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Review

Discriminating Between the Roles of Androgens and Estrogens in Cardiovascular Disease

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A B S T R A C T

Cardiovascular disease shows a distinct difference in incidence rates between men and women, a fact that has been known for many years. While initial theories supported that this could be attributed to the protective effect of estrogens in women, attempts to correlate endogenous estrogen levels with cardiovascular risk factors and the progression of atherosclerosis-related indexes indicate otherwise. Similarly, endogenous androgen levels seem to correlate with opposite effects in males and females, whereas exogenous treatment with either androgens or estrogens fails to correspond to scientific expectations entirely. A brief discussion of the merits and pitfalls of placing either estrogens or androgens alone at the root of the problem shows that current understanding is inadequate concerning this major anthropological issue, as it refers to the primary global mortality and morbidity cause.

Key words: *androgens, estrogens, sex, cardiovascular disease, atherosclerosis, cardiovascular risk factors*

Introduction

Cardiovascular episodes comprise an important cause of disability and mortality among adults. As such, they have been carefully observed and studied since the ancient times. The oldest description in fact dates back to 2000 years ago and has been attributed to Seneca, who gave a written account of a myocardial ischemia episode. Naturally, a lot has changed since that first account, but the anthropological and medical interest remains continuously high. One of the most notable observations made in relation to this field is the fact that sex seems to constitute a major risk factor, although the mechanism of this dimorphic effect is unclear.

Androgens versus Estrogens: Which One Should We Blame?

It is a well established fact that cardiovascular deaths show a predominantly higher rate in men than in women, a difference that remains consistent across 52 countries, despite a wide variety of environmental and socio-economic diversities[1]. Since this sex-specific protection of women persists, even after adjusting for any known risk factors, it was only natural to assume that, like with most other aspects of sexual dimorphism[2], androgens and estrogens should be, directly or indirectly, responsible[3]. Initially, however, only the supposedly beneficial effect of estrogens was taken into consideration. A more attentive inquiry into the distribution of cardiovascular events across various age groups failed to support this common belief. For instance, it is clearly evident that cardiovascular event rates are not affected by the onset of menopause, in the same way that other estrogen-dependent conditions are. In support of the latter case one might compare cardiovascular events to breast cancer death rates, whereby it becomes evident that there seems to be no threshold value for increased cardiovascular event incidence, reflecting the sudden deprival from estrogens that occurs in menopause[4] (Figure 1). On the contrary, the overall curve for cardiovascular deaths in women seems very similar to that in men with the sole exception of a five to ten years' period of delay[4,5] (Figure 2).

Given these observations, scientific interest slowly began to turn towards the, up until recently mostly neglected, androgens. An inspection of various prospective studies has shown that there seems to be no correlation between endogenous testosterone levels and adverse cardiovascular outcomes[5]. On the contrary, observational studies insist that men with a history of cardiovascular

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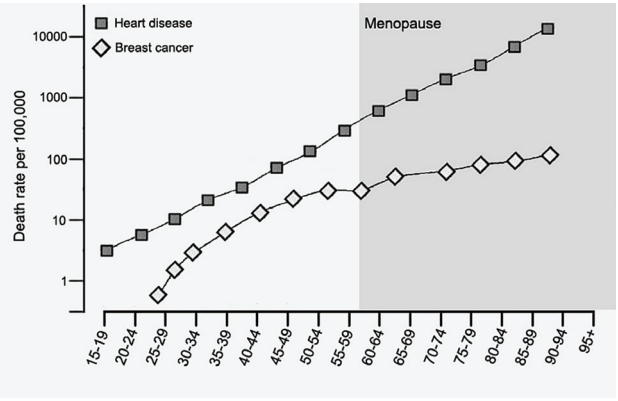

Fig. 1. Cardiovascular and breast cancer mortality rates on a logarithmic scale. Estrogen-dependent conditions, such as breast cancer, display a breaking point in mortality in the age group that corresponds to menopause, due to sudden estrogen deprivation. Cardiovascular mortality, however, fails to display any such changes, a fact that advocates against estrogens being the underlying mechanism for the differences in cardiovascular disease incidence between the two sexes. (Redrawn from the work of Liu[2]).

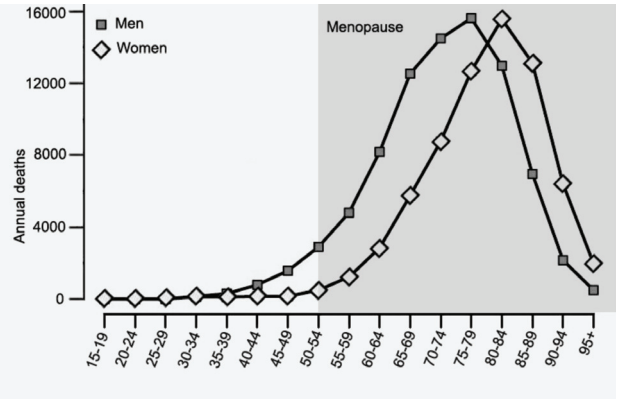

Fig. 2. Incidence of annual coronary deaths on a linear scale. The curve for coronary deaths in women is almost identical to that for men, with the sole exception of a five to ten years' worth of delay. Coronary deaths in women equal and then surpass those in men in later age groups. (Redrawn from the work of Tunstall-Pedoe[3]).

disease tend to display lower endogenous testosterone levels[6]. While this might be interpreted as a common result of many chronic disorders, the nature of this relationship remains unclear[7].

Furthermore, androgens seem to have a complex relationship with several proven risk factors for coronary heart disease (CHD). More interestingly, endogenous testosterone levels appear to have opposite effects in men and women, with regard to cardiovascular protection[5]. In particular, circulating testosterone levels have been positively correlated with HDL-C and inversely correlated with LDL-C, fibrinogen and plasminogen activator type 1 (PAI-1) serum levels in men. These inverse correlations seem to extend to body mass index, waist circumference, waist-to-hip ratio, amount of visceral fat and leptin, insulin and free fatty acid levels to a degree that can account for the above. However, in women, circulating testosterone displays a precisely opposite profile, barring us from reaching any definite conclusions as to the role that androgens may play in the progression of cardiovascular disease.

On the other hand, although more consistent in their behavior, estrogens do not seem to correspond to the role originally supposed for them either. Circulating estrogen levels seem to contribute towards a less favorable lipid profile in women[8,9] and the progression of atherosclerosis in men[10], as opposed to what one may have expected. Thus, the exact contribution of each type of sex steroids in cardiovascular disease progression remains debatable.

Estrogens: the HRT Paradox

Since its conception, hormone replacement therapy (HRT) was meant to prolong the protective effects of estrogens in women past the onset of menopause. Initially, this was considered to apply to the cardiovascular system as well. However, with the implementation of the first randomized controlled trials of its effects on cardiovascular disease rates, it became apparent that HRT was hardly as beneficial as clinicians had expected it (and hoped) to be. One particular trial showed an increase in acute coronary events among women with ischemic heart disease that underwent HRT[11], thus challenging the effects of HRT on women with an already present cardiovascular history. Subsequently, the Women's Health Initiative (WHI) randomized controlled trial showed an increase in CHD events and strokes among healthy women receiving HRT[12]. While this sort of evidence has yet to evict HRT from its current therapeutic indication for post-menopausal women, it has already been established that certain patient groups might benefit more by refraining from it, at least until the matter has been properly resolved.

Then again, if that is the case, then what prompted the initial popularity with which HRT was greeted? Looking back, an explanation seems to lie in the fact that this particular hypothesis was initially supported by case-control observational studies that reported lower cardiovascular event rates among women receiving HRT. A major limitation, however, is that those initial studies most likely ignored the selective recruitment of healthier and wealthier women that could afford and were more likely to be well-enough informed in order to require about or receive HRT[3]. This detail highlights the importance of designing and implementing well-structured, randomized trials before establishing therapeutic policies.

As a matter of fact, the deleterious effects of estrogens on the cardiovascular system had already been long known with regard to their administration to men, since observational data made among prostate cancer patients treated with estrogens date back to the 1960s[13]. In other words, it becomes apparent that exogenous administration of estrogens fails to meet therapeutic expectations and seems in fact to bring about the opposite effect on both sexes.

Androgens: Special Population Groups

While estrogen treatment has become more commonplace with the form of hormone replacement treatment, there are certain limitations in the study of the effects of artificially altered androgen levels. For this purpose, special population groups have been used in the past. These included normal men after castration[3], female-to-male (F2M) transsexuals that are treated with testosterone[3] and women with polycystic ovaries syndrome (PCOS)[5]. Castrated men, especially those undergoing castration at an early age, are consistently exposed to lower levels of androgens, while F2M transsexuals and women with PCOS are genetically females, but display a constant exposure to androgen excess. In all cases, no adverse androgen effect was found as far as the cardiovascular system was concerned. On the contrary, it has been observed that, despite the presence of various other risk factors in women with PCOS, there was no increase in the overall cardiovascular risk. And even though a few of those other factors, namely obesity and insulin resistance, have been attributed by some to hyperandrogenemia itself, it has yet to be proven that such a relationship exists.

Furthermore, in the light of recent trends, more attention is being granted to the effects of anabolic steroid abuse in sports. Although several case reports of cardiovascular complications have been recorded, it has been argued that without an estimation of the size of the reference population that makes use of anabolic steroids we cannot speculate about their true incidence rates. For example, according to classified documents saved after the collapse of the German Democratic Republic (GDR) in 1990, the Eastern German national sports doping program reported a variety of regularly occurring complications, but no adverse cardiovascular effects[14]. Besides, we cannot ignore the fact that anabolic steroid abuse usually involves highly supra-physiological concentrations of synthetic androgens. Still, given the widespread use of such substances in the sports world despite our best efforts, it will probably prove beneficial to look into their short-term and long-term complications even more carefully, especially due to the recent revelation of their multiple actions in metabolic physiology and reproductive health[15–16].

Conclusion

Although the sex-specific differences in cardiovascular incidence rates have long been known, we are still a long way from fully understanding what truly lies beneath. The existing studies about the effects of circulating sex steroids, as well as their exogenously treated counterparts, have yet to provide any conclusive evidence concerning the mechanism underlying sex differentiation in cardiovascular disease. As such, prompting scientists towards further research in this field may yield valuable information in the future, allowing anthropologists to comprehend differential survival opportunities for existing human populations.

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RAZLIKOVANJE ULOGA ANDROGENA I ESTROGENA KOD KARDIOVASKULARNIH BOLESTI

S A Ž E T A K

Kardiovaskularne bolesti pokazuju izrazitu razliku u prevalenciji među muškaracima i ženama, što je poznata činjenica već dugi niz godina. Dok su početne teorije tvrdile kako se to može pripisati zaštitnom učinku estrogena kod žena, povezivanje prirođene razine estrogena s kardiovaskularnim čimbenicima rizika i pokazateljima progresije ateroskleroze ukazuju na suprotno. Također, prirođene razine androgena povezuju se sa suprotnim učincima kod muškaraca i žena, dok liječenje bilo androgenom ili estrogenom ne odgovara znanstvenim očekivanjima u cijelosti. Kratka rasprava o osnovanosti i zamkama liječenjem bilo estrogenom ili androgenom u korijenu problema pokazuje da je trenutno razumijevanje neadekvatno u vezi ovog velikog antropološkog pitanja, jer se odnosi na primarni globalni uzrok mortaliteta i morbiditeta.