Evaluate the evidence for and against the use of testosterone to extend lifespan

Background and introduction

Testosterone is a steroid hormone which was first isolated in 1935 (David, Dingemanse, Freud *et al*, 1935, cited by Freeman, Bloom, McGuire, 2001). It is secreted by the testes of males in large quantities and the ovaries of females in much smaller quantities. It is an anabolic, androgenic steroid which means it has both muscle building and masculinizing properties (Pope and Brower, 2005). In men, testosterone levels peak in early adulthood, then start to decrease by approximately 1-2% per year (Harman, Metter, Tobin *et al*, 2001). For example, at a median age of 40 years, Harman *et al* found that mean total testosterone levels peak at 470ng/dl, decreasing significantly to 350ng/dl at a median age of 85 years. Many of the adverse effects of aging including increased fat mass, low energy and impaired mobility in males, are thought to be caused by this decrease in testosterone levels (Harman, *et al*, 2001), and some evidence shows a correlation between low testosterone levels and a decreased lifespan (Hyde, Norman, Flicker, *et al*, 2012). Consequently, there has been a recent focus on testosterone treatment for males (Swerdloff and Wang, 2011). However, the topic of testosterone treatment is controversial, as some argue that testosterone treatment can actually increase risk factors for cardiac, respiratory and skin disorders (Corona, Rastrelli, Monami *et al*, 2011). This essay will evaluate the evidence for and against the use of testosterone to extend lifespan.

Evidence **for** the use of testosterone treatment

Low testosterone levels increasing the risk of cardiovascular disease and cancer

Low testosterone levels have been linked to an increased risk of cardiovascular disease (Hyde, *et al*, 2012). In fact, up to one in four men with cardiovascular disease have been found to have low testosterone levels (Jones, Nettleship, Kapoor, *et al* 2005). It is thought that these low testosterone levels increase the risk factors for the disease, including insulin resistance, obesity and type 2 diabetes (Hyde, *et al*, 2012). A study of 4249 participants provides evidence for this, as it was concluded that lower free testosterone levels were associated with an increased risk of death from cardiovascular disease (Hyde, *et al*, 2012). Cardiovascular disease is responsible for approximately one in three premature deaths in men (British Heart Foundation, 2012), reflecting the fact that low testosterone levels can indirectly reduce lifespan by increasing the risk of cardiovascular disease.

Low testosterone levels are also associated with an increased risk of cancer; prostate cancer in particular has been found to be more severe in men with low testosterone levels (Schatzl, Madersbacher, Thurridl *et al,* 2001). Statistics from 2010 show that over 10,000 males died prematurely from prostate cancer in the UK (Cancer research UK, 2012), and low testosterone levels may have a role in this.

Testosterone treatment to reduce cardiovascular disease risk and the adverse effects of aging

Testosterone treatment has been found to reduce risk factors for cardiovascular disease, including improving abdominal obesity and the lipid profile (Shabsigh, Katz, Yan, *et al,* 2005). In one study, 67 men with low testosterone levels were randomly allocated to 5mg testosterone treatment or placebo patches daily for one year. The body fat of the treatment group reduced from 26.3±5.8% to 24.6±6.5% (Kenny, Prestwood, Gruman, *et al* 2001). Many studies have found that obesity is an independent risk factor for cardiovascular disease, and increased mortality rates (Poirier, Giles, Bray, *et al*, 2006). A meta-analysis conducted in 2012 showed how testosterone treatment can reduce mortality from heart failure, which caused 17% of premature male deaths in 2010 (British Heart Foundation, 2012), by increasing mobility (Toma, McAlister, Coglianese *et al*, 2012). They found that patients treated with testosterone had improved exercise capacity, which reduces mortality rate and improves quality of life. Therefore there is evidence for a relationship between testosterone treatment and reduced cardiovascular disease, therefore extended lifespan, and reduced mortality from heart failure.

Approximately 30% of men aged 60 and over are thought to have low total testosterone levels (below 250 ng/dl))(Laughlin, Barrett-Connor and Bergstrom, 2008), which have been associated with adverse effects of aging, such as osteoporosis, and an increased risk of falls and hip fracture (Orwoll, Lambert, Marshall, *et al,* 2006). Hip fractures, for example, not only cause a level of disability, but can also cause increased mortality among the elderly (Chrischilles, Butler, Davis, *et al*, 1991). However the study conducted by Kenny, *et al* (2001) found that 5mg testosterone treatment daily can prevent bone loss at the femoral neck. The average gain in femoral neck bone mineral density in the treatment group was 0.3%, whereas the control group lost 1.6% over the year. This decrease in bone loss may reduce the likelihood of osteoporosis and hip fractures, and therefore extend lifespan.

Testosterone treatment to directly extend lifespan

One recent study has shown that testosterone treatment in men is directly related to an extension in lifespan. The study (Shores, Smith, Forsberg, 2012) included 1031 men with low total testosterone levels (250 ng/dl), 398 of these men having testosterone treatment. They found that the mortality in testosterone-treated men was less than half (10.3%) that of untreated men (20.7%) (P0.0001). Figure 1 compares the percentage survival in untreated men compared to treated controls. Overall, testosterone treatment was associated with a decreased risk of death. This is one of few studies that have shown a direct relationship between testosterone treatment and extended lifespan, however the results of this study must be considered tentatively. It was an observational study in a clinical setting, where subjects were not randomized to treatment. This means that there is a degree of bias as physicians may have only given testosterone treatment to men who were well enough, and therefore were more likely to survive anyway (Frederick, 2011). Consequently, one cannot determine whether testosterone was the cause of the lower death rate or just that the treated men were healthier.

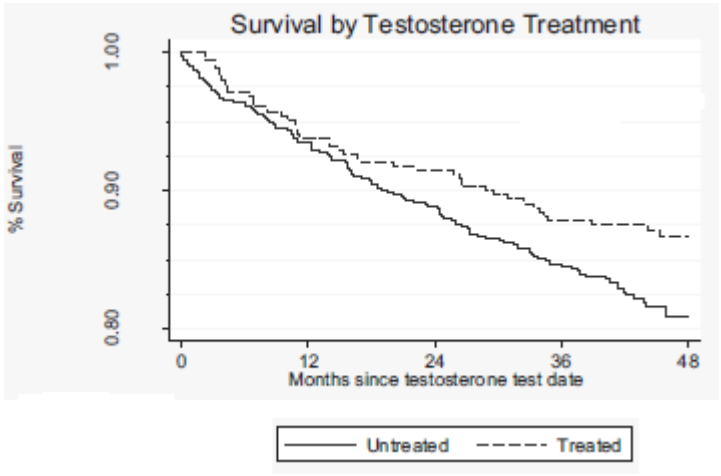

Figure. 1. A survival curve showing that testosterone treated men had a higher percentage survival than untreated men. For example after 36 months of testosterone treatment the percentage survival was 0.876 in the treated group compared to 0.850 in the untreated group (Shores, *et al,* 2012).

Evidence **against** the use of testosterone treatment

Increasing cardiovascular disease risk

Although some studies have found that testosterone treatment can increase lifespan, others have found the opposite of this. One recent study had to be terminated early due to a significantly higher number of cardiovascular events in the testosterone treated group (treatment with 100mg testosterone gel daily) compared with the placebo group (Basaria, Coviello and Travison, *et al,* 2012), as shown in figure 2. This randomized, double blind trial included men aged 65 years and over, who all had low total testosterone levels (between 100 and 350ng/dL) and limitations in mobility. Although there was found to be an increase in muscle mass and grip strength in the men, a greater number of participants in the testosterone group developed peripheral oedema, elevated blood pressure, stroke and arrhythmia. This was after adjustment for age, body mass, smoking status and many other factors, showing that it is likely that the testosterone treatment caused these adverse outcomes. Although it is not known if the same effects would have occurred in younger men treated with testosterone, these findings are a cause for concern, and cast doubt on how testosterone treatment affects lifespan.

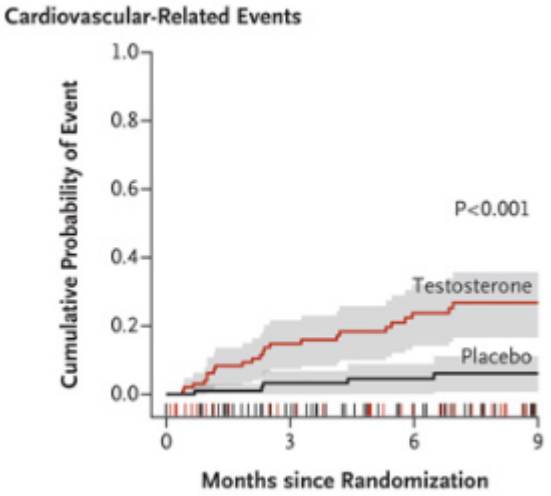

Figure.2. A graph to show the probability of the incidence of cardiovascular related events in the testosterone group compared to the placebo group (Basaria, *et al,* 2012).

The effects of high doses of testosterone

The effect of testosterone treatment varies depending on dose. Athletes have been known to take large doses of testosterone to increase muscle mass and strength, with the intention of trying to enhance performance (Kanayama, Hudson and Pope, 2008). Athletes have been known to take up to 5000mg of testosterone per week, which is up to 100 times greater than the amount of testosterone naturally produced by human testes (Reyes-Fuentes and Veldhuis, 1993, cited in Kanayama, *et al*, 2008). Administering these high doses long term has been found to increase the occurrence of cardiovascular events, for example dyslipidaemia and acceleration of the development of atherosclerosis (Bonetti, Tirelli, Catapano *et al,* 2007, cited in Kanayama, *et al*, 2008). It is these effects that are thought to be the cause of premature death in some young athletes due to them using large doses of testosterone in order to increase muscle mass (Di Paolo, Agozzino, Toni, *et al,* 2007). This raises the question of whether it is safe to administer testosterone to extend lifespan.

Testosterone administration

Another negative aspect of the use of testosterone to extend lifespan is that the administration involves many possible problems and risks (Rhoden and Morgentaler, 2007). Common administration methods include injection, or transdermal patches. Injection requires frequent hospital visits and can be painful, and patches often cause skin irritation. Testosterone treatment is currently used in the UK only on prescription for men with low testosterone levels, to improve wellbeing, quality of life and reduce the risk of osteoporosis (NHS foundation trust, 2012).

Conclusion

In conclusion, many studies have found that testosterone treatment can extend lifespan by reducing mortality from cardiovascular disease and cancer, and reduce the adverse effects of aging. However as this essay shows, the evidence is inconsistent and controversial. Some studies have shown that treatment with testosterone reduces lifespan, and increases the likelihood of cardiovascular related events. Trials in this subject are challenging as they are expensive and difficult to randomize (Frederick, 2011). For example the study conducted by Shores *et al* in 2012 was an observational study, therefore was not randomized, so there may have been some bias in who was chosen for testosterone treatment. Few trials are conducted over long periods of time, therefore the long term effects of testosterone treatment are unknown (Frederick, 2011), and it is these effects that are of clinical significance. Also the dose of testosterone is important; high doses can also cause cardiovascular events, so decreasing lifespan. The practicalities of testosterone treatment need to be considered, as methods of administration can cause discomfort.

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