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Chronic heart failure (CHF) represents a debilitating condition with morbidity and mortality comparable to other end-stage disease states.¹ Non-oedematous weight loss in the context of chronic heart failure is associated with adverse prognosis, as it is a strong independent risk factor for mortality in patients with CHF and cachexia: patients with CHF with wasting have a mortality at 18 months as high as 50% compared to 17% in those without cachexia.² A number of different mediators have been implicated in the wasting process, including activation of pro-inflammatory cytokines, secretion of neurohormones and peptides, including PYY, ghrelin, leptin, growth hormone and insulin, and a relative deficiency of micronutrients and macronutrients.³ It has been suggested that a low testosterone level may represent one of the factors contributing to the anabolic/catabolic imbalance characteristically present in many patients with advanced CHF.⁴

In the study by Güder *et al* (see [page 504](#)) total (TT) and free serum testosterone (FT), dehydroepiandrosterone sulfate (DHEAS), and sex hormone binding globulin (SHBG) were studied in a cohort of 191 patients with heart failure (mean age 64 years; NYHA class I–IV 24/35/35/6%).⁵ Free testosterone (0.5–3% of the total testosterone) represents the biologically active unbound testosterone fraction. The current gold-standard method of determining free testosterone is equilibrium dialysis, but this is technically demanding and laborious, and in clinical practice, a derived method for free testosterone is employed, calculated from the total testosterone, serum albumin and SHBG. There is good correlation between the two methods. The bioavailable testosterone represents the fraction of testosterone that is unbound (free) plus the albumin bound testosterone, which is

readily dissociable and thus 'bioavailable'. A reduction in free testosterone and DHEAS in 79% and 23%, respectively, was found in the aforementioned study, whereas total testosterone was within the normal range in the majority of patients (91%). Interestingly, the reference range used to detect a low total testosterone was 180 ng/dl for patients aged >50 years and 260 ng/dl for younger patients, in accordance with their local laboratory reference ranges. The median age of the study population was 66 years (IQR 58–74 years). In a recently published recommendation for diagnosis and treatment of late-onset hypogonadism (LOH) a total testosterone less than 230 ng/dl was suggested as a lower normal range cut-off.⁶ Therefore, Güder *et al* may be underestimating the number of patients with heart failure with a total testosterone in the hypogonadal range. Similarly, a calculated free testosterone lower than 9 ng/dl was used to identify patients with low free testosterone. There is no generally accepted normal range for free testosterone; however, the aforementioned guidelines suggest a free testosterone level below 225 pmol/l or 6.5 ng/dl as thresholds when considering testosterone supplementation.⁶ Thus, the use of a relative high cut-off lower limit for free testosterone may have resulted in a higher percentage of patients with reduced free testosterone being identified.

Furthermore, in the study by Güder *et al*, DHEAS and free testosterone were found to be inversely associated with NYHA class ($p < 0.01$ for both). During a median follow-up of 859 days, 59 (23%) patients died. Interestingly, lower free testosterone and DHEAS and higher SHBG predicted all-cause mortality risk. Adjustment for age and NYHA class slightly diminished the prognostic value of the androgens and SHBG, whereas when variables were identified that were associated with both the respective hormone and the outcome and when the level of adjustment was expanded to the full list of those confounders, any prognostic significance of free testosterone, DHEAS or SHBG vanished. Confounders included renal

function, the presence of atrial fibrillation, the systolic blood pressure, C-reactive protein, NTproBNP, cortisol, total cholesterol and medication including the use of statins, diuretics and ACE inhibitors.

This finding contrasts with a previous study of 208 men with CHF (median age 63 years; New York Heart Association class I/II/III/IV 19/102/70/17) that identified TT, eFT, DHEAS and IGF-1 levels as predictors of mortality, independent of age, LVEF, NYHA class, GRF and pro-BNP levels.⁷ In the latter study, a control group of 366 healthy men was used to identify anabolic deficiency as a hormone level less than or equal to the 10th percentile calculated for the equivalent age categories in the cohort of healthy men. Longitudinal data suggest that total testosterone, free and bioavailable testosterone and DHEAS decline with age, while SHBG increases.⁸ Prospective population-based studies have shown a role of testosterone in predicting mortality in healthy individuals.^{9–10} On the other hand, androgen deficiency is known to occur in several chronic disorders and evidence on the benefit of substitution therapy often not found.¹¹

Correcting sex steroid axes in chronic heart failure has largely concentrated on testosterone replacement. Two randomised controlled trials to date of testosterone therapy in men with moderate CHF demonstrated a mean improvement in exercise capacity.^{12–13} In the trial by Malkin *et al* exercise capacity on incremental shuttle walk test (ISWT) improved in men treated with testosterone patches for up to 12 months. Improvement in ISWT significantly correlated with increase in serum bioavailable testosterone ($p = 0.01$) and NYHA class improved by at least one point in 13 (35%) patients on active therapy compared to three (8%) on placebo ($p = 0.01$).¹² A recent study by Caminity *et al* demonstrated improvements in exercise capacity, muscle strength, insulin sensitivity and in baroreflex sensitivity with the use of intramuscular testosterone for 12 weeks in 35 men compared to placebo.¹³ It is interesting that the baseline peak oxygen consumption (VO_2) and quadriceps isometric strength showed a direct relation with baseline serum testosterone concentration and that changes in testosterone levels correlated significantly with changes in peak VO_2 and in maximal voluntary contraction. In both studies, the mechanism of benefit with testosterone therapy was unclear; the functional improvement was thought to be due to an

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effect of testosterone on skeletal muscle rather than on myocardium.

Morphological and functional muscle abnormalities are present in patients with CHF, including fibre atrophy and a prevalence of type II fibres with a predominance of glycolytic over oxidative metabolism. The 'muscle hypothesis' in heart failure proposes that muscle alterations in CHF trigger prolonged neurohumoral activation and abnormal haemodynamic, autonomic and ventilatory responses to exercise; these may contribute to heart failure symptomatology and also be involved in the pathophysiology of the heart failure syndrome.¹⁴ Interventions aiming to reverse peripheral muscle alterations, such as exercise training, have been shown to improve muscle structure and function, ventilatory response to exercise and peak oxygen consumption in CHF. Androgens promote anabolism and treatment with testosterone improves muscle mass and strength, bone density and reduces visceral fat. Although the mechanism of action is largely unknown, the androgen receptor is present in bone and muscle. A suggested pathway for androgen action in the muscle involves the local expression of IGF-1 and the nuclear accumulation of the pro-myogenic, antiadipogenic stem cell regulatory factor β -catenin.¹⁵

The effects of testosterone on cardiomyocytes also suggests a direct role of testosterone in the myocardium. Testosterone receptors are present in endothelial cells, vascular smooth muscle cells and cardiomyocytes. On the vascular arterial wall testosterone induces vasodilation; in cardiomyocytes, it induces protein synthesis and hypertrophy in several species, including humans.⁴ Patients with Klinefelter's syndrome have an increased risk of dying from heart disease. In a review of 25 patients with Klinefelter's syndrome, the left ventricular systolic long-axis function was significantly

reduced in patients compared with age-matched controls and the peak systolic velocities correlated with free testosterone levels ($r=0.63$, $p<0.01$).¹⁶

Androgen deficiency is often seen in chronic disease states, where it is often multifactorial, and potentially maladaptive; it may contribute to physiological impairment in the context of a multi-hormone deficiency syndrome. Although serum levels of different androgens have been shown to be low in men with heart failure compared with healthy individuals, no clear prognostic role has been defined as yet in this setting. The cause of this high prevalence of biochemical hypogonadism and its significance remains unclear. However, different controlled studies have shown measurable short-term benefits of testosterone supplementation in this setting, and these are additional to the current treatment modalities. The muscle hypothesis and the potential improvement in insulin sensitivity provide attractive explanations. Further studies are needed to better characterise the role of anabolic hormones in this setting.

Competing interests None.

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