

Natural Compounds to Counteract Testosterone Depletion in Aging

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Aging is accompanied by many biological and physiological changes in the body, including the depletion of sex hormones such as testosterone. Testosterone is an important sex hormone for many physiological and biological functions in the body, and depletion of it may cause changes that can be negative to the normal functioning of the body. Aging is associated with a gradual depletion of testosterone of about 2-3% annually, starting from the age of 30 [1]. This depletion of the sex hormones has many implications in the physiological functions in the body, such as effects in muscle mass, liver function and immune function [2]. These negative effects can render the body susceptible to diseases and many adverse symptoms. Testosterone depletion is also associated with vulnerability to disease in hormone-responsive tissues, such as the brain, and it has been seen that androgens and estrogens have very beneficial effects in increasing spine density and synaptic plasticity [1]. This is a key subject to be researched as there have been studies that found a relationship between brain level in testosterone and levels of soluble Amyloid Beta, indicating a correlation between hormone depletion and risk of neurodegenerative diseases [3]. It is important to find this relationship and find new and novel ways to counteract this testosterone depletion in a way that is natural, risk-free, and cost effective.

Testosterone replacement therapy in aging men is becoming more widespread through the years [4]. Though some research have been unable to find conclusive results presenting a relationship between the use of synthetic testosterone and prostate cancer and/or cardiovascular disease, there are still common potential adverse effects seen in case reports. A lot of these adverse reports are hard to measure because of a lack of control groups and likelihood of cardiac events being underreported [5]. This can lead to the potential dangerous effects of synthetic testosterone to be underestimated. Yet, there are various cases reporting potential adverse effects of synthetic testosterone including infertility, hepatotoxicity, physiological abnormalities and gynecomastia [5]. Because testosterone replacement therapy with supplemental, synthetic, testosterone does place a potential threat to other health issues as seen in some of the case studies, it is important to find other ways of treatment for testosterone depletion upon aging. The healthier approach would involve the replacement of testosterone in an aging individual via natural compounds, such as natural flavonoids. Natural compounds, like fruit flavonoids, can be found in normal diet [6], which shows that these compounds do not place a threat to other health areas, like synthetic testosterone does. Therefore, natural flavonoids may be a better and healthier choice in terms of therapy to counteract testosterone depletion.

The depletion of testosterone in an aging individual must involve a change in its biosynthesis itself, which is a subject that must be studied in order to counteract this depletion. In studies trying to find the pathways of testosterone biosynthesis, it has been found that Steroidogenic Acute Regulatory Protein, or StAR protein, is important in the acute regulation of steroid hormone biosynthesis. This protein is involved in the transfer of cholesterol from the outer membrane to the inner membrane of mitochondria [7]. Synthesis of steroid hormone requires cholesterol as precursors for biosynthesis, and acts as a rate-limiting step [7,8]. So, there is a clear requirement for StAR protein to perform the transfer of cholesterol for steroidogenesis. In studies, it has

been seen that mutations in StAR protein result in sometimes lethal condition called, congenital lipoid adrenal hyperplasia, which involves a blockage in the synthesis of steroid hormones, again expressing the importance of StAR protein function to produce testosterone [7]. StAR protein is expressed via a response to trophic hormone and it is cAMP-mediated [8].

With this information, one can conclude that aging is related to a decrease in the levels of StAR protein and, thus, a decrease in testosterone biosynthesis. There are mechanisms in place that lead to the blockage in StAR protein production. In one study, it was found that the expression of cyclooxygenase-2 increases as a response to aging, and as this increases, StAR protein decreases [9]. Cyclooxygenase-2, or COX-2, can then have an effect of steroidogenesis via StAR protein synthesis mechanisms. This study also showed that when COX-2 is inhibited, it causes an increase in StAR protein and, therefore, an increase in testosterone levels. Potential therapies to counteract testosterone depletion must then focus on these molecular mechanisms to restore StAR protein production and function, in order to naturally restore testosterone levels [10].

The presence of potential natural compounds that can counteract the testosterone depletion seen in aging individuals must then affect the mechanism in which COX-2 is synthesized or induces signal; thus, inhibiting its production or signal. In a study, it was found that apigenin, a natural fruit flavonoid, interrupts COX-2-dependent signaling via the blocking of TBX-A2 receptor, which normally regulates DAX-1 protein, which is a transcriptional repressor of StAR gene and, thus, inhibits the production of StAR protein [11]. The interruption of COX-2 will then cause the normal transcription of StAR gene and an increased expression of StAR protein and testosterone levels. Flavonoids are food constituents that alter metabolic processes [6], and in this case it alters the process of the COX-2 pathway and causes the increase in StAR protein and, thus, increases in testosterone levels in a natural way via these natural compounds that can be found naturally in food.

Other natural flavonoids could have the same effect as apigenin in counteracting the testosterone depletion that is present in aging individuals. Further research is needed to explore the molecular basis of counteracting this testosterone depletion by the use of natural flavonoids. Successful results can lead to the discarding of synthetic testosterone as treatment, which is potentially dangerous in other

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Received January 09, 2014; **Accepted** February 20, 2014; **Published** February 28, 2014

Citation: Rojas DP, Pandey AK (2014) Natural Compounds to Counteract Testosterone Depletion in Aging. J Steroids Horm Sci 5: e112 doi:[10.4172/2157-7536.1000e112](https://doi.org/10.4172/2157-7536.1000e112)

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aspects of health and fertility. The restoration of testosterone levels in aging individuals can have many benefits, such as increased bone density, better liver function, better immune system, and physiological well-being. The restoration of testosterone can also have a benefit in reducing the risk of neurodegenerative diseases in aging individuals, as it has been seen that depletions of testosterone can lead of effects in synapse plasticity and increase in amyloid beta levels.

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Citation: Rojas DP, Pandey AK (2014) Natural Compounds to Counteract Testosterone Depletion in Aging. J Steroids Horm Sci 5: e112 doi:10.4172/2157-7536.1000e112

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