

## Introduction

Although it is now widely recognized that a testosterone deficiency (TD) can negatively impact various organ functions and quality of life (QoL), there is consensus among scientific societies to only offer testosterone therapy (TTh) in symptomatic patients with confirmed low total serum testosterone levels. In detail, international guidelines only recommend TTh in the case of compatible signs and symptoms and a subnormal serum testosterone concentration confirmed on two or three separate occasions. However, the threshold testosterone value for starting TTh remains controversial.

Both the European Association of Urology (EAU) guidelines and the International Consultation for Sexual Medicine (ICSM) suggest starting TTh in the case of hypogonadal symptoms and total testosterone levels of  $<12$  nmol/L (350 ng/dL), whereas the American Urological Association (AUA) sets as a threshold value for low total testosterone at 10.4 nmol/L (300 ng/dL). Normal total testosterone values range between 303 to 852 ng/dL (10.5 to 29.5 nmol/L) using the 5th and 95th percentile, respectively. Based on these considerations, at the moment we do not have a clear indication on what the minimum threshold value of total testosterone is at which it is necessary to start the replacement therapy in symptomatic patients. At the same time, male hypogonadism is a cluster of different clinical conditions that require a proper diagnosis before treatment may be considered. Testosterone treatment can reduce symptoms and improve glucose homeostasis, reduce cardiovascular risk and improve life expectancy and QoL. It is therefore important to identify patients with functional hypogonadism and other testosterone deficiency-associated conditions early. Guidelines provide an excellent frame for physicians to individualize treatment, but we consider it desirable to have a fixed threshold level of T, below which symptoms of TD and adverse health outcomes should necessarily indicate TTh.

In order to provide a useful tool for physicians to decide about TTh in everyday clinical practice, we developed and validated a nomogram named TRACE (Testosterone ReplACEment) for predicting the need of TTh in men with symptoms of TD and low-normal total testosterone values.

## Introduzione

*Sebbene sia ormai ampiamente riconosciuto che una carenza di testosterone (TD) può avere un impatto negativo su varie funzioni degli organi e sulla qualità della vita (QoL), esiste un consenso tra le società scientifiche nell'offrire la terapia con testosterone (TTh) solo nei pazienti sintomatici con bassi livelli di testosterone sierico totale confermati. In dettaglio, le linee guida internazionali raccomandano la TTh solo in caso di segni e sintomi compatibili e una concentrazione di testosterone sierico subnormale confermata in due o tre occasioni separate. Tuttavia, il valore soglia del testosterone per iniziare la TTh rimane controverso. Sia le linee guida dell'Associazione Europea di Urologia (EAU) che l'International Consultation for Sexual Medicine (ICSM) suggeriscono di iniziare la*

TTh in caso di sintomi ipogonadici e livelli di testosterone totale <12 nmol/L (350 ng/dL), mentre l'American Urological Association (AUA) stabilisce come valore soglia per il basso testosterone totale a 10,4 nmol/L (300 ng/dL). I valori normali del testosterone totale variano tra 303 e 852 ng/dL (10,5 e 29,5 nmol/L) utilizzando rispettivamente il 5° e il 95° percentile. Sulla base di queste considerazioni, al momento non abbiamo un'indicazione chiara su quale sia il valore soglia minimo del testosterone totale al quale è necessario iniziare la terapia sostitutiva nei pazienti sintomatici. Allo stesso tempo, l'ipogonadismo maschile è un insieme di diverse condizioni cliniche che richiedono una diagnosi corretta prima che il trattamento possa essere preso in considerazione. Il trattamento con testosterone può ridurre i sintomi e migliorare l'omeostasi del glucosio, ridurre il rischio cardiovascolare e migliorare l'aspettativa di vita e la qualità della vita.

È quindi importante identificare precocemente i pazienti con ipogonadismo funzionale e altre condizioni associate alla carenza di testosterone. Le linee guida forniscono un'eccellente cornice per i medici per personalizzare il trattamento, ma riteniamo auspicabile avere un livello soglia fisso di T, al di sotto del quale i sintomi di TD e gli esiti negativi sulla salute dovrebbero necessariamente indicare TTh. Per fornire ai medici uno strumento utile per decidere se sottoporsi a TTh nella pratica clinica quotidiana, abbiamo sviluppato e convalidato un nomogramma denominato TRACE (Testosterone ReplACEMENT) per prevedere la necessità di TTh negli uomini con sintomi di TD e valori di testosterone totale bassi-normali.

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