patients derived from eight RCTs suggested that combination therapy (testosterone and PDE5Is) was superior when compared to PDE5Is alone in improving erectile function [94]. The specific beneficial effect derived from the combined use of testosterone therapy and PDE5Is is unclear [87]. Similarly, information related to the combined use of testosterone therapy with other ED drug therapies is lacking [3, 89].

The Sexual Function Trial of the Testosterone Trials (TTrials) (one of the largest placebo-controlled trials on testosterone therapy) documented consistent improvements in 10 of 12 measures of sexual activities in older (≥ 65 years) hypogonadal men, particularly in frequency of intercourse, masturbation and nocturnal erections (as measured by PDQ-Q4) [95]. The magnitude in improvement was shown to be proportional to the increase in serum total testosterone, fT and E2 levels, it was not possible to demonstrate a threshold level [96]. A study of 220 men with MetS with or without T2DM also found that sexual function improved in men who reported sexual problems with improvement in IIEF scores, with specific increases in libido and sexual satisfaction [30].

3.4.2.2 Vitality and physical strength

The role of testosterone in stimulating muscle growth and strength is well established. Accordingly, androgenic-anabolic steroids (AAS) have been used as performance-enhancing agents to increase physical performance in competitive sport [97]. In this regard, testosterone therapy in hypogonadal men has been shown to increase muscle mass and reduce fat mass, with limited effects on final weight [41]. Despite this evidence, the role of testosterone therapy in older men with mobility limitations remains unclear. The National Health and Nutrition Examination Survey 1999-2004 [98] was unable to detect any association between overall circulating testosterone levels and the amount of physical activity. However, among non-obese men, those in the highest physical activity tertile were significantly less likely to have low or low-normal testosterone than those in the lowest tertile. Data from TTrials indicated that testosterone therapy did not substantially increase the fraction of men whose 6-minute walking distance increased > 50 m or the absolute increase in the distance walked by those enrolled in the physical function trial [95]. However, when the whole population of the TTrials was considered, a significant, although modest, positive effect on these two parameters was reported [95]. Similar data were derived from the Vitality Trial [95]. As support of the aforementioned considerations, a recent meta-analysis including 2043 subjects older than 60 years failed to show a significant improvement of muscle strength of testosterone therapy when compared to placebo [99].

3.4.2.3 Mood and cognition

Several observational studies have documented a relationship between depressive symptoms, reduced QoL and hypogonadism [100, 101]. However, the specific relationship between hypogonadism and the incidence of depression is still unclear [101]. Only a few placebo-controlled RCTs have investigated the role of testosterone therapy in improving depressive symptoms. Data derived from TTrials showed that testosterone therapy improved mood, and depressive symptoms as continuous measures using several instruments [95]. However, the final effect was small in magnitude. In line with this data, the largest meta-analysis of available studies, including 1,890 hypogonadal men (baseline total testosterone < 12 nmol/L or fT < 225 pmol/L) men from 27 RCTs, documented that the positive effect of testosterone therapy was particularly evident in patients with milder symptoms [102]. The BLAST study of testosterone therapy in T2DM reported that those men with depression were less likely to respond with regards to symptoms of sexual dysfunction compared to men without depression [36]. Findings from the TRAVERSE trial [78], showed that testosterone therapy alone did not appear to represent an effective treatment option for most men with clinical depressive disorders [103].

Robust data on the effect of testosterone therapy on QoL are limited. Although recent meta-analyses suggest a significant effect of testosterone therapy over placebo, the magnitude is low and the heterogeneity high, therefore reducing the scientific value of the effect [90, 104].

The role of testosterone therapy in patients with cognitive impairment is even more uncertain. The TTrials evaluated the effect of testosterone therapy in 493 individuals with age-associated memory impairment to assess possible improvement of several aspects of cognitive function. However, results failed to demonstrate any beneficial effect of testosterone therapy in improving cognitive function [95]. Similarly, a meta-analysis involving 17 studies enrolling 1,438 patients with a mean age of 70.4 years and a mean follow-up of 45.6 weeks did not find any effect of testosterone therapy on cognitive domains [105].

3.4.2.4 Body composition and metabolic profile

Late onset hypogonadism is associated with a greater percentage of fat mass and a lesser lean mass compared to testosterone-repleted men [106]. The major effect of low testosterone is to increase visceral adiposity but it also leads to deposition of lipids in the liver and muscle and is associated with atherosclerosis [25]. Some published data have suggested that testosterone therapy reduces percentage body fat and increases lean mass [107]. Testosterone therapy has also been found to decrease waist circumference, body weight and BMI, with these effects more predominant after twelve months of treatment [107-109]. Over two years, the T4DM