not lead to sustained weight loss over the long-term. On the other hand, bariatric surgery is proving to be the only evidence-based method for inducing weight loss as well as resolving or improving major obesity-associated co-morbidities.<sup>7-11,16</sup> The Swedish Obese Subjects Study, (a prospective nonrandomized study involving a total of 4047 obese subjects) found that at 2- and 10- year follow-up both recovery and incidence rates of diabetes, hypertriglyceridemia and hyperuricemia were more favourable in the surgically treated group than in the control (medically treated) group. Moreover, at 10 year follow-up the surgically treated subjects exhibited greater weight loss, increased physical activity and lower energy intake than controls.<sup>12,17</sup> This same study also looked at overall mortality 10 years after bariatric surgery and demonstrated a hazard ratio of 0.71.<sup>5,18</sup> Furthermore, a recent paper from this ongoing study looked at the effects of bariatric surgery on cardiovascular events and found that over a median follow-up of 14.7 years surgically treated subjects had a reduced number of cardiovascular deaths and a decreased incidence of cardiovascular events (including myocardial infarction or stroke).<sup>5,19</sup>

Thus, it is not surprising therefore, that the total number of bariatric surgery procedures performed worldwide is increasing, with nearly 350 thousand procedures performed globally in 2008.<sup>20-22</sup> Bariatric procedures have been traditionally classified according to their physiologic mechanism of action namely: restrictive (adjustable gastric band, sleeve gastrectomy and vertical banded gastroplasty) malabsorptive (biliopancreatic diversion and duodenal switch) and those that have both a restrictive and malabsorptive component (Roux-en-Y gastric bypass). Although bariatric surgery can be performed using both the open or laparoscopic approach, the latter modality is proving to be more popular with over 90% of bariatric surgeries being performed laparoscopically in 2008.<sup>21-23</sup> Of note, the procedure leading to greatest excess weight loss is the biliopancreatic diversion/duodenal switch (diversionary procedures) and the least is for banding procedures (purely restrictive).<sup>9-10,20</sup>

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Increased understanding of the multiple hormonal alterations which occur following different surgical approaches to obesity is providing new insight into the more plausible hormonal mechanisms responsible for the control of appetite and weight loss as well as improvement in glycemic control then the putative mechanical ones which inspired the different bariatric techniques.<sup>24</sup> Several studies have repeatedly confirmed that bariatric surgery is associated with better glycemic control then conventional (medical) therapy and that amelioration in carbohydrate metabolism frequently precedes weight loss and often occurs within days of the bariatric procedure.<sup>25-28</sup> It is now known that homeostatic alterations of certain gastrointestinal hormones - notably the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP) are the main contributory factors towards the improvement in diabetes control following bariatric operations. The reason for this has been postulated to be the sustained increase in release of GLP-1 from the L-cells of the distal small intestine which occurs following procedures where nutrient flow bypasses the duodenum and proximal jejunum such as the Roux-en-Y gastric bypass. The incretin effects of GLP-1 include enhanced insulin release and islet cell mass and improved insulin sensitivity all of which promote normal plasma glucose, plasma insulin and glycated haemoglobin levels following surgery.<sup>29</sup> Furthermore, GLP-1 has also been implicated in the regulation of appetite such that it induces early satiety and thus reduces food intake.<sup>29</sup> Another important gut hormone implicated in appetite control is the orexigenic hormone ghrelin. Ghrelin is a peptide hormone which is secreted from the stomach and upper intestine in the pre-prandial phase and is suppressed rapidly following food ingestion. Studies have shown conflicting results with respect to plasma ghrelin levels following bariatric surgery with some stating there is a decreased, similar or even increased level 24 hours following gastric bypass surgery.<sup>24</sup> The reasons for such heterogeneity in these results remain yet to be elucidated, however, interestingly diabetic patients often exhibit reduced suppression of post-prandial ghrelin release which may delay the onset of satiety. Thus, the varied spectrum of altered baseline and postprandial gut hormone profile which occurs following certain bariatric procedures is currently under intense scrutiny with the aim being to search for novel medical or surgical treatment modalities for refractory morbid obesity.

Hence, in order to ensure the best possible surgical outcomes, the bariatric patient must be selected carefully and undergo a rigorous preoperative assessment to assess suitability for surgery. Currently the clinical guidelines endorsed by different societies (including British, Scottish, American and European guidelines) generally state that patients should be considered for bariatric

surgery if they have a BMI  $\geq 40$  kg/m<sup>2</sup> or a BMI  $\geq 35$  kg/m<sup>2</sup> with one or more obesity related co-morbidity which is expected to improve following surgically induced weight loss.<sup>7-12</sup> Recently there has also been some published data demonstrating the benefits of bariatric surgery in mild to moderate obese patients (BMI 30–34.9 kg/m<sup>2</sup>) in terms of weight loss and cardiometabolic improvements. One randomised controlled study stated that subjects with mild to moderate obesity undergoing laparoscopic adjustable gastric banding had better outcomes with regards to weight loss and resolution of features of the metabolic syndrome then their non-surgically treated counterparts.<sup>11, 31-33</sup> This has led to the US Food and Drug Administration (FDA) to approve the use of laparoscopic banding in patients with mild to moderate obesity and an obesity-related co-morbidity.<sup>11, 34</sup> However, further well designed studies are needed with longer follow-up periods to further assess the long term risk/benefit ratio of surgery in this cohort of patients.<sup>11</sup>

Another area of interest is the age cut-off used by different bariatric programs. Although some authors state that advanced age ( $\geq 45$  years) is associated with increased perioperative morbidity and mortality, in the Longitudinal Assessment of Bariatric Surgery (LABS) Consortium, age was not significantly associated with adverse outcomes.<sup>30,35</sup> Moreover in another study, elderly age ( $\geq 65$ ) did not pose any limitations and led to sustained weight loss and improvement in quality of life with a negligible mortality rate and acceptable morbidity profile.<sup>11, 13, 15, 36</sup>

Prior to surgery, the potential candidate must have a comprehensive interdisciplinary assessment ideally involving a specialist bariatric physician and surgeon as well as a dietician, psychologist or psychiatrist and a social worker.<sup>11-16</sup> In the preoperative evaluation one should try to get a detailed medical, psychosocial and nutritional history.<sup>11-12, 16, 21, 24</sup> The medical history should include a weight history including previous attempts at weight loss and previous management strategies as well as a family history of obesity. One should also ask for any symptoms suggestive of co-morbidities such as a history of snoring or daytime somnolence for obstructive sleep apnoea or a history of shortness of breath or chest pain for cardiovascular disease and so forth. One should also consider asking for any symptoms that could suggest a secondary cause for obesity (such as symptoms relating to hypothyroidism, Cushing's syndrome or polycystic ovary syndrome [PCOS]) if indicated. Furthermore a nutritional history should be pursued including eating habits, the types of food eaten as well as triggers for eating and activity levels.<sup>11</sup> A detailed psychological evaluation is important as unidentified underlying psychiatric illnesses might interfere with giving informed consent and also might influence the type of bariatric surgery to be

performed.<sup>21</sup> It has been stated that patients with a strong-obsessive compulsive component would not be suitable for gastric banding as this procedure requires co-operation and self control on the part of the patient.<sup>21</sup> During this preoperative encounter, one is also able to assess the willingness and motivation of the patient and their potential to adhere to long term follow-up especially with regards to dietary recommendations and behavioural modifications that are required after surgery.<sup>12, 16</sup> At this point one can also evaluate the patients' expectations as well as the risks/benefits of surgery including discussion about the different procedures available and choice of surgical intervention, potential complications as well as perioperative mortality (table 1). The candidate should also be made aware of patient support groups and to enquire about support from family members. It is thought that patients who do not have long-term family support fare much worse than patients who have support from family members.<sup>10, 16</sup>

The physical examination should include weight and the BMI as well as a comprehensive systemic exam. One should look out for signs suggestive of a secondary cause of obesity such as features of Cushing's syndrome or hypothyroidism or signs suggestive of the presence of co-morbidities such as hypertension, cardiac failure, arthritis, evidence of diabetic retinopathy or neuropathy, acanthosis nigricans, eruptive xanthomata and so forth.

Laboratory investigations should be carried out as for any other major abdominal surgery, however, further tests should be directed according to the findings on history taking and physical examination. Thus one should screen the patient for the presence of co-morbidities including diabetes (fasting plasma glucose or HBA1c), hyperlipidemia or non-alcoholic steatohepatitis (liver function tests and clotting studies). Hormonal evaluation should be carried out if one suspects a secondary (endocrine) cause for obesity (such as thyroid function tests, 24-hour urine free cortisol or androgens if suspecting PCOS). Nutrient screening including iron studies as well as folate, vitamin B<sub>12</sub> and vitamin D levels should be obtained especially if the patient will undergo malabsorptive procedures.<sup>11, 16</sup> Baseline cardiopulmonary testing including a chest x-ray and an electrocardiogram should be undertaken with further investigations carried out as prompted by the history and physical exam.<sup>11</sup>

The most recent guidelines (issued by the American Association of Clinical Endocrinologists [ACCE], The Obesity Society [TOS] and the American Society for Metabolic and Bariatric Surgery [ASMBS]) go further to discuss the elements which will lead to 'medical clearance' for bariatric surgery. In it they discuss certain

issues which could influence the outcome of surgery in the bariatric patient.<sup>11</sup>

Pre-operative weight loss has been debated over the past few years. Some studies have shown that 5% excess body weight loss is associated with beneficial short term outcomes including shorter operative times, reduced hospital stay and higher post-operative weight loss.<sup>7, 11 37</sup>

However one French study did not find any relationship between pre and postoperative weight loss, 48 months after surgery.<sup>38</sup> Some studies have also described that preoperative weight loss leads to a reduction in liver size as well as intrahepatic fat and abdominal wall depth facilitating operative technique. However, there is no conclusive evidence with regards to preoperative weight loss on long-term outcomes. On the other hand it has been thought that preoperative weight loss will help with improving and optimizing glycemic control preoperatively as well as promote patient compliance and better chance of diabetes remission in the postoperative period.<sup>7, 11</sup>

Another important aspect in patient preparation prior to surgery is evaluation of obstructive sleep apnoea (OSA). A significant number of patients may have undiagnosed sleep apnea, however a good medical history and physical examination should alert the clinician to screen for OSA with polysomnography studies and if positive further tests such as spirometry and echocardiography should be undertaken. Preoperative treatment entails using continuous positive airway pressure and postoperatively, the majority of patients experience resolution or improvement in their symptoms.<sup>7, 10-11</sup>

There have also been some studies regarding preoperative evaluation of the gastrointestinal tract. Some centres advocate routine screening with preoperative upper gastrointestinal (UGI) endoscopy in such patients.<sup>7, 39</sup> The rationale for this stems from the fact that following gastric bypass, evaluating of the UGI tract may be problematic. One study stated that significant pathological findings of the UGI tract were found in nearly 80% of patients but only 20% had reported symptoms.<sup>40</sup> In another study by UGI tract screening resulted in low yield for anatomical findings with UGI tract symptoms also not correlating with the endoscopic findings.<sup>39</sup> Preoperative *Helicobacter pylori* screening is also controversial with some authors reporting lower incidences of postoperative marginal ulcers and others saying such ulcers were related to surgical technique and not due to *H. pylori* exposure.<sup>7, 11</sup> Further randomised controlled studies are needed in this area, however endoscopic screening should be considered in high risk patients as it might alter surgical strategy.<sup>11, 40</sup>

**Table 1:** Overview of the current bariatric procedures performed including a comparison of efficacy, complication and mortality rates.

Adapted from L. Vu et al. *Best Practice & Research Clinical Endocrinology & Metabolism*, 2013; 27: 239-246.

<sup>a</sup> Weight loss is expressed in terms of excess body weight (EBW).  $EBW = \text{current weight} - \text{expected body weight based on height and gender}$ . Percentage excess weight loss (EWL) is calculated as  $(\text{weight loss/excess weight}) \times 100$ .

Type of bariatric surgical procedure	Adjustable Gastric Banding	Roux-en-Y Gastric Bypass	Sleeve Gastrectomy	Biliopancreatic Diversion and duodenal switch
<b>Procedure</b>	An inflatable silicon band is placed in the proximal portion of the stomach to create a pouch which can be adjusted to allow tailoring of the stoma outlet leading to decreased meal capacity and rate of emptying of pouch.	The stomach is reduced to a gastric pouch of around 30mL in size which is then anastomosed to the distal jejunum via a <i>roux limb</i> of around 100cm. The remaining distal end of stomach and proximal small intestine are drained via a <i>biliopancreatic limb</i> . These 2 limbs eventually anastomose further down in the small intestine to create the roux-en-Y.	Around 75% of the stomach is resected along the greater curvature with the open edges attached together using surgical staples. This creates a narrow gastric tube along the lesser curve limiting intake and also removing most of the ghrelin-producing cells of the gastric mucosa.	The gastric reservoir is reduced by excising 75% of the stomach creating a gastric sleeve. The small intestine is then divided in two places – at the duodenum and ileum such that the proximal end of ileum is connected to proximal part of duodenum thus bypassing a significant amount of small bowel and the remaining distal end of duodenum is reconnected in the ileum.
<b>Effect on weight</b>	Excess weight loss <sup>a</sup> at 5 years ranges between 45.4% - 48%. <sup>8,10,21,23</sup>	Excess weight loss <sup>a</sup> ranges between 60 – 70% 5 years after procedure. <sup>8,10,21,23</sup>	Excess weight loss <sup>a</sup> at 1-3 years post surgery is comparable to gastric bypass surgery and ranges between 55-66%. <sup>10,21,23</sup>	This procedure is associated with 70.1% excess weight loss <sup>a</sup> – the most effective operation at inducing weight loss. <sup>10,23</sup>
<b>Effect on type 2 diabetes</b>	Resolution of type 2 diabetes occurs in approximately 56% of patients 2 years after procedure. <sup>9-10,21,23</sup>	Diabetes remission occurs in around 80% of patients 2 years following surgery. <sup>9-10,21,23</sup>	Diabetes remission occurs in around 66% of patients. <sup>21,23</sup>	Diabetes resolution is highest with this procedure with remission rates of around 95% at 2 years. <sup>10,23</sup>
<b>Complication and mortality rates</b>	This procedure is considered to be the safest with literature data stating an operative mortality rate of between 0.05 to 0.1%. However, mechanical complications can arise at a rate of 11.6% including outlet obstruction, band slippage or band erosion requiring reoperation. <sup>10,21,23</sup>	Earliest complications include anastomotic or staple line leak (incidence rate 0.4 to 5.2%). Other complications include marginal ulcers, bowel obstruction, internal hernia dumping syndrome and roux limb ischemia. Late complications include nutrient deficiencies (vitamin B12, folate, iron). Operative mortality is low with reported rates up to 0.5%. <sup>9-10,21,23</sup>	Early complications include bleeding and ischemia followed by postoperative gastroesophageal reflux. Nutritional deficiencies (including vitamin D, calcium and iron) occur with variable rates. Operative mortality is reported as being 0.33 ±1.6%. <sup>21,23</sup>	This procedure is associated with the highest rate of both early (operative) and long term complications such as anastomotic leaks and micronutrient deficiencies (including calcium and vitamin D deficiency) respectively. This procedure is also linked with the highest rate of perioperative mortality at a rate of 1.1%. <sup>9-10,23</sup>

As stated previously a thorough psychosocial-behavioural evaluation should be carried out especially if the patient has a previous history of psychiatric illness or substance abuse/ dependence. The European guidelines and several other authors state that uncontrolled psychiatric disorders as well as drug dependencies are specific contraindications for bariatric surgery as this may interfere with the consent process and may also impair the patients' adherence to post-operative follow up.<sup>7, 9-10, 16, 21</sup> The Scottish guidelines on the other hand state that such disorders should not be considered as absolute contraindications.<sup>13</sup> Thus, constant psychological support should be available both preoperatively as well as in the postoperative phase for such patients.

Another important issue is monitoring for micronutrient and vitamin deficiencies. The majority of obese patients are known to be deficient in vitamin D<sup>7, 41</sup> as well as vitamin A<sup>42</sup> and some other micronutrients such as ferritin and iron (more so in women).<sup>7, 42</sup> Appropriate preoperative measurements especially if the patient will undergo extensive malabsorptive procedures are prudent and micronutrient or multivitamin supplementation should be provided where necessary.<sup>7, 11,13</sup>

Finally, the choice of surgical procedure must be made jointly by the patient and the bariatric surgeon, taking into account all the above factors as well as the experience of the surgeon and the facilities and equipment available.<sup>7, 11-12, 16</sup>

As one can see bariatric surgery in the carefully selected obese patient, remains superior to any other nonsurgical forms of treatment for weight loss and improvement in surrogate markers of metabolic disease. However, further properly designed randomised controlled studies are needed to assess long-term benefits and durability of such outcomes.

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# Medico-Legal Litigation: The clinical contractual nature of the Obstetric Anaesthetist -Patient relationship

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Once the hand-maiden of obstetrics, obstetric anaesthesia, now a fully fledged sub-speciality today provides indispensable multi-faceted services mainly but not solely to the peripartum obstetric patient. Be it in routine as well as acute obstetric work, the speciality is an integral part of the team made up of obstetrician, midwife and neonatologist. Its input ensures modern optimal care to the parturient patient and her baby.<sup>1</sup> The anaesthetist's unique resuscitatory skills and critical care experience makes him/her particularly valuable, especially in high-risk patients<sup>1</sup> as evidenced by the struggle of units lacking such a service in overcoming numerous administrative, financial and logistical problems to reach this paragon of standard of care.<sup>2</sup> By the very nature of the acutely challenging situations it deals with, this speciality is especially vulnerable to medico-legal litigation.

## Conceptualising medico-legal liability

To the medical practitioner facing a court case with all its 'psychological, corporeal and behavioral practice changes',<sup>3</sup> it may matter little, but a fierce and endless legalistic argumentation exists as to whether medical malpractice cases should fall under the law of Tort or that of contractual relationships. This is no airy-fairy battle fought in legal fora. Suffice it to mention one point out of many, namely the prescriptive difference of the two. However, the argument we shall sustain here, purely conceptually speaking, is to look at malpractice litigation under the Law of Contract. For the often poorly legally informed physician (here the obstetric anaesthetist) looking at malpractice as the presumed breaking of the Law of Contract may effect a clearer understanding than invoking the meanderings of the law of Tort.

## Poor knowledge of the Law

The poor knowledge of the law by most medical doctors is often acknowledged widely. In a whitepaper on Legal Knowledge, Attitudes and Practice at the Queen Elizabeth Hospital in Barbados, 52% of senior medical staff and 20% of senior nursing staff knew little of the law *pertinent to their work*.<sup>4</sup> We believe this to be a rather accurate universal. However one must reflect on the situation *before* one receives the court summons. We recommend that the obstetric anaesthetist assumes the habit of thinking that he/she is embarking on a legal contract with a patient. This contract demands a legal responsibility from him and if this responsibility is not fulfilled, problems may result. If such failure is found to have been responsible for resultant harm than he/she is liable at law. Far from encouraging defensive medical practice, the concept adds a valuable new perspective which we believe should be inculcated even at undergraduate level without de-humanising the 'most noble profession of all'. Invoking the law of contract is a positive legal concept telling you how to safeguard your contract while the law of Tort latter tells you *retrospectively* where you went wrong. The contractees – the physician and the patient – are bound by a legal agreement which demands "good practice" as deemed by current peer practice or quoting the Bolam<sup>5</sup> test "

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*If a doctor reaches the standard of a responsible body of medical opinion, he is not negligent".*

### The cold reality of court

To the healer, the term contractual relationship sounds alien, impersonal, legal and non-medical. It is. Medical doctors have wanted to and eventually been suitably qualified and licensed to heal, relieve suffering and distress of body and mind. However, the well documented emotional and physical stress resulting from medico-legal litigation<sup>6</sup> should rapidly awaken the obstetric anaesthetist (in this case) to the legally binding conscious or unconscious contractual latitude supervening on the therapeutic nature of the doctor-patient relationship. 23% of doctors identified medico-legal litigation as their most stressful life experience.<sup>7</sup> In a scenario with rapidly changing socio-legal dynamics there is general exhortation to diminish the plague of malpractice claims which has reached epidemic proportions<sup>8</sup> Of all anaesthetic sub-specialities the obstetric anaesthetist is the commonest to retire from work due to medico-legal concerns.<sup>9</sup> One official survey revealed that 89% of respondents had been sued during their lifetime with an average of 2.6 cases per individual<sup>9</sup> Kuczkowski commenting on the current medico-legal climate in Australia and New Zealand points out that 47.2% of obstetric anaesthetists were seriously concerned about the viability of their practice vis-a-vis indemnity premiums and 20.2% were planning outright to retire in the following two years because of the issue.<sup>9</sup> Hence we speak of a problem with intense effects on the individual and ending in a negative multiplier effect with a demographic finality.

Awareness of malpractice action as well as instilling at least a basic working knowledge of the law are an urgent necessity and we believe should be stressed from undergraduate level. Working on the medico-legal aspect of the anaesthetist-patient relationship on a contract basis is a good beginning. The contractual relationship between doctor and patient was also stressed in the Annual International Medical Journal of 1983.<sup>10</sup> A number of court pronouncements have indeed stressed the existence of such a contractual bond between medical practitioners and patients.<sup>10</sup> One can appreciate this if one bears in mind that a contract is defined as 'an agreement between two or more competent parties in which an offer is made and accepted, and each party benefits. The agreement can be formal, informal, written, oral or just plain understood.'<sup>11</sup> In this case, the patient and the anaesthetist enter into a signed agreement where the latter offers his/her services to the patient who in return will effect payment with mutual advantage. In a way, even NHS patients can be considered as paying - albeit indirectly - through their NHS contributions.

### Raising patient awareness of the role of the Obstetric Anaesthetist.

It is possible that the *gradual* development of the sub-speciality of obstetric anaesthesia underlies a certain cinderella-like attitude towards it by specialists and doctors outside the speciality. While the speciality's cornerstone support of modern obstetrics goes unquestioned, it tends to suffer from what we term the "Commando Syndrome". Like "action man", SEALS or Commandos, the anaesthetist tends to be *inserted* in a field of action, *perform* his mission and *withdraw* out of the targeted field- with all due apologies to the unintended puns. Few see these people at work as they effect their high risk job and by the time of the big bang they're almost out of the picture already. Another analogy comes from Alfred Tennyson's quote from his "The Charge of the Light brigade" – "Ours is not to question why, Ours is to do or die". The establishment of *regional* anaesthesia has at least contributed much to direct *patient* awareness of her anaesthetist. With *general* anaesthesia say for a C-section, the patient may hardly have ever even said "hello". But when a problem arises and people are indicted, then everybody knows who the anaesthetist had been.

Invoking the Law of Contract to conceptualise pre-empting malpractice quandaries, demands a minimal aspect of doctor-patient bonding. And bonding as a minimum demands one person acknowledging the existence of another. Bonding may allow allegedly impaired contractual obligations to be discussed, reviewed, sorted out especially if the contractees have befriended one another to any extent. Lack of fulfilment of contractual obligations by a faceless person are like nature abhorring a vacuum – they are magnets for some litigious lawyer who may fan frustration, anger or hurt whether justifiable or not. We cannot over-stress the role of the anaesthetist being introduced to the patient and his/her bonding (albeit limited) as the first step in pre-empting, eliminating, minimising or sublimating malpractice court action.

The anaesthetist's disadvantage at establishing rapport and patient bonding is a universal default mode in any acute labour ward situation. Accepting that such bonding is crucial in minimising the chance of malpractice suits,<sup>12</sup> the anaesthetist should visit the patient well before the administration of anaesthesia in any form if the scenario permits. We are not referring to situations like abruptio placentae or a cord prolapse but in an elective caesarean section for example, time spent examining the patient and discussing one's role on the eve of the case is time well invested indeed. Likewise a visit the day following the section may go a long way in cementing a short but hopefully not unpleasant doctor-patient relationship. On the big day itself re-explaining, reassuring, congratulating are all facets which bring out



the obstetric anaesthetist's humanity and which give the anaesthetist's role a face to be remembered. Urgent situations of life and death still allow follow up visits and explanations by the anaesthetist. In a labour ward set-up, attending the obstetrician's wards rounds may be a further help. The obstetrician himself should well remember that besides obstetricians, anaesthetists are frequently named in cases with bad neonatal outcome.<sup>13</sup> Using his/her own long built bonding relationships with the patient and spouse or partner, the obstetrician should introduce the anaesthetist and raise the patient's awareness of their colleagues' service. This is also advisable in expected serious or difficult cases.

### **Making the acquaintance of your co-signatee.**

It is crucial to stress that the anaesthetist should *not* make the patient's acquaintance in the operating theatre where the patient's attention may be easily dulled by the tension, fear and distractions of an impending operation. Severe stress has a negative effect on both the brain's ability to encode information as well its later recall.<sup>14</sup> Park *et al.* have shown that information garnered just before shock induced stress by rats resulted in its amnesia.<sup>15</sup> The "contract" should be preferably signed and discussed in at least a ward environment rather than an operating theatre environment.

### **The contractual terms of reference – the consent form.**

Under the general principles of the law of Contract and its obligations there is a voluntary exchange of an offer of a service and its voluntary acceptance. The service must be made clear along with its limitations, dangers, advantages and disadvantages, admittedly not always easy. We maintain that truly imparting *all* the necessary information and risks is not possible in a practical and functional way especially to a non-medical patient. *In fact we believe that it is not possible to obtain a hundred per cent legally viable consent form.* This is not due to conscious withholding of any information but rather through the sheer unworkable complexity of truly explaining all potential risks and advantages. Such an explanation would entail a lecture or ten on biology, chemistry, physics, anatomy, physiology, medicine, surgery, anaesthesia etc. The consent form requires disclosure of risks and alternatives that a reasonable patient (as opposed to a reasonable physician) would consider material. Yet physicians who fail to provide the required information risk liability, even if the physician was not negligent in performing the procedure. Having said all this, we also believe that the art of Medicine finds one of its finest expositions in the way the obstetric anaesthetist delivers his information which must be correct, truthful and as complete in a functional and practical manner as

possible. However we genuinely maintain that what is universally called a "consent form" should in practice be referred to as a "functional consent form". In a world witnessing the massive rise of the medico-legal epidemic<sup>16</sup> one must beware of the full implications of the written medical contractual agreement as presently understood in the term "consent form" which must be an "an informed consent form". "Functional" here refers to language, cognizance and practicality. Cancelling a simple transvaginal sling urethropexy for severe stress incontinence after the patient was spoken to by a houseman legally bent on avoiding 'Inadequate preoperative planning'<sup>17</sup> is precisely one of the wrongs to be avoided, (personal case of the medical author).

The obstetric anaesthetist must also be careful of withholding knowledge which may draw him/her in a disadvantageous light e.g. his/her inability to perform regional analgesia as an alternative to general anaesthesia for a C-section or avoiding mentioning that epidural anaesthesia for a C-section may be safer than a spinal in avoiding unwarranted episodes of hypotension.<sup>18</sup> All is well when all goes well. When it does not, universally adopted and practiced bad habits are poor defence in court.

### **Holistic practice as alternative to defensive practice**

In 1984, defensive medicine added \$2 billion annually to medical costs in New York state<sup>19</sup> and all over the USA the cost is \$15 billion or \$1.19 per week for every American.<sup>20</sup> Borrowing a working definition from Simon, albeit originally quoted in terms of psychiatry, "defensive medicine refers to any act or omission performed not for the benefit of the patient but solely to avoid malpractice liability or to provide a good legal defense against a malpractice claim."<sup>21</sup> We know that medical liability does not improve the quality and safety of health care, for example when applied in nursing homes – it decreases it slightly.<sup>22</sup> With regard to the individual e.g. the obstetric anaesthetist, it may "paralyze flexible and patient-centered decision making to the point where it may actually be harmful to the patient."<sup>22</sup> Taking one example initiated by obstetricians with anaesthetists being party to, is the defensive performance of performing c-sections through over-diagnosing electronic fetal monitoring artefacts as fetal distress.<sup>23</sup>

We believe that merely 'focusing one's attention on reducing the potential for major injuries may have little effect on solving the medico-legal dilemma in obstetrics'.<sup>24</sup> We also believe one answer lies in effecting 'good practice' combined with "therapeutic alliance"<sup>20</sup> with the patient. The latter implies sharing of information with the patient to increase *her* empathy with the doctor or using reverse empathy, empathy being defined as a positive cognitive attribute leading to

‘feeling with’ the patient and understanding her perspectives as a separate individual.<sup>25</sup> In “therapeutic alliance”, the patient is encouraged to step into the doctor’s shoes. We lightly suggest that one can imagine that is trying to talk a houseman through the obstetric anaesthetist’s day without scaring him away into another profession. At the end of the day this is yet another way of communicating with the patient and any form of communication is another positive step towards bonding. The effort to bond might come easy to some and virtually impossible to others. In the present medico-legal scenario it is indispensable but even without this a patient always appreciates her carer’s humanity.

### Ward showdown or court battle

Pre-emptively invoking the law of contract should never challenge the anaesthetist’s humanity. This is a sine qua non requirement of medicine and may automatically avoid negative feelings. The Closed Case Database (which reflects the consumer’s viewpoint) massive content of minor problems is instructive. Among the commonest complaints are of patients feeling ignored and mistreated.<sup>24</sup> In our opinion this lends much weight to Meyers’ theory that malpractice litigation may serve the dual purpose of reparation of injury for substandard care but also one of *emotional vindication*.<sup>24</sup> To which we add a corollary namely that emotional catharsis expressed post operatively *per voce* a day or two after surgery may eliminate emotional vindication. In a highly emotive situation it is easy for patient s and/or husbands to accumulate stress and imagine misgivings and if allowed to, vocally vent frustrations, hurt, anger and tears it may suffice to end the matter. Out of all the patient who seek court remedial action for some aspect of negligent care only 2%<sup>24</sup> have their claims upheld. Furthermore anaesthetists are frequently named in bad fetal outcome claims which are deemed *not* justifiable and hence do not lead to payments.<sup>26</sup> A common mistake is to confuse giving an excellent medical service with the patient’s *perception* of what constitutes satisfactory medical service. A bruised ego suffered at the most stressful time of labour<sup>26</sup> may be assuaged by a vitriolic discussion, an explanation and maybe an honest apology. And here one must differentiate the Law of Contract as applied to medicine and not, say the selling of an apartment. Where human life and health are concerned the arena has many multi-faceted and multiplier phenomena where over-all satisfaction is often beyond legal definition. We believe that this phenomenon underlies the fact that legal claims in the highly emotive field of obstetrics and obstetric anaesthetic claims, far surpass the non-obstetric ones in the “minor injury” nature of the cases.<sup>26</sup>

### Clear contractual conditions, accurate file documentation

Having given all pertinent information to the patient and both duly signed the consent form, we believe that it is important for the obstetric anaesthetist *to have witnesses to this fact as well as to fully document all, including witnesses’ names in the patient’s records*. Accepting the contractual nature of the doctor-patient relationship implies abiding by contractual norms. Language must be simple, clear and accurate. Telling a 150 kg woman that “you are a bit overweight and there are a few more risks because of this” is *not* honest fulfilment of contractual obligations. This is where one bold anaesthetist’s approach may differ from a more shy one. The correct form of this address would be “Madame you are very overweight and this does make your operation substantially riskier” *and this must be said to both patient and husband/partner, be witnessed by a third person and all annotated with date and time registered in a clear legible manner in the patient’s clinical file*. Such are the medico-legal vagaries of modern life in Medicine that such doings must become habitual even if they are currently not. As in the good book, it is the one sheep that strays that counts not the ninety nine lying quietly in their pen.

Where multiple anaesthetists are involved, if a court case ensues, all anaesthetists may be be sued for a given claim.<sup>27</sup> Hence we advise that all anaesthetists sign the functional consent form(s) and make their individual observations in the patient’s file, although the same witness may suffice for all . Delegating part or all of his/her work to another does not legally exoneratethe the original doctor and legal responsibility will be assumed of both in a court of law.<sup>28</sup> In the presence of multiple anaesthetists there seems to be a psychologically reassuring factor for ‘herd protection’ which evaporates in the courtrom.

### Conclusion

We have here suggested a working pre-emptive hypothesis conceptualising the obstetric anaesthetist’s medico-legal responsibility under the Law of Contracts rather than the Law of Tort. The concept applies across the board of medical specialities and all physicians need to know the relevant sections of the law. The modern medical practice must be safe and peer reviewed, practiced with sense and honed to be delivered humanely. A holistic attitude to patients rather than defensive medicine is promulgated. We also exhort obstetric/anaesthetic units to hold regular fora to ensure the practice not only of good anaesthetists but also of a medio-legally sound one. The suggestions here imparted advocate the crowning of good practice with communication and bonding which also enhance the humanity of medical practice at times of maximal stress.

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# Cardiovascular risk assessment and management in rheumatoid arthritis: are guidelines being followed?

Rosalie Magro, Malcolm Buhagiar, Nikita Taliana, Andrew A. Borg

## Abstract

**Aim:** The aim of the audit was to determine whether the cardiovascular risk assessment and management in rheumatoid arthritis patients at Mater Dei Hospital is in concordance with the recommendations by the European League Against Rheumatism (EULAR).

**Background:** Patients who suffer from rheumatoid arthritis have an increased risk of morbidity and mortality from cardiovascular disease. This is due to both the high prevalence of traditional risk factors, and systemic inflammation.

**Method:** This audit was carried out retrospectively on 91 patients by using the medical notes to collect data on demographics, co-morbidities, drug history and cardiovascular risk assessment and management over a two year period (August 2010 to July 2012). The data was then analysed in order to assess whether the management of cardiovascular risk in rheumatoid arthritis patients was in concordance with EULAR recommendations.

**Results:** Cardiovascular risk factors were documented as follows over the two year period audited: weight in 27.5%, BMI in 0%, smoking status in 72.5%, blood pressure in 72.5%, blood glucose in 72.5% and lipid profile in 54.9%. Smoking cessation advice was given in 15.8% and advice on other lifestyle changes in 14.3%. 81.1% of hypertensive patients were on treatment recommended as first-line by the guidelines and HbA1c was adequately controlled in 85.7% of diabetic patients in whom it was monitored.

**Conclusion:** Cardiovascular risk factors are highly prevalent in rheumatoid arthritis patients. This audit identified aspects of cardiovascular risk assessment that require improvement. This would enable a better identification of cardiovascular risk factors that could be treated in order to reduce the patients' cardiovascular morbidity and mortality.

**Keywords:** rheumatoid arthritis, risk factors, medical audit

## Aims and Objectives

The aim of the audit was to determine whether cardiovascular risk assessment and management is being carried out in rheumatoid arthritis patients at Mater Dei Hospital in concordance with the "EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis" published in 2010.<sup>1</sup> A further aim was to identify whether the rheumatoid arthritis disease activity is adequately controlled.

Moreover, the prevalence of the traditional risk factors (including diabetes, hypertension, hyperlipidaemia and smoking) in our cohort of Maltese rheumatoid arthritis patients was determined.

## Background

Rheumatoid arthritis is a chronic systemic inflammatory disease that typically presents with a symmetrical polyarthritis with occasional extra-articular involvement of other systems including the skin, heart, lungs and eyes. The aetiology is unknown and the prevalence is approximately 1%. Women are affected approximately three times more often than men.

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Patients with rheumatoid arthritis have multiple co-morbidities of which cardiovascular disease is the most important. Studies have shown that rheumatoid arthritis patients have a markedly increased risk of death compared with the general population.<sup>2</sup> This is largely due to the increased risk of ischaemic heart disease and cardiovascular death.<sup>3-5</sup> Solomon *et al* observed an approximate doubling of the rate of myocardial infarction and stroke in patients with rheumatoid arthritis and the rate of cardiovascular death was increased by 30%.<sup>6</sup> Moreover, a meta-analysis of fourteen controlled observational studies showed that the risk of incident cardiovascular disease is increased by 48% in patients with rheumatoid arthritis compared to the general population.<sup>7</sup> A cross-sectional study, the CARRE investigation, showed that the prevalence of cardiovascular disease in rheumatoid arthritis is increased to an extent that is at least comparable to that of type 2 diabetes.<sup>8</sup>

A cross-sectional study on 400 rheumatoid arthritis patients showed that hypertension is highly prevalent (70%) in rheumatoid arthritis patients. In this study, it was noted that hypertension is under-diagnosed especially in young patients, and under-treated in older patients who have multiple co-morbidities.<sup>9</sup> Moreover, an adverse lipid profile (lower high density lipoprotein cholesterol (C-HDL), apolipoprotein A1 and B and higher total cholesterol (CT) to C-HDL ratio and low density lipoprotein cholesterol (C-LDL) to C-HDL ratio) has been noted in rheumatoid arthritis patients when compared to the general population.<sup>10</sup>

The excess cardiovascular burden cannot be fully explained by traditional cardiovascular risk factors alone. Systemic inflammation in rheumatoid arthritis contributes to the risk of cardiovascular events.<sup>11-14</sup> Current evidence shows that both the traditional risk factors and markers of rheumatoid arthritis severity contribute to cardiovascular risk.<sup>15-17</sup> Thus screening and management of traditional cardiovascular risk factors as well as adequate control of inflammatory arthritis are necessary to prevent cardiovascular events in rheumatoid arthritis patients.<sup>18</sup>

The EULAR guidelines make the following main recommendations, which we have used as gold standards for the audit:

1. An annual cardiovascular risk assessment including measurement of blood pressure and random lipids is advised in rheumatoid arthritis patients. The SCORE model should then be used to determine the degree of cardiovascular risk. (Figure 1) This is an easy-to-use chart that helps calculate the ten year risk of fatal cardiovascular disease by taking into account traditional risk factors including age, gender, smoking, systolic blood pressure and

cholesterol level.<sup>19</sup> The EULAR guidelines recommend the use of the total cholesterol/HDL ratio when the SCORE model is used. Moreover, the risk should be multiplied by 1.5 if the patient has 2 of the following 3 criteria: a) disease duration of more than ten years, b) positive rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA), c) presence of severe extra-articular manifestations. In patients with low cardiovascular risk and inactive disease, a lower frequency of assessment such as every 2-3 years could be adopted.

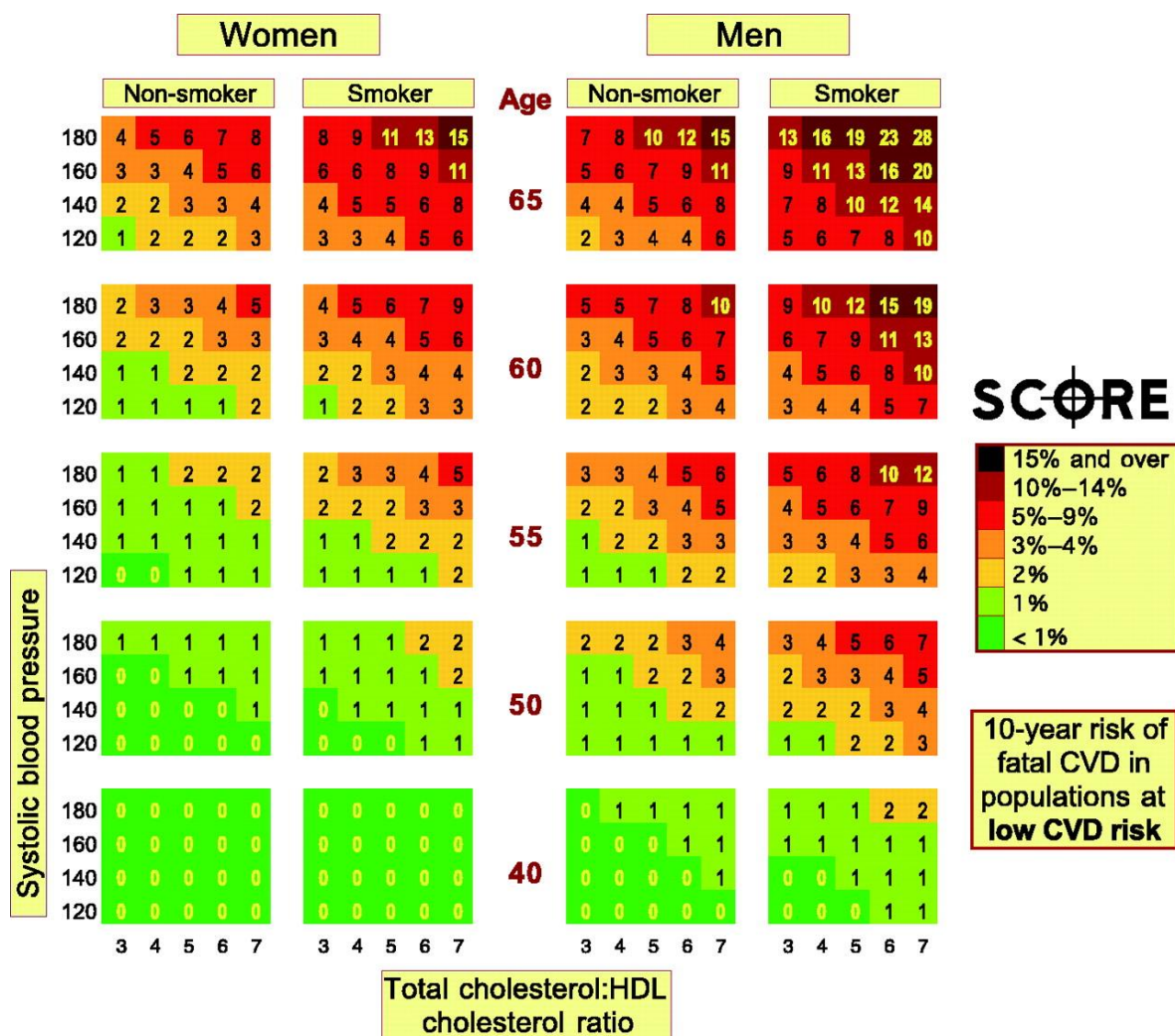
2. Intervention should be carried out using local guidelines or if unavailable using the SCORE model. Cardioprotective treatment should be initiated when the estimated 10-year cardiovascular risk is above the risk threshold for each country. Since there are no local guidelines on the subject, the SCORE model and the "European guidelines on cardiovascular disease prevention in clinical practice" published in 2012 have been used for our purpose. These recommend that cholesterol-lowering therapy should be started if cardiovascular risk is >5 to <10% and LDL is  $\geq 2.5\text{mmol/L}$  or if cardiovascular risk is  $\geq 10\%$  and LDL is  $\geq 1.8\text{mmol/L}$ .<sup>20</sup>
3. Statins, angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are preferred treatment options when indicated.
4. Disease activity should be controlled adequately to further lower the cardiovascular risk.
5. Smoking cessation should be recommended.
6. Lifestyle modification advice should be given to all patients.

Since there is no mention on the ideal targets for the control of diabetes by the EULAR guidelines, the recommendations by the "European guidelines on cardiovascular disease prevention in clinical practice" have been used as a gold standard in the audit.<sup>20</sup> These recommend that the target HbA1c for the prevention of cardiovascular disease in diabetes is <7%.

## Method

91 consecutive patients with definite rheumatoid arthritis according to the 2010 ACR/EULAR Rheumatoid Arthritis classification criteria were recruited from the database of patients under the care of a medical consultant.<sup>21</sup> For every patient a proforma was completed using the medical notes, as well as the I-soft programme to collect the results of the blood investigations.

**Figure1:** The SCORE model used to calculate the ten year risk of fatal cardiovascular disease.<sup>19</sup>



The data collected included basic information such as demographic data, past medical history of ischaemic heart disease and its traditional risk factors, drug history and smoking history. Data on cardiovascular risk assessment (including measurement of blood pressure, lipid profile, blood glucose) over a one year period (from August 2011 to July 2012) was also collected. If such data was absent since it was not measured or not documented, data from the previous one year period (August 2010 to July 2011) was collected if available. In those cases where data on age, gender, smoking, blood pressure and lipid profile was complete, the 10 year risk of fatal cardiovascular disease was calculated by using the SCORE chart. The total cholesterol/HDL ratio was used as a measure of cholesterol in the SCORE chart as advised by the EULAR guidelines. Moreover the risk was multiplied by 1.5 if the patient had 2 of the 3 criteria: a) disease duration of more than ten years, b) positive RF or ACPA, c) presence of severe extra-articular manifestations. The data was then analysed in

order to determine whether cardiovascular risk management was being carried out as recommended by the guidelines. Thus it was determined whether hypertensive patients were being treated with ACE inhibitors or ARBs when indicated; whether hyperlipidaemic patients were being treated with statins when recommended; whether smoking cessation and lifestyle advice was being given and documented; whether DAS28, ESR and CRP were being measured and if disease activity was adequately controlled.

Approval to carry out this audit was obtained by the data protection department at Mater Dei Hospital and by the University Research Ethics committee.

## Results

Of the 91 patients audited 59 (64.8%) were female and 32 (35.2%) were male. The mean age was 62.7 years. The duration of rheumatoid arthritis was documented in 79 patients (86.8%). The mean duration was 7.6 years. Rheumatoid factor result was documented



in 82 patients (90.1%), of which 62 patients (75.6%) were rheumatoid factor positive. ACPA result was documented in 48 patients (52.7%), of which 29 patients (60.4%) were ACPA positive.

The patients' weight was documented in 25 patients (27.5%). The height and BMI was not documented in any of the patients audited. The patients' smoking status was documented in 66 patients (72.5%). Of these 19 were smokers, 11 were ex-smokers and 36 were lifelong non-smokers. Out of the 19 current smokers, smoking cessation advice was given and documented in 3 patients (15.8%). In all the patients audited, lifestyle changes advice (including diet, exercise and weight loss) was given and documented in 13 patients (14.3%).

The blood pressure was checked and documented at least once in the one year audited in 49 patients (53.8%). It was checked in the two year period in 66 patients (72.5%). Out of the patients audited, 37 suffered from hypertension. Of these, 23 patients were on an ACE inhibitor and 7 were on an angiotensin receptor blocker (ARB). Overall 81.1% of hypertensive patients were on an ACE inhibitor or ARB.

Random or fasting blood glucose was measured in the previous year in 52 patients (57.1%). It was checked in the previous two years in 66 patients (72.5%). Out of the patients audited, 15 were diabetic. Of these HbA1c was checked in 7 patients (46.7%) over the two year period audited. This was 7% or more in only one patient.

Out of the patients audited, 12 were known to suffer from hyperlipidaemia. Lipid profile was monitored in 35 patients (38.5%) in the previous year and in 50 patients (54.9%) in the previous two years. The ten year cardiovascular risk could be calculated in 29 patients (31.9%) since these had complete data with regards to age, sex, smoking history, blood pressure and lipid profile. Eight of these patients were on a statin. When taking into account the cardiovascular risk and the last lipid profile, statins were indicated according to the guidelines in 5 out of these 29 patients; only one of these 5 patients was on a statin. Statins were most likely also indicated in the remaining 7 patients on statins, since the lipid profile used to calculate the ten year cardiovascular risk was one taken over the last two years when the patient was already receiving a statin.

An ESR was checked in the previous year in 87 patients (95.6%) and it was checked in the previous 2 years in all patients. The CRP was checked in the previous year in 84 patients (92.3%) and it was checked in the previous two years in 89 patients (97.8%). DAS 28 was calculated in the previous year in 19 patients (20.9%) and in the previous two years in 39 patients (42.9%). Out of these 39 patients, a high disease activity was noted in 5 patients; a moderate disease activity in 18 patients; a low disease activity in 7 patients; and 9 patients were in remission.

## Conclusions

The prevalence of diagnosed hypertension in our cohort of rheumatoid arthritis patients was 40.7%; diabetes was 16.5%; hyperlipidaemia was 13.2%; and ischaemic heart disease was 6.6%. The prevalence of hypertension in the Maltese general population over 15 years of age has been estimated to be 22%; while that of diabetes is 8%.<sup>22</sup> This shows that the traditional risk factors for cardiovascular disease are highly prevalent and their monitoring and treatment is essential in order to decrease the mortality of rheumatoid arthritis patients.

An improvement in the measurement of weight and height, and the calculation of BMI would be useful since it would prompt advice on weight loss, diet and exercise. Moreover the documentation of smoking status would encourage giving smoking cessation advice to smokers.

The measurement of the traditional risk factors requires improvement. Blood pressure was measured in 53.8%, blood glucose in 57.1% and lipid profile in 38.5% over a one year period. This improved to 72.5%, 72.5% and 54.9% respectively when a two year period was considered. Of note, blood pressure measurements taken by general practitioners that were not documented in the hospital notes were not accounted for in this audit. A good proportion (81.1%) of hypertensive patients were being treated with ACE inhibitors or ARBs as recommended. Monitoring of diabetic patients by measurement of HbA1c requires improvement since it was checked in 46.7% of diabetic patients. Control of diabetes in patients in whom HbA1c was checked was adequate.

An improvement in the monitoring of the risk factors for cardiovascular disease would enable the calculation of the 10 year risk of fatal cardiovascular disease by using the SCORE chart in a larger proportion of patients. Hence this would enable the treatment of hyperlipidaemia when indicated. In fact, out of the 29 patients in whom the cardiovascular risk could be calculated by using the SCORE chart, four patients who would benefit from treatment with a statin (and were not on any lipid lowering drugs) were identified.

Monitoring of disease activity by measurement of ESR and CRP was adequate. However, the calculation of DAS28 was lacking (20.9% in a one year period; 42.9% in the two year period). This finding is in concordance with the findings of another audit where only 50% of patients starting treatment with a biologic agent had a DAS 28 score documented in the year prior to starting this treatment.<sup>23</sup> This requires improvement since the calculation of DAS28 enables a better identification of patients with a high disease activity that in itself increases the risk for cardiovascular disease. Our results show that in those patients in whom DAS28 was calculated, 41% were in remission or had a low disease activity.



**Table 1:** Summary of the percentage of patients in whom risk factors and disease activity measurements have been measured over the period audited.

<i>Risk factor / Disease activity measurement</i>	<i>Percentage of patients in whom risk factor is documented (over a one year period, if applicable)</i>	<i>Percentage of patients in whom risk factor is documented over a two year period (if applicable)</i>
Weight	27.5%	
BMI	0%	
Smoking status	72.5%	
Blood pressure	53.8%	72.5%
Blood glucose	57.1%	72.5%
Lipid profile	38.5%	54.9%
ESR	95.6%	100%
CRP	92.3%	97.8%
DAS 28	20.9%	42.9%

The audit shows that ACPA was not measured or documented in 47.3% of rheumatoid arthritis patients. This requires improvement, especially in view of its prognostic significance.<sup>24</sup>

Thus from our audit we can conclude that the management of cardiovascular risk factors is reasonable when these have been identified. However, a better cardiovascular risk assessment of the rheumatoid arthritis patients would enable the identification of risk factors that could then be treated to help decrease the patients' morbidity and mortality from cardiovascular disease. This could be done by introducing a proforma (including cardiovascular risk factors and the calculation of the 10 year risk of fatal cardiovascular disease), that would be filled in on a yearly basis during the patients' visit at outpatients. This would serve to remind the clinician of the current recommendations and ensure that the cardiovascular risk factors are monitored and documented.

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## Vale Jiří Rondiak - 1934 – 2013

Albert Farrugia



Jiří Rondiak, an eminent Czech physician and specialist in blood transfusion died in September 2013 after a long illness. Rondiak was born in 1934 in Hořice v Podkrkonoší, a small East Bohemian town where his father was a renowned and loved general medical practitioner who died when Jiří was young, thus increasing his interest in the study of medicine. Over 1952 – 1959 he studied at the Medical Faculty of Charles' University in Prague and over 1959 – 1960 he worked at the Dept. of internal medicine in Hořice, and initially intended to specialize in obstetrics until he was impeded by a physical injury. Obstetrics' loss was transfusion's gain and in 1960 he started working at the Blood Bank of the Faculty Hospital in Hradec Králové, where he passed board examinations in blood banking and also underwent the Tropical medicine course of Ministry of Health of the Czech Republic. By 1977 he had been appointed head of the Blood Bank of the Faculty Hospital in Hradec Králové and was the Chief Blood transfusion specialist for the East Bohemian region, holding these posts until 2002 and to the 1990's respectively, responsible for the performance of the blood banks in the whole region. His achievements in his home environment included the building and continuous improvement of the transfusion service, including the challenges of infectious agents in the 1980s-90s and the establishment of one of the first plasmapheresis centres in the country as the Czech Republic emerged from the Russian-domination era and moved towards self sufficiency in blood products. His interests also included the HLA system and the stem cell area, in which he collaborated and published internationally.

Rondiak's eminence at home led to him engaging in several projects outside his country and he contributed to the development of blood services in Zambia, Malta and Yemen over the 1970s to the late 1980s. In Malta, he was one of a number of Czech specialists who helped the health service during the period 1979-82. In September 1979, as a young science graduate from the university of Malta I joined the blood transfusion unit of the Department of Pathology in Saint Luke's Hospital. It was there that I met Jiří who was trying to introduce improvements in a very basic and primitive service, and a partnership was born. It is no exaggeration to say that Jiří became my first professional mentor and was responsible, for better or for worse, for initiating my career. During his tenure, we initialized all the improvements in laboratory methods, donor screening and component production which led to a route of continuous progress and underpins

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the system today. Jiří worked tirelessly, as he told me frequently, to "leave something" behind him when he left. He certainly did, as he oversaw the transfer of the unit for two rooms in the pathology (out patients) corridor to the old nursing sisters house. He left this mission in 1982 and I returned to Malta in 1984 from my studies in the UK to continue his work with other Czech colleagues including Vladimír Veselý and Jan Pintera, all fine transfusionists who also contributed greatly to the development of the Maltese service.

Over the years since then, I'm pleased to have met Jiří several times in the international transfusion circuit after the changes in Eastern Europe led to travel restrictions being lifted. I continued my friendship with him, and in 2006 was honored with his presence in the audience when I spoke at an international plasma products conference in Prague. Seeing my old friend in the front row much affected me, and I made a few spontaneous remarks recognizing him and his fine country, and found myself needing to compose myself as I saw Jiří's clear emotion. Afterwards we walked around Prague for over three hours, and finished with dinner with other Czech colleagues shown in the accompanying picture.

***Caption:*** Lenka Walterova, Albert Farrugia, Jiří Rondiak and Petr Turek enjoy a meal in Prague, March 2006.



I heard that he had suffered a stroke in September 2012 when I was in Prague again in October 2012 speaking at a haemophilia meeting. Unfortunately he was unable to receive visitors. A year later the news of his death in September 2013 was communicated to me by our mutual friend Lenka Walterova. He is survived by his wife and daughter, both physicians.



# Dr. Norman Griscti Soler - 1942 - 2014

Daniel Griscti Soler



Dr. Norman Griscti Soler, 71, of Springfield Illinois passed away peacefully at Memorial Medical Center on January 27, 2014.

Dr. Soler was born in Malta in 1942, to loving parents Frank and May Griscti Soler. He was the eldest of five children – Claudia, Albert, Anthony, and Patrick.

Dr. Soler qualified as a doctor in 1964 in Malta at the age of 22. In 1967, he was awarded a Commonwealth Scholarship and moved to England as a senior registrar in medicine, specializing in Diabetes, at the General Hospital and Queen Elizabeth Hospital in Birmingham. In particular, he focused on diabetic pregnancy. In Birmingham, Dr. Soler met his beloved wife, Dr. Susan Soler, and in 1977, together with their two young sons, Richard and John, they accepted an opportunity to move to United States and Springfield Illinois, where Dr. Soler became a Professor of Medicine, Director of Medicine Clerkship, and Chief of Endocrinology at Southern Illinois University School of Medicine in Springfield Illinois. Shortly thereafter, their daughter, Kate, was born.

In 1989, Dr. Soler established the Springfield Diabetes and Endocrine Centre (SDEC) where he was Medical Director and Director of Research until his retirement last year. Over the 24 years until his retirement, he led the SDEC to become a leading national center for diabetes care and research and one of the largest endocrine practices in the U.S., having over 5000 active patients in its database. He conducted research and clinical trials for virtually every pharmaceutical company involved in diabetes care. Rarely did a product make it to market that he had not already tested and become familiar with. A few years ago, the pharmaceutical giant Eli Lilly recognized and celebrated SDEC's excellent long-term clinical outcomes in the treatment of type 1 diabetes. The SDEC continues today as an affiliate of HSHS Medical Group.

Dr. Soler became a member of the Royal College of Physicians (London, 1969); earned his Ph.D. with a thesis on Diabetes in Pregnancy (Birmingham 1970); and was fully accredited by the Royal College of Physicians as a specialist in Endocrinology and Diabetes in 1977. Other professional memberships included the American Association of Clinical Endocrinology, American Diabetes Association, Obesity Research Network, American Medical Association, and the Illinois State Medical Society.

Dr. Soler has conducted over 100 research projects throughout his career. Besides caring for his patients who came from all over downstate Illinois, he was passionate about mentoring and teaching others, lecturing extensively in England and other European countries, as well as in the U.S., on a variety of topics related to diabetes and obesity.

Dr. Soler was preceded in death by his parents, Frank and May Griscti Soler. Dr. Soler is survived by his beloved wife, Dr. Susan Soler of Springfield; three loving children, Richard (Rini) Soler, John Soler, and Kate (Dave) Darneille, and his grandson, Pano; his brothers, Albert (Kathleen) Griscti Soler, Anthony (Carmelina) Griscti Soler, Patrick (Odette) Griscti Soler; his sister Claudia (Godfrey) Sant; and many nieces and nephews. He will be dearly missed by his loving family, his SDEC family, his medical colleagues, and his many patients.

Dear Lord grant him eternal rest. Amen.