Testosterone (T) Information Document

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Prepared by Dr. Kerry Kuehl at Oregon Health & Science University

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Introduction

Fire fighters may receive conflicting messages about the effect of low testosterone (T) on health and may have questions about risks and benefits of testosterone replacement therapy (TRT). In the U.S., direct to consumer marketing targets fire fighters through various social media platforms. This marketing may overemphasize potential positive effects without adequately noting the potential dangers of TRT and without discussing lifestyle interventions that should be used initially by most men to increase T levels.

Although published data are not yet available, anecdotal and preliminary data suggest that IAFF members may use TRT at greater rates than the general U.S. or Canadian populations. This may be due to the unique occupational challenges of fire fighting such as the extreme physical demands resulting in the need for a high level of physical fitness throughout a fire fighter's career. Common risk factors associated with fire fighting, such as sleep disturbance and work related stress, may also be involved.

Therefore, the IAFF has prepared this information document to:

1. Answer IAFF member questions about the symptoms of low T;
2. Describe accurate T testing and how to avoid practices that do not meet medically accepted standards;
3. Help IAFF members understand how work and non-work factors can decrease T levels and the positive impact exercise, diet, and good sleep hygiene can have on T levels;
4. Help IAFF members understand the potential benefits and health risks associated with TRT.

SECTION 1 – PREVALENCE OF LOW T IN THE U.S. AND SIGNS AND SYMPTOMS OF LOW T

How common is low T?

The number of men with low T varies by age and how the condition is defined. There is no one accepted definition, but most include one or more T level lower limits with associated symptoms.[1,2] A gradual, age-associated decline in serum total testosterone levels begin in men in their mid-30's and continues to decline at an average rate of 1.6% per year (Qaseem A, Horwitch CA, Vijan S. Testosterone Treatment in Adult Men with Age-Related Low Testosterone: A Clinical Guideline From the American College of Physicians. Annals of Internal Medicine, January 2020.) This condition is referred to as age-related low testosterone and usually accompanied by clinical symptoms associated with androgen deficiency (ie. sexual dysfunction, fatigue, mood disturbance and depression, reduced lean body mass, loss of body hair and facial hair, muscle weakness). In the Massachusetts Male Aging Study, 4.1% of participants from 40-49 years of age (the youngest group studied) were classified as androgen deficient (T level < 200 or 400 ng/dL depending on symptoms).[3] However, after an average of 8.8 years of follow-up, 7.1% of participants (now in the 48-59 year old group) were found to be androgen deficient. In 1475 Boston men, approximately 22% from 30-39 years of age had T levels < 300 ng/dL; this increased to 25% in those between ages 40-49.[4] However most of those men did not have any related symptoms (approximately 3 and 6%, respectively, had symptoms

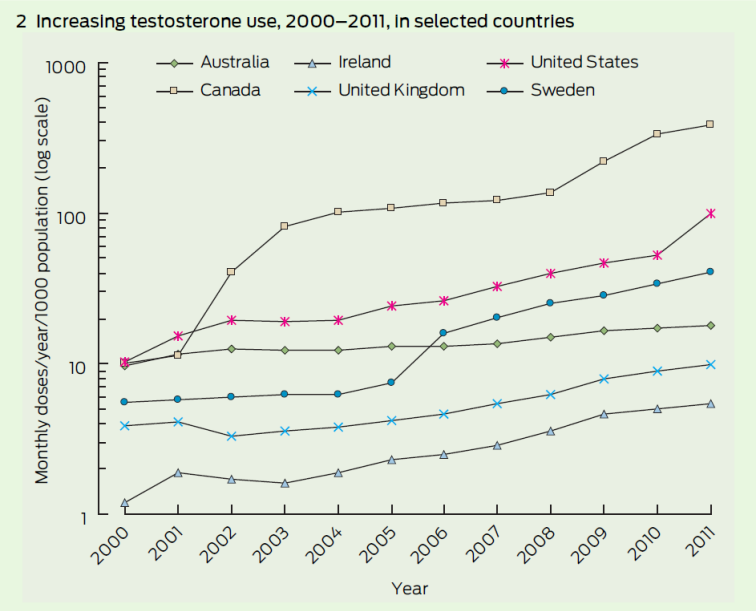
the researchers connected to low T) and so did not meet the study definition of androgen deficient. A study of 2162 US men, who were seen at primary healthcare clinics, found that 34% from 45 to 54 years of age (the youngest group studied) had T levels < 300 ng/dL or were on T therapy.[5] Low T levels are more common in men with obesity, type II diabetes and/or metabolic syndrome (high blood pressure, blood sugar, cholesterol and abdominal body fat which increases risk for heart disease and type II diabetes).[2]

How common is low T among fire fighters?

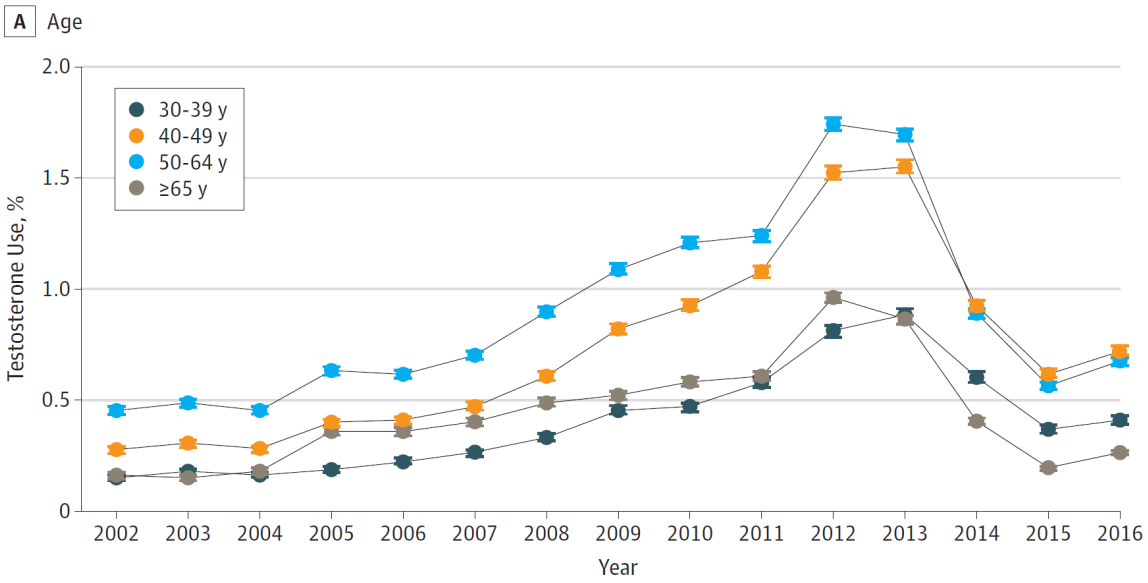
A study of 341 US career fire fighters, whose average age was 37.5 years found that nearly 11% had T levels < 264 ng/dL (the proportion of fire fighters with T levels < 300 ng/dL was not reported).[6] A study of 72 fire fighters, whose average age was 25 years, reported a decrease in T levels from 732.6 ng/dL to 464.4 ng/dL over their first year of work.[7]

How common is TRT?

TRT is now a multi-billion dollar business. In the 2000s, T prescriptions increased dramatically in the US, Canada and a number of other countries as shown below:[8]



In US men age 30 and older, TRT peaked at 3.2% in 2013 and then declined to 1.7% in 2016.[9] New prescriptions also peaked and declined in all age groups as shown in the figure below:[9]



Only 80 (3.7%) of the men seen at primary healthcare clinics in the study discussed above were on TRT.[5] Although this information was not provided by age group, it is clear that most men with T < 300 ng/dL were not on replacement. In the study of Boston men mentioned above, 11 were on TRT which was 12% of those considered androgen deficient but less than 1% of the total population.[10]

In 2017, the proportion of men in the US military who were on TRT was less than 1% for those under age 50 and 1.5% for those older than 50 years of age.[11] The authors stated that only 44.5% of men on TRT met clinical practice guidelines for this treatment. Data on TRT in fire fighters have not been published. However, reports of fire fighters in their 20's and 30's who are receiving TRT despite inconsistent, and at times questionable, testing procedures, during a time when they are still of reproductive age are of great concern.

When are low T levels a disease?

T levels normally decline with age by approximately 1-2 % per year.[12] T levels that are important medically have been defined and labeled in various ways by different organizations.

The American Urological Association defines ***T deficiency*** as **T levels < 300 ng/dL combined with specific symptoms and/or signs**.[13]

The Endocrine Society uses the term ***hypogonadism*** to refer to **failure of the testes to produce normal concentrations of T and/or a normal number of sperm**.[14] This can be caused by a problem with the testes (primary hypogonadism) or with the hypothalamus or pituitary gland which release hormones that stimulate the testes to release T (secondary hypogonadism). They recommend that the **diagnosis of hypogonadism be made in individuals with both symptoms and signs of T deficiency and T measurements that are clearly and consistently low (often considered < 264 ng/dL for healthy non-obese men from 19 to 39 years old).**

T supplement manufacturers may use the terms ***low T*** and ***andropause*** for a variety of symptoms**.**

What are the symptoms and signs of T deficiency?[14]Error! Bookmark not defined.

The symptoms and signs of T deficiency vary from those that clearly indicate disease to those that can be caused by many things.

Signs **clearly indicating disease** from low T levels include:

- Incomplete or delayed sexual development
- Loss of body (axillary and pubic) hair
- Very small testes

Symptoms and signs that **suggest disease** include:

- Reduced sexual desire
- Decreased spontaneous erections, erectile dysfunction
- Breast discomfort or enlargement (gynecomastia)
- Inability to father children, low sperm count
- Height loss, low-trauma fracture, low bone mass density
- Hot flashes, sweats

Finally, there are a several symptoms and signs that could be due to T deficiency but are just as likely, if not more likely, to be due to another reason. These are called **nonspecific symptoms and signs** and include:

- Decreased energy, motivation, initiative, and self-confidence
- Feeling sad or blue, depressed mood
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild unexplained anemia
- Reduced muscle bulk and strength
- Increased body fat

Nonspecific symptoms are a major challenge in making the correct diagnosis. As an example, the table below compares the non-specific symptoms that the Endocrine Society lists for hypogonadism and notes that they can also be present in patients with selected other diagnoses.

Symptom	**Hypogonadism/ T deficiency**	**Sleep deprivation**[15]	**Depression**[16]	**Post-Traumatic Stress Injury/Disorder**
Decreased energy	X	X	X	X

Concentration and memory difficulties	X	X	X	X
Sleep disturbance	X	X	X	X
Depressed mood	X	X	X	X

What are other reasons for low T?[14]

Some low T levels are considered "functional" meaning that they are due to another cause rather than the T hormonal pathway. For these patients, the specific cause should be addressed rather than just prescribing T. Examples include:

- Medications such as opioids, anabolic steroids, and cholesterol lowering statins (Schooling et al, The effect of statins on testosterone in men and women, a systematic review and meta-analysis of randomized controlled trials. BMC Med. 2013;11:57.
- Alcohol
- Marijuana
- Nutritional deficiency
- Excessive exercise/overtraining
- Obesity
- Obstructive sleep apnea
- Chronic illness

Do fire fighters have occupational risk factors that may contribute to low T?

The following, all of which are common in fire fighters, have been shown to decrease T:

- Sleep deprivation[15]
- Excessive exercise/overtraining
- Obesity
- Work demands/stress[17]
- Poor diet
- Alcohol use

SECTION 2 – DIAGNOSIS AND TESTING PROCEDURES

How should T level be measured?

- T should be measured in the morning (for example, 7-9 am) after a full night's sleep, an overnight fast and before eating breakfast
- The sample should be sent to a lab whose T assay has been certified by a quality control program such as the Centers for Disease Control and Prevention (CDC) Hormone Standardization Program for Testosterone

    - Using this assay, the normal range in a healthy non-obese population of European and American men, 19 to 39 years, is 264 to 916 ng/dL.[18]
    - A current list of these labs can be found at: https://www.cdc.gov/labstandards/hs_certified_participants.html
- If the first result is low, it should be repeated
- Free T (not bound to proteins in the blood) can also be measured in addition to total T or when the total T level is found to be abnormal.

Why is it important to follow all these steps for T measurement?

- Laboratories have difficulty measuring T. When the **same low T sample was sent to 1,133 laboratories, the measured values ranged from 45 to 365** ng/dL.[14]
- T levels vary over the course of a day and are highest in the morning. In some healthy young men, T concentrations drop below the normal range at some point during a 24-hour period.[14]
- T levels vary from one day to the next. For example, 30% of men with an initial low T concentration have a normal level when the test is repeated.[14]
- T levels may be lowered by food so T should be measured in the morning after an overnight fast.

Who should get T levels measured?

- **The Endocrine Society does not recommend routine screening of men in the general population** because low T concentrations "occur frequently without symptoms or signs of testosterone deficiency, and these low levels (alone) do not establish a diagnosis of hypogonadism."[14]
- There are **no validated questionnaires** that can be used to decide which men to test including the "low T" (http://www.lowt.ca/)

Which men with low T should be diagnosed with T deficiency/hypogonadism?

T levels decline naturally in men as they age. Therefore, it can be difficult to determine when this decline is abnormal. The Endocrine Society recommends diagnosing hypogonadism in men with symptoms and signs of T deficiency and consistently low serum total T which is a level that declines with aging.[14] The American Urological Association recommends diagnosing T deficiency in men with symptoms and signs and a total T level below 300 ng/dL.[13]

SECTION 3 – RISKS OF LOW T, RISKS OF TRT, AND POTENTIAL BENEFITS OF TRT

It is important to realize that we still don't know a lot about the risks having low T or the risks and benefits of TRT. Keep in mind that, for years, hormone therapy was thought to safely treat menopause-related symptoms and even prevent heart disease in women. However, the Women's Health Initiative study, which was a placebo controlled study - a very strong research

design - found that older women using hormone therapy actually had small increased risks of breast cancer, heart attacks, strokes, and blood clots.[19] This study totally changed the use of hormone therapy in women.

Can low T cause health problems?

The Endocrine Society noted that a meta-analysis – a strong study design in which smaller studies are combined to give more accurate results - reported that lower T concentrations were associated with higher risk for death, especially from heart disease. However, they also noted that it is possible that T is a marker of health, and those who are at higher risk of dying have lower T concentrations.[14]

TRT risks and benefits

TRT is completely different than T abuse sometimes reported in athletes and body builders. The Food and Drug Administration notes that high T doses, often used with other anabolic steroids, "is associated with serious safety risks affecting the heart, brain, liver, mental health, and endocrine system. Reported serious adverse outcomes include heart attack, heart failure, stroke, depression, hostility, aggression, liver toxicity, and male infertility. Individuals abusing high doses of testosterone have also reported withdrawal symptoms, such as depression, fatigue, irritability, loss of appetite, decreased libido, and insomnia."[20]

In addition, much of the data on TRT comes from the Testosterone Trials (T Trials). The men in these trials were much older than active fire fighters (790 men age 65 and older). In this study, participants with low levels of T and symptoms that might be due to this were randomized; half were treated with T gel and half received a placebo gel. One year of TRT improved bone density and corrected anemia, but also increased coronary artery plaques (fat deposits that reduce blood flow to the heart if large enough).[21] TRT did not improve memory or other cognitive function. T had a beneficial effect on sexual function, mood, and walking distance.[14]

Benefits - both the Endocrine Society[14] and the American Urological Association[13] agree that TRT:

- Improves sexual function - both erectile function and libido
- Increases muscle size and strength
- Increases bone mineral density
- Improves mood

Risks – both the Endocrine Society[14] and the American Urological Association[13] agree regarding the following related to TRT:

- **Suppression of spermatogenesis** - TRT suppresses sperm production and has been studied as a form of male birth control. Therefore, it should not be used by men who are attempting to conceive with their partners.

- **Erythrocytosis** – TRT causes an increase in the number of red blood cells circulating in the blood, which is called erythrocytosis. Erythrocytosis increases the risk for blood clots which can cause strokes or heart attacks.
- **Secondary exposure** - There is a risk of T gel being transferred from the person applying the medicine to other people, which is called secondary exposure. There have been cases of secondary exposure causing T-related body changes in infants and children who are held or touched by an adult using TRT.[22,23]

In the Endocrine Society and the American Urological Association guidelines, the data on risk for **blood clots (venous thromboembolism)** was considered less certain. Some studies and case reports had noted an increased risk after starting TRT even without developing erythrocytosis.[13,14] However, a study[24] published after these guidelines found an increased of blood clots that was greatest in the first three months of starting TRT.[24] This may be due to underlying blood clotting disorders.[25] The US Food and Drug Administration requires T drug labels to include a warning about this risk.

The following risks are less certain due to limited and inconsistent research:
- **Cardiovascular disease** – Both guidelines have concluded that the data are insufficient to determine if TRT increases heart disease risk. Reflecting the underlying inconsistent research, the US Food and Drug Administration requires T drug labels to mention a possible increased risk for cardiovascular disease.[26]
- **Prostate cancer -** T stimulates the growth of metastatic prostate cancer and therapy to reduce T levels is used for some prostate cancers. This has resulted in concern that TRT may increase prostate cancer risk. The research to date has not supported this concern but is still considered insufficient. The US Food and Drug Administration requires T drug labels to include a warning about this risk. The Endocrine Society guidelines generally discourage TRT in men with a history of prostate cancer.[14] In contrast, the American Urological Association states that healthcare providers should inform patients of the absence of evidence linking T therapy to the development of prostate cancer.[13] Both guidelines recommend evaluation for prostate cancer before starting treatment.

Are any risks from treatment potentially greater in fire fighters?

- The risk from greater numbers of red blood cells (erythrocytosis) is a specific concern for fire fighters. This is because heat and physical exertion involved in fire suppression cause dehydration. As a result, the red blood cells in the bloodstream become more concentrated (thicker) and may clot more easily. This is thought to contribute to the increased risk for heart attacks after fire suppression. Stroke is another major risk from blood clotting. Fire fighters who start TRT should have their red blood cells (hematocrit and hemoglobin) monitored regularly while on supplementation.
- The possible increased risk for prostate cancer with TRT is also a concern due to the increased risk for this cancer in fire fighters.

Fire fighters undergoing TRT should discuss these risks with their doctors and ensure their hemoglobin and hematocrit levels are monitored.

SECTION 4 – LIFESTYLE INTERVENTIONS AND TRT

What can raise testosterone levels other than TRT?[27, 28]

Lifestyle modification through **diet, exercise, sleep improvement, optimal body weight, reduced substance use, and stress reduction** is the essential first step rather than TRT.

Diet

The Mediterranean Diet which is high in fruits, vegetables, whole grains, lean protein and healthy fat, was positively associated with total sperm count.[27] A meta-analysis of 21 studies of various types of low calorie diets found that **for every 5 kg of weight lost, T increased by 28.8 ng/dL**.[28] Five different meta-analyses have all reported that T levels increase after bariatric surgery with resulting weight loss. The average increase was large, ranging from 230 to 290 ng/dL.[28] To date, no specific diet has been identified as the best.

Exercise

Exercise increases lean body mass and lowers body fat which increases T levels. A meta-analysis of 8 studies of the effect of various types of physical exercise on T levels over an average of 15 weeks found that T levels increased.[28] Surprisingly, in the exercise studies, a 5.5 kg weight loss only increased T levels by a third of that from similar weight loss from diet. Regular physical activity reduced the risk of erectile dysfunction by 50% in one study.[28] A study of 41 overweight or obese men who participated in a 12 week exercise and diet program reported a significant increase in T levels in those in the higher physical activity group; T levels were increased in relation to the number of steps taken.[29] To date, no specific exercise program has been identified as the best.

Obesity

Reducing body weight alone in obesity studies increases T. According to a Harvard Men's Health Watch article, a five-point increase in body mass index (e.g., from 30 to 35) lowers T levels as much as 10 years of aging.[30] In a study of 2,395 men ages 40-79 followed over an average of 4.4 years, T increased significantly in those who lost 10% or more of their initial weight compared to those who remained within 10% of their baseline weight.[31] In contrast, a 10% or more weight gain resulted in significantly decreased T.

Stress

Both acute and chronic stress can reduce T levels so a healthy stress management program to reduce mental and physical stress is essential.

Sleep

Improving sleep quality by treating sleep apnea can increase T levels. In contrast, sleeping less than 5 hours per night has been shown to decrease T levels by 10%[32] which contrasts with

normal aging which decreases T by 1-2% per year.[12] A good sleep hygiene program is essential for fire fighters to increase T.

Substance Use
Heavy alcohol and marijuana use significantly decreases T so an important lifestyle modification is to reduce alcohol to no more than 2 drinks per day (or one drink per day for women) or 5 drinks at one time (four for women).[33]

Who should start taking TRT?

Treatment should be tailored to each individual and so cannot be covered in a general document. However:

- If you have potentially reversible causes such as those listed under "What are other reasons for low T?" above, these should be treated first since this may avoid the need for TRT. As discussed above, **fire fighters should establish positive lifestyle practices such as a regular exercise regime including cardiovascular exercise and weight training, a healthy diet, a plan for improving sleep, weight loss, and the identification of and support for underlying behavioral health issues.**
- Table 7 in the Endocrine Society guidelines lists conditions in which T should not be prescribed even if otherwise indicated. These include men planning to procreate, men with breast or metastatic prostate cancer or PSA test results above specific levels and other reasons.[14]
- Avoid clinics that market to men and focus only on non-specific symptoms. Avoid clinics that don't follow the T measurement criteria discussed above.
- Consider getting a second opinion from an endocrinologist.
- An oral form of T was approved by the US Food and Drug Administration in March 2019.[34] This has not been approved for age-related T deficiency/ hypogonadism.
- After starting therapy, follow-up with your physician periodically to have T levels and other lab tests – in particular hemoglobin and hematocrit levels – checked to make sure the therapy is not causing any problems with your prostate or blood chemistry. Monitoring hematocrit is especially important for fire fighters.

SUMMARY

- Low T levels are increasingly common with aging and are not of concern unless associated with symptoms and/or signs.
- Symptoms and signs of T deficiency range from those clearly indicating disease, such as incomplete sexual development, to those that can be from many causes, such as lack of energy. These non-specific symptoms that can be caused by several diseases require a careful medical evaluation rather than assuming that TRT is needed.
- T measurement is difficult and levels can vary a great deal from day to day. Therefore, blood should be drawn in the morning after a full night's sleep and an overnight fast and before eating breakfast. The blood should be tested in a lab that is certified by the Centers for

Disease Control and Prevention. Normal values should be age-based using data from large populations. Low results should be repeated.

- There are no accepted screening questionnaires for low T and guidelines do not recommend that men routinely have T measured.
- A lot remains uncertain about the risks from low T and the risks and benefits of TRT. Research to date suggests that TRT improves sexual function, increase muscle size and strength and bone mineral density and improve mood. Risks for heart disease and prostate cancer remain unclear.
- One well known risk of TRT is suppression of sperm production so this should not be used by men who are attempting to conceive with their partners.
- Erythrocytosis (increased red blood cells/"thicker blood") is another known risk from TRT. This can cause blood clots leading to strokes and heart attacks. This is a particular risk for fire fighters since the extreme physical exertion of active firefighting already increases the risk of dehydration, heat stress, and cardiovascular emergencies such as heart attack and stroke.
- Low T has many causes, including obesity, disrupted sleep patterns, stress, drug and alcohol use, certain medications, and poor diet. Several of these factors are common in fire fighters.
- Reports suggest that IAFF members may be using TRT at a greater rate than the general public. This may be due to the low T causes common in fire fighters noted above. However, lifestyle modification through diet, exercise, sleep improvement, optimal body weight, reduced substance use, and stress reduction is the safer first step rather than going directly to TRT.
- When considering TRT, avoid care from clinics that market to men and focus only on non-specific symptoms.

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