The Independent Medical Expert Group (IMEG)

Report and recommendations on medical and scientific aspects of the Armed Forces Compensation Scheme

March 2015

Topic 4 – Outcome after traumatic extremity amputation

A. Non cardiovascular effects

1. Since the introduction of the AFCS, we have been continuously involved in conflict; even so the majority of claims and awards under the Scheme are for non-combat related injuries due to physical and adventure training and sport.

2. The AFCS is an individual jurisdiction which makes awards where on balance of probabilities claimed injuries and disorders are caused by service. The Scheme pays particular attention to the effects on function rather than simply diagnosis and aims to make awards full and final as early as possible. In that way claimants, especially the most seriously injured, may have early financial certainty and be able to focus on recovery and where possible, reintegration into families and community including paid employment. Article 5 of the AFCS Order (2011) sets out how descriptors are to be interpreted. A descriptor is to be construed as encompassing the expected effects of the primary injury and its appropriate clinical management, short of a discrete diagnosable disorder, including, but not limited to:

> Pain and suffering due to the primary injury, the effect of operative intervention including pain, discomfort and scarring; the effects of therapeutic drug treatment; the use of appropriate aids and appliances and associated psychological effects.

3. Where a diagnosable disorder is consequential to the primary injury a separate stand-alone award will be considered.

4. An important function of IMEG is to ensure that the descriptors and associated awards for the various categories of injuries reflect contemporary medical understanding and best practice treatment and that horizontal and vertical equity is maintained. Horizontal equity refers to the need for different categories of injury with similar functional effects to attract similar award levels. Vertical equity means that within a single injury category, the award level should increase appropriately with injury severity and functional compromise. For the first report (January 2011) IMEG investigated relativities for upper and lower limb amputations, recommending a revision to the previously held position in UK public no fault compensation schemes that upper and lower limb loss should be considered precisely equivalent. Amongst the casualties of 20th century wars and industrial accidents, amputees were the most seriously injured survivors with the highest statutory assessments and awards. Assessments in UK public schemes are in a treated state and take account of suitable aids. An issue raised recently with IMEG is whether the functional impact of recent advances in prosthetics should lead to downward revision of the awards for lower limb amputation.

5. AFCS awards aim to be full and final taking account of the long-term functional effect of injuries and disorders. Understanding of the impact of current digitised prosthetics and new rehabilitation approaches will become available only many years from now, following major longitudinal study. For the present we are dependent on the extant published literature. This paper is informed by review of the literature and considers the effects of lower limb amputation other than cardiovascular.

6. In the military context, extremity injuries have been an issue since at least the Great War. To-day lower limb amputations from roadside bombs or improvised explosive devices (IED) are the typical injuries of Iraq and Afghanistan. While survival from battlefield injuries in the Second World War was around 70%, with improved body armour, pre-hospitalization care and aeroevacuation that figure has now risen to almost 90%, in the recent Iraq conflict (1).

7. Upper limb amputations are usually more seriously disabling for the individual than the equivalent lower limb loss but because they are more common the overall impact of lower limb amputations on care and disability benefit costs etc. are much greater. Similarly, in Western societies, most amputations are for vascular disease, with traumatic amputations only accounting for about 10% of incidence but, occurring mainly in young people, the prevalence of traumatic amputation is much greater. A recent US figure quoted in the paper is 48% (2).

8. There is a significant literature dating back to the 1950s on the effects over time of upper and lower limb amputations in both the military and civilian contexts, including both vascular and traumatic causes of amputation. The military studies cover casualties from the Great War onwards and are mainly from US, UK, mainland Europe (including Finland, the Netherlands, Germany) and Israel. Although true longitudinal studies are rare, the literature and expert discussion that have informed this report provides overall evidence that, the effects of limb loss are serious and prolonged with need for continuing care (3) (4). In terms of recent combat related injuries there are, however, limitations. To- day's amputations are rarely isolated injuries, but part of complex multiple injury, caused by several mechanisms, often affecting different body zones. High energy trauma to the lower limbs disrupts almost all tissues and structures and there is high risk of fragmentation, contamination and infection. A major clinical challenge is the decision as to whether a limb is salvageable. To date despite extensive research no valid decision-making tool is available. Individual decisions based on overall evidence continue to be required.

Specific effects

9. Pain - Chronic pain is common following traumatic lower limb amputation. There are several types of pain and it can be long-lasting with psychological effects and adverse impact on function and employability. Phantom limb sensation is included here for completeness.

10. Phantom limb sensation occurs early in almost all traumatic lower limb amputees and is regarded as normal. It is the sensation that the amputated part is still present, or the feeling that the missing part is still moving or able to adopt certain postures, sometimes with associated itching or tingling. These sensations are not themselves painful, and rarely pose any clinical problem (5) (6). Over time there is typically gradual shrinkage of the phantom limb (telescoping), so that in the case of lower limb amputation the foot may feel as if it is located within the stump.

11. Phantom Limb Pain (PLP) occurs in 60 to 80% of amputees regardless of reason for amputation, age at amputation, number or level of amputation, though pre-amputation pain increases the risk of development of PLP (6) (7). PLP is neuropathic in type, and not yet fully understood. It is often intermittent, frequently occurs in severe paroxysms and, over time, the frequency and intensity of the pain usually lessens. While in amputees overall, severe PLP is reported to persist life-long in 5 to 10% of cases (6), in a study of British military veterans, the proportion with persistent PLP of varying severity was about 50% (8). Functional Magnetic Resonance Imaging (MRI) has now shown that changes in the central nervous system may occur post amputation and in those with PLP (9). These include a shift in cortical representation of

neighbouring anatomical areas and structures into the cortical amputation zone. For example with upper limb loss, mouth and face areas which are situated close to the part of the cerebral cortex concerned with upper limb function move into the arm area. As a result chewing or blinking, touching the face or nose etc. can elicit PLP (10). These changes suggest that PLP might diminish if these cortical effects can be reduced or reversed and normality restored. Mirror therapy, motor imagery and sensory discrimination have now shown some success at reducing or abolishing PLP (11). These are areas of active study. Medical treatment of PLP is unsatisfactory. There is limited and inconsistent evidence from controlled clinical trials of some degree of effective pain control with tricyclic antidepressants, gabapentin, morphine and ketamine (6).

12. Stump pain (residual limb pain) is pain in the stump, often extending proximally in the limb above the level of the amputation itself. Mechanical stimulation of the stump, for example by a prosthesis, may provoke stump pain and phantom limb sensations, and in some amputees may trigger episodes of PLP (6). Amputees often find it difficult to separate stump pain and PLP and the two are strongly correlated. In one study of 648 amputees, stump pain was present in 61% of amputees with PLP but in only 39% of those without PLP (12). The prevalence of persistent stump pain varies considerably in published series, but is greater in those with traumatic amputations. Overall, stump pain persists in about 68% of all amputees and is severe in about 14% (6). Stump pain can be related to neural factors, particularly neuromas that form on major severed limb nerves, and which may be irritated by mechanical stimulation, notably by prostheses (6). It may also occur where there are traumatic or surgical scars, soft tissue damage or problems with muscle reconstruction or flaps. In general the non- neural causes can be treated successfully (13). Treatment of the neuropathic components of stump pain includes topical local anaesthetic and transcutaneous electrical stimulation, and systemic drug treatment. Clinical trials lend some support to the use of anti-depressants, some anticonvulsants, and opioids (14).

13. Heterotopic Ossification (HO) - Another cause of residual limb pain seen in the recent conflicts in high energy traumatic injury which leads to amputation, especially where the mechanism of injury is blast, is heterotopic ossification, is the formation of bone out with the skeleton (15). The causes of HO are poorly understood and multifactorial. HO also occurs in other circumstances. As well as very rare genetic causes, such as fibro dysplasia ossificans progressiva, it can occur in relation to burns, hip and elbow fractures, especially those requiring surgery, and where wounds are closed through the level of injury; total hip arthroplasty and traumatic spinal cord and brain injury. In the military context the most common situation is combat related blast damage. Bone in HO is formed at a much faster rate than normal and is very active metabolically. In a recent US series of combat related amputations 63% of residual limbs had radiographic HO (16). Many patients had no symptoms; in some, pain was relieved by manipulation of the prosthesis, but 25 required surgical excision of the bone. This produced good symptomatic effect, reduction in pain and low recurrence of bone formation up to 12 months follow-up.

14. Although, HO was known as early as the American Civil War and reported in successive wars and in civilian practice, the fact that there is little discussion of the condition in the literature suggests it was rarely clinically problematic. In terms of the Iraq and Afghanistan series quoted above, the occurrence of HO in amputated limbs was predicted by the fact that blast injury had led to the amputation and that the amputation level was in the zone of the initial injury. Zone of injury, but not blast mechanism of injury also correlated with the degree of HO. In this population, as the authors point out, other factors such as possible occult mild traumatic brain injury (mTBI) cannot be completely ruled out as influencing the development of HO.

15. In terms of treatment of HO complicating amputation, historically conservative treatment with modification of activity and prosthesis alteration was followed by a waiting period to permit

maturation of the HO bone. There is no evidence of the efficacy of such an approach and in an amputee population prolonged inactivity potentially delays mobilisation and rehabilitation. The current US military treatment of traumatic amputation–related HO is to proceed with surgical excision should conservative management and prosthesis modification fail to resolve the problem quickly. The symptomatic and functional results of surgical excision following traumatic and combat related amputation are reported to have low recurrence, decreased medication requirement and low complication rate (16). Although full evaluation has not been carried out in any context.

16. Prophylaxis of HO has been studied in joint replacement surgery. Primary preventive measures (i.e. to prevent initial development of HO) involve non-steroidal anti-inflammatory drugs (NSAID) and local radiotherapy, used singly but with some evidence of a synergistic effect if both are used together. That is standard practice after elective total hip arthroplasty and operative treatment of acetabular and elbow fractures. These measures are not used in US military practice in acute combat trauma because the amputations are so often a part of multiple critical injuries affecting several body zones.

17. Development of HO in a small UK combat related amputee population was compared with the US group above (17). The overall prevalence of HO and its severity in the two groups was similar but none of the UK patients required excision of symptomatic lesions. The presence of HO in UK amputees was not predicted by zone of injury but did correlate with traumatic brain injury, Injury Severity Score (ISS) and use of topical negative pressure wound treatment.

18. Back and joint pain - Back pain is common in the general community and a cross sectional survey of 255 amputees, six months or more post amputation showed more than half complaining of low back pain. Most reported pain intermittently, describing it as mild to moderate and not interfering with function. About 25% described significant interference with function (18). Back pain has been especially common after traumatic amputation (13). Studies are inconsistent, but there is often some relation with amputation site and level, back pain being more common with above knee amputation. Biomechanical change, such as altered gait and energy use when using a prosthesis, and myofascial changes may be risk factors and pain can also occur in the remaining joints of the residual limb or in the unaffected limb (19). Pain in the opposite knee occurs in more than half of lower limb amputees and is more common in above knee compared with below knee cases. Residual limb knee pain is uncommon in transtibial amputees (20). Prosthetic factors such as material, weight and shape, may be relevant and it will be important to establish whether the 21st century prosthetics, usually lighter and with different anchoring systems make a difference.

19. Energy cost of walking - A number of early studies investigated the energy cost of walking in amputees, but generally the studies involved small numbers, looked at only one level of amputation or speed of walking at a single time point after amputation. A more definitive study in 1976 compared the energy cost of prosthetic walking in 70 amputees with unilateral traumatic and vascular amputations at various levels (21). These were compared with each other and normal age sex-matched controls. Speed of walking and energy expenditure varied with amputation level (22). Vascular amputees walked more slowly than traumatic amputees in the main because of their greater age. The true net energy cost of walking measured as oxygen uptake per metre showed a clear effect of amputation level. This will also be affected by type of prosthesis.

20. Skin disorders – hyperhidrosis (increased sweating) is an almost universal problem in amputees with other skin disorders which can adversely impact quality of life from skin adhesion to bone, folliculitis, contact dermatitis and skin ulcers (23). Lower limb amputation sites, especially transtibial, can develop painful bursae, due to inadequate myodesis i.e. stabilisation of muscle distal to the amputation by suturing muscle or tendon to bone so that soft tissue moves directly over the

tibia. Bursae can also be caused by poorly fitting prostheses. Bursae and bursitis are usually successfully treatable conservatively but may require surgery (24).

21. Psychological disorders - The emotional response to traumatic loss of a limb follows the usual pattern of bereavement reactions with grief, disbelief, despondency, anger followed by acceptance and then sadness and despair. In the military context survivor guilt can also be present. Against this background, formal psychiatric disorders are not inevitable but are common. These include disturbances of mood, adjustment, post-traumatic stress disorder and body image problems (25). The extent of psychological problems depends on issues related to the injury, the amputation and the extent of post-operative rehabilitation (26) as well as factors unrelated to these (27). Depression and anxiety are common in the.

19. first two years after amputation and then reduce in prevalence; body image concerns may persist (26). A good psychological outcome is associated with the time elapsed since amputation, social support, premorbid resilience, satisfaction with the prosthesis, a lower anatomical level of amputation, and less phantom and stump pain (28) (26).

22. These psychological reactions are found in civilian and military populations although in different studies there is a range of incidence and prevalence. It is important to be alert to the possible development of psychological symptoms and illness, perhaps years after the original injury and as the person ages. A large study of 796 mainly male UK service veterans, (mean (SD) age of 74 (12), range 26 – 92,) who had lost a lower limb a mean (SD) of 43 (21) years previously, used a hierarchical regression analysis to investigate the associations of psychological distress (29). They confirmed the importance of time elapsed since amputation predicting better adjustment, but also found that coping styles were a strong association of outcome, with fear avoidance being most strongly associated with a poor outcome; problem solving and seeking social support were associated with a better outcome. These findings support the value of treatments such as cognitive behaviour therapy.

23. There is limited research into the psychological sequelae of upper limb amputation, but a small case control study suggested that this is associated with more depression and Post Traumatic Stress Disorder (PTSD) than lower limb amputation (30).

24. Sexual and psychosexual problems are most common after genital injury but one would anticipate limitations in sexual activities in some amputees. In traumatic amputation, difficulty may result from physical limitation or pain or negative self-image. A recent Dutch review confirmed that the literature is sparse with studies of small numbers, using different terminology and outcomes, making comparisons difficult. Overall, studies show varying levels of dissatisfaction with sexual function; there is some evidence that being married or having a partner is associated with fewer problems. It was also noted that little support or treatment is provided and the authors recommended routine periodic enquiry on sexual function in amputees (31).

25. A number of studies have assessed physical and mental outcomes using self-report measures such as SF 36 (32) comparing amputees with a control population. Results suggest that below knee amputation is not associated with adverse mental health outcomes. Mental and emotional health was significantly worse with transfemoral traumatic amputation, alone or accompanied by another significant injury, while following below knee amputations this was only recorded where there was accompanying severe injury (28).

26. Employability – For most military amputees, who are young people with a disability but in most cases without continuing illness, the aim of medical care and rehabilitation is more than a

prosthesis to allow them the minimums of life. An important goal, to achieve high levels of physical and psychosocial well-being wherever possible, is successful integration into civilian paid work. Unemployment has adverse effects on physical and mental health and evidence is beginning to accumulate that paid employment, especially full time work, has a positive effect on health and well-being (33).

27. There is a considerable international literature on the relationship between traumatic amputation (civilian and military) and subsequent employment, but the findings are diverse and often appear contradictory. Studies differ markedly in size and power; whether they are looking at upper or lower limb loss; the date of amputation and length of study follow-up; and the presence of other injuries. While international best practice clinical management of amputation is broadly similar, there are wider influences, at least as important, to successful job integration, beyond the control of clinicians, support workers and the patients themselves. These include economic climate, availability and type of social support and vocational rehabilitation arrangements in different countries, societal attitude to disability and employer responsibility for disabled workers.

28. Employability studies in amputees are almost all cross sectional in design; case selection is often subject to bias and in many series there are no controls. A particular omission is the absence of an adequately powered longitudinal study that will allow exploration of issues such as how long people remain in jobs; what leads to change of job or becoming unemployed; and if and how these issues might be addressed.

29. Individual patient factors identified in the present literature as influencing employability in amputees include, age at amputation, pre injury skills and training, the presence of associated injuries, residual limb length, prosthetic fit and comfort and number of hours worn per day and mobility (34). Other factors include social support and disability vocational rehabilitation systems and economic conditions.

30. There are limits to the relevance of existing amputee employability studies for to-day's military amputees and future civilian work. A major factor is the changing nature of UK employment during the last thirty years. The reduction in unskilled industrial employments has been balanced by an increased number of jobs in the service sector and jobs requiring high levels of skill and training. Digitisation has meant fewer ancillary / support jobs and there are no longer protected employments for people with disability. In addition, worker requirements and aspirations for high quality jobs have changed. Studies from US and Europe after the Second World War in general reported high levels of long term civilian employment for both upper and lower limb amputees, no matter the level, which included heavy work such as farming and fishing (35). The numbers who "return to work" in the individual studies is variable. However most published studies have short follow-up and contain little detailed information on job content, changes of job over time, whether work is full-time or part-time and what modifications have been made to workplace access or work station. There is also rarely comment on work pattern, or what help / support is provided by other workers.

31. Most studies have found that the average time to return to work for a person with a single amputation is at least a year (2). The reasons for this include the need for job re-training after medical rehabilitation. Civilian studies have also found that when people are not at work for a long period, in addition to financial detriment, they can lose touch with colleagues and involvement with the world of work. This in turn can have a negative impact on self-esteem, confidence and mental health and further delay return to work. The nature and ethos of military life and the fact that salary is maintained throughout medical downgrading regardless of duration, means that these may be less prominent issues for the military, while in service.

32. In most series, amputees return to a physically less demanding job than previously but many are able to work full-time and long term. Where people try to return to demanding physically active jobs, including their own pre injury job, outcomes are less successful (35). In some but not all studies there is a relation between successful return to work and level of amputation (36). In the 2003 study of 46 Vietnam trans-femoral amputees, followed up for approximately 28 years after amputation, over 80% had been employed on average more than 20 years (28). The paper however provides no information on the range of jobs or actual functions or tasks involved or whether people remained in the same job throughout.

33. Published studies rarely report on amputees' perspectives and to date there are few studies of microprocessor controlled prosthetics. A small study of eight civilian patients with trans-femoral amputation looked at both of these (37). All eight had about twenty years use of a prosthesis, with an average of 21 months using a microprocessor – controlled prosthetic knee joint. The study looked at personal satisfaction with the prosthesis, functional independence in role performance and body image. A significant relationship was found between use of the prosthesis, functional role performance and self-efficacy, social integration and personal relationships, with an inverse relation between use of a digitised prosthesis and psychological distress. The amputees reported improvement in walking, climbing stairs, sports and recreation, work and social activity. They had an improved body image believing their gait to be more normal, with greater stability and less risk of falls. The study has limits but is encouraging and provides a reminder that successful prosthetic fitting and rehabilitation has the potential to transform lives. Survival of extremity trauma resulting in amputation or retention and reconstruction of a severely damaged limb, are hallmarks of the recent conflicts owing much to advances in forward surgery, aeroevacuation, anaesthesiology and digital processor techniques. There remain many gaps in understanding and to ensure sustainable solutions, IMEG strongly recommends urgent setting up of international collaborative studies, jointly by Defence, Health Departments and academia.

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B. Cardiovascular effects

1. Evidence suggesting that amputees might be at higher risk for cardiovascular diseases emerged as Great War amputee veterans began to age and since the 1940s a significant literature has emerged. The impact of to-day's new surgical techniques, the revolution in digitised prosthetics on the long term effects of amputation, with recent understanding of cardiovascular risk factors and the benefits of modern prevention measures, will only become apparent in the future following suitable cohort prospective study.

2. For the present, evidence to inform medical aspects of AFCS policy must be based on the literature to date. Limitations of some of the early studies on possible cardiovascular effects in amputees include study design, small numbers, omission of or inadequate choice of control groups. Studies variously consider mortality, morbidity and cardiovascular risk factors with often inconsistent results. In this regard it is important to recall the very different approaches of some countries to post amputation treatment and rehabilitation, including in relation to atherogenesis, diet and life style. This paper aims to provide a brief overview of key papers and evidence from the 1950's onwards.

3. There were an estimated 27,000 UK amputees as result of the Great War and in 1954 Sir Ernest Rock Carling was invited by the then Chief Medical Officer, Ministry of Pensions and National Insurance, to consider cardiovascular disorders and mortality in amputees. Carling's committee compared mortality of lower limb amputees with that of veterans with seriously wounded, but retained, lower limbs and the general population. In their conclusion the Committee advised the Chief Medical Officer:-

> "Limb amputations and the subsequent wearing of a prosthesis do not, in time, produce effects on the body as a whole which may initiate, or aggravate, cardiovascular disorders to any significant extent.
>
> There is no material difference between the mortality rates of amputees, by reason of amputation and that of the corresponding rates for pensioners who have suffered wounds not leading to amputation. Such excess as there is in both classes over that in the general population is quite small." (1)

4. Following the Second World War, Finland had about 5,000 traumatic amputees, the majority being lower limb and below knee. The average age at amputation was 18 years. In the early 1960s, twenty years after injury, a number of descriptive and other studies were carried out.

5. Solonen (2) in 1965 reported that, in general, the men were in good condition. More overweight persons were found in the lower limb amputee group especially amongst those with high amputations. This finding was at variance with a study in 1956 (3) of 1,100 mid-thigh amputees who did not have an increased tendency to be overweight. Similarly, Loos in 1957 (4) suggested no difference in numbers of overweight persons amongst lower limb amputees compared with the general population. The Solonen study also looked at resting ECGs and found 7% to be abnormal, a similar number to normal controls. For all upper or lower limb amputees at any level the prevalence of hypertension was similar to controls. A further study by Meyeringh et al (5) in contrast found that obese amputees had higher blood pressure than those of normal body weight.

6. In 1969 George Bakalim observed that death rates amongst Finnish Second World War amputees had been rising steadily in the previous ten years. His study considered the main certified causes of death in a group of 4,782 amputees from 1946 until the end of 1965. The age distribution of the Finnish male population and that of the amputees was very different and so an equivalent theoretical comparator population was constructed using two methods. Overall death rates from all causes in the amputee and control populations were similar but when cerebrovascular and cardiovascular causes were investigated separately, the death rates in the amputees were significantly higher than in the comparator population. For cerebrovascular deaths overall, the numbers of deaths in amputees was 71% higher than expected, while for cardiac deaths the excess was 63%. For both types of disorder the excess mortality was highest in the lower age groups. Suicide rates were also increased (40%) particularly in the immediate aftermath of the war and again amongst younger amputees (6).

7. Two factors emerge as possible explanations for these findings. The category "cardiovascular diseases" included myocardial infarction, pulmonary infarction, peripheral embolism, cardiac failure and atherosclerosis. Many deaths occurred in younger amputees and in the immediate post war period, including when they were still hospitalized. The mortality from cardiovascular diseases in the 25 - 44 year age group was almost 200% higher than expected when compared with the control general population group. The causes of death were thought likely to include thromboembolic disease. A second issue is the control population. Military personnel even in conscripted service are a selected population on average fitter, physically and mentally, than the general population and it would have been informative to have had a military group comparator.

8. The 1976 Hrubec Ryder US report, in response to Congressional decree addressed these issues (7). The study sample was derived from army hospitalizations during 1944 - 45 yielding over 12,000 potential subjects. Three main groups were assembled for evaluation, from all military personnel.

i) Proximal amputation i.e. amputation at or above knee and amputation at or above elbow

ii) Disfigurement i.e. disfigurement other than head, face or skull or disfiguring scar adherent / painful

iii) Distal amputation i.e. loss of part of hand or foot

9. There were about 4,000 personnel in the first two groups and almost 3,000 distal amputations. The groups were matched by age and length of service and followed up from January 1946 until April 1977. Mortality rates for the groups for various causes of death were computed over the period and compared with the US Standard Mortality Rate (SMR) for 1976.

- The overall death rates amongst disfigurement and distal amputations were less than that expected from the US general population.

- Differences in overall mortality between the proximal amputees and disfigurement groups appeared early in the follow-up period and remained fairly constant over the period.

- The early all cause mortality of both proximal and distal amputees was similar to the US general normal population, but the mortality rate of the proximal group increased in comparison to US general normal population markedly with time.

- The distal group by contrast maintained its similarity to the general community rate throughout while the disfigurement group which at the outset had considerably lower overall mortality than the general population comparator eventually caught up.

10. Looking at specific causes of death, in particular cardiovascular diseases in the early follow-up period, mortality rates were similar in proximal and distal amputees and only a little higher than in the disfigurement or US normal control population. Over time the difference increased, primarily due to increased cardiovascular mortality amongst the proximal amputees.

11. In the disfigurement group, the mortality rate was constant over time, and slightly lower than expected as compared to the general population, while amongst the distal amputees cardiovascular death rates eventually moved upwards towards that of the general community.

12. Over the entire follow-up period, age and length of service matched death rates from all causes for proximal amputees were 1.4 times higher than those with disfigurement and 1.3 times more likely than for distal amputees. Cardiovascular mortality was highest in bilateral above knee amputees being 3.5 times higher than the group with disfigurement.

13. Amongst the groups, neither age at injury nor the presence of complicating wound infection / osteomyelitis / gas gangrene / or sub-acute bacterial endocarditis affected mortality.

14. The study did not investigate possible reasons for the findings but in the conclusion section, the authors discuss the then known coronary risk factors including

i) non modifiable risk factors of age sex and family history:

ii) modifiable risk factors listed as serum lipids, diet, hypertension, cigarette smoking and diabetes mellitus and

iii) minor modifiable risk factors obesity: sedentary life style, personality type and psychosocial tension.

15. None of these factors was expressly addressed in the study but the authors pointed out that since there was no increased risk of deaths in any of the cohorts from lung cancer, this suggested that cigarette smoking was not a confounder. They had no information on lipid levels or the presence of abnormal glucose metabolism or frank diabetes mellitus. They in fact remarked that at that date there were no published studies on diabetes and traumatic amputation.

16. They concluded by suggesting that the increased rates of cardiovascular disease in high-level lower limb amputees might be due to the associated sedentary life style and risk of chronic psychosocial / emotional stress.

17. More recently an Iranian cross sectional study investigated cardiovascular risk factors in 327 Iranian bilateral lower limb amputee veterans of the Iran-Iraq war followed up twenty years post injury. The war lasted eight years with 11,000 combat related lower limb amputees of whom about 5% were bilateral (8).

18. There are limitations to this study: only 56% of those invited took part and comparisons were with the general Iranian population and based only on documentary data from earlier published studies. The average age at the time of injury was 20 years and 42 years at follow-up. Some 40% had had below knee amputations. Clinically the rates of cardiac symptomatic disease were similar to the general Iranian population. The study also looked at abdominal obesity, hypertension and hyperlipidaemia. 83% of the amputees had abdominal obesity compared with 14% of the general Iranian population, 32% smoked cigarettes, while that figure was 22% in the general population. There were also higher rates of hypertension (28% compared with 20%) and hyperlipidaemia, 37% compared with 19% in the general population.

19. A German cross sectional study of Second World War veterans compared them with veterans who had not lost a limb. They found an increased risk of abdominal aortic aneurysm in above knee amputees which they related to altered haemodynamics (unilateral flow reduction in the iliac artery) at the aortic bifurcation (9). This finding was not however confirmed in a later prospective study of German veteran amputees and controls which found similar rates of aortic aneurysm in both groups (10).

20. There is then a body of evidence which suggests that lower limb amputation, especially proximal amputation, is associated with an increased risk of cardiovascular disease. The mechanism of the observed increased rates of cardiovascular diseases remain unknown, but in the period since Hrubec Ryder a number of studies have explored the issues.

21. Insulin has been considered to have a possible role in atherogenesis for many years, especially in the obese or those with abnormal glucose metabolism. A role for insulin in cardiovascular disease in amputees was first proposed by Rose in 1986. This was in a small study originally designed to throw some light on the findings of the Hrubec Ryder report (7). In particular that increased cardiovascular mortality was greatest in bilateral above knee amputations and appeared early. The Rose study investigated cardiovascular disease and risk factors in 19 Vietnam veterans with bilateral above knee amputees (BAKA) (11) (12). These were compared with a group of 12 unilateral below elbow amputees (UBEA). 10 of the BAKA were hypertensive and 9 normotensive. One UBEA was a known hypertensive. Prior to injury and at entry to service the BAKA amputees were all taller and heavier than the UBEAs. There were no differences in age at injury, years since injury, race or years of education. None of the veterans in either group, had symptoms of coronary artery disease, ECG and exercise stress testing were also normal as were serum lipids.

22. The normotensive BAKA amputees and the normotensive UBEA had normal lean body mass while the hypertensive BAKA group who although big men had body weight at maturity within normal range but had become obese post injury. Weight gain was not universal but where present it was noted to have occurred in the first two years after service termination. It is of note from the wider literature e.g. Framingham and Manitoba studies (13) (14) that while obesity is not clearly linked to risk of atherosclerosis in older men it is a predictor of cardiovascular disease and death in men younger than 40.

23. The hypertensive obese BAKA group at the time of the study had abnormal glucose tolerance and were markedly hyperinsulinaemic in response to glucose challenge. The glucose levels did not fulfil the criteria for a diagnosis of pre-diabetes, but the increase in blood glucose in response to oral glucose load was very marked.

24. Another possible factor increasing the risk of coronary disease in BAKA is the fact that they are heavily dependent on their arms. Arm exercise is generally accepted as potentially hazardous to able bodied men with underlying ischaemic heart disease. Even static upper body exercise can increase heart rate, blood pressure and blood catecholamine levels. However training may overcome these effects to an extent and the BAKA in this study had levels of VO2 max equal to that of the control subjects using leg exercise.

25. Amongst conventional risk factors smoking cigarettes, blood lipid abnormality and decreased cardiovascular fitness were not different in the two groups, upper and lower limb amputees. The study concluded that the long term cardiac risks of amputation might relate to metabolic and haemodynamic sequelae of excessive weight gain in young men immobilized by loss of their lower limbs and over time having prolonged exposure to cardiovascular risk factors.

26. As well as hyperinsulinaemia, increased sympathetic activity has been associated with atherosclerotic cardiovascular disease and its risk factors. Following the Rose studies in 1995 an Israeli group published a report looking at the relation between insulin resistance and autonomic function in unilateral traumatic lower limb amputees (15). A difficulty in studying autonomic function is its measurement in a robust and repeatable way. This study used heart rate variability and plasma catecholamine levels.

27. The study compared life style, indices of autonomic function and cardiovascular disease risk

factors in 52 subjects and 53 controls. The subjects were male unilateral lower limb traumatic amputees aged 50 - 65 years who had been wounded between 1948 and 1974. Age matched controls were drawn from a nation wide longitudinal study on obesity, hypertension and glucose intolerance. Both groups had similar rates of ischaemic heart disease symptoms. The amputees were slightly younger (56 years compared with 59 years) and had lower calorie and fat consumption than controls. The two groups had similar levels of the conventional risk factors for ischaemic heart disease including blood pressure, lipids, physical activity, cigarette smoking, BMI etc.

28. The amputees had higher mean insulin at baseline (including after accounting for BMI, physical activity, diet, smoking). There was at base line a slight tendency to enhanced low and high frequency power of heart rate variability amongst amputees. During glucose tolerance test the amputees had significantly higher insulin levels than controls at all time points. Glucose levels were the same in the 2 groups i.e. the Insulin: Glucose ratio was raised. Insulin resistance in amputees was independent of risk factors such as obesity, hypertension etc.

29. This study differs from Rose's small Vietnam study in that hyperinsulinaemia is reported in unilateral amputees who are not obese, hyperlipidaemic or hypertensive. Part of the study's aim was to determine whether the insulin resistance in lower limb amputees was associated with abnormal autonomic function. The study unfortunately was unable to throw light on the sympathetic hypothesis. It would be expected that loss of a leg due to a war injury might be an ongoing emotional stressor. In turn emotional stress activates the sympathetic nervous system and the adrenomedullary system, whose hormones antagonize insulin effects. At rest autonomic activity in both control and amputee groups was similar. Heart rate variability and plasma catecholamine increased in both groups in response to oral glucose. Glucose load would be expected to trigger insulin release, in turn reducing glucose levels and stimulating adreno-medullary secretion.

30. At one and two hour after glucose ingestion plasma catecholamine levels were higher in amputees than in controls. These findings suggest that amputees in this study might then have increased sympatho neural responsiveness and / or reduced suppression of adrenomedullary secretion during glucose challenge.

31. In an extension of this study using the same control population, Modan et al (16) evaluated the 24 year mortality of 201 of the male unilateral traumatic lower limb amputees and compared them with 1,832 from the nationwide longitudinal national study (15) described at paragraph 26-28 inclusive above. Mortality was significantly higher in amputees than controls. The figures were 22% and 12 %. This was mainly due to cardiovascular deaths. When cardiovascular risk factors were looked at in the groups, matched by age and ethnicity the amputees had higher plasma insulin, both fasting and in response to glucose challenge and increased blood coagulation activity. No difference were found in clinical ischaemic heart disease symptoms or classical risk factors e.g. obesity, hypertension, lipoprotein, physical activity.

32. This study adds increased coagulability to the previously established factors, increased insulin resistance and autonomic activity function which might influence cardiovascular disease. The authors suggest, in conclusion, that hyperinsulinaemia and the other differences may not be secondary to changes in lifestyle, diet, decreased cardiac fitness or reduced active muscle tissue occurring as a result of the amputation but rather they are functions of the amputation itself.

33. A final paper from Israel (17) in 2008 adds psychosocial factors and haemodynamic alterations proximal to the amputation as further possible risk factors contributing to the observed increased rates of ischaemic heart disease in amputees, and points out that current cardiac risk

factors and algorithms for assessing risk typically account for no more than 50% of cardiovascular events, with many people suffering ischaemic symptoms or events having no conventional risk factors. Current algorithms still take no account of haemodynamic nor psychosocial factors. These omissions might have some bearing on the potentially underestimated cardiovascular risk in lower limb amputees.

34. In conclusion,

1) Although the evidence is not wholly consistent there is a growing body of evidence which suggests the risk of cardiovascular disease is increased, particularly in amputees with above knee amputations.

2) The mechanisms underlying this are unclear, but may relate to reduced exercise, obesity and hyperinsulinaemia.

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