THE AGE AT WHICH TESTOSTERONE STARTS DECREASING IN MEN NOW-A-DAYS

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ABSTRACT

Objective: *The aim of this study was to determine the age at which testosterone starts decreasing in male subjects.*

Methodology: *This comparative study was conducted on two groups; group 1 included male subjects with 18–21 years of age and group 2 included male subjects with 22–25 years of age. Subjects having history of hypogonadism, hyperthyroidism, hypothyroidism, mental illness like depression were all excluded. Serum testosterone was analyzed by Radio Immuno Assay method on gamma counter in Institute of Radiotherapy and Nuclear Medicine (IRNUM), Peshawar. The serum testosterone levels of the two groups were compared for a significant difference by using student-t test.*

Results: *Group 1 included 80 subjects and group 2 had 75 patients. In group 1, testosterone level was >12 ng/ml in 22.5% (n=18/80), 7-12ng/ml in 58.75% (47/80) and <7 ng/ml in 18.75% (n=15/80) cases. In group 2, testosterone level was >12 ng/ml in 8% (n=6/75), 7-12ng/ml in 54.6% (n=41/75) and <7 ng/ml in 37.3% (n=28/75) cases. Mean testosterone level was 9.40±2.986 ng/ml in group 1 and 7.89±2.891 ng/ml in group 2 (p<0.05).*

Conclusion: *The testosterone level in male subject is significantly lowered at 22–25 years of age as compared to 18–21 years of age. Well planned and large scale studies are required to address the issue in detail and to find out the causes of early decline of the testosterone level in young male subjects.*

Keywords: *Testosterone, Aging, Hypogonadism, Optimal Health*

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INTRODUCTION

Testosterone production in the male begins when the pituitary gland, located deep inside the brain, secretes lutenizing hormone (LH), which in turn, stimulates the Leydig cells in the testicles to produce testosterone. It is estimated that men are born with 700 million Leydig cells and they begin losing 6 million each year after their twentieth birthday.[1]

There is no general agreement on what testosterone levels are normal for healthy aging men. A recent endocrine society annual andropause consensus meeting suggested that 300 nanograms per deciliter (ng/dl) is the lower limit for normal testosterone levels, and total testosterone levels less than 200 ng/dl clearly indicate hypogonadism in healthy young men.[2]

At puberty the Testosterone (T) level starts increasing reaching a peak and then starts decreasing. The normal level of testosterone in male adults is 300 – 1000 nano grams per deciliter ng/dl or 3–10 ng/ml.[3,4]. Several cross-sectional studies of ethnically comparable but geographically distinct cohorts have generally shown that total testosterone declines in adults with each year of age.[5-9] Longitudinal studies later confirmed the fall in testosterone with increasing age.[10-12]

There is very much controversy in literature about the ages at which testosterone peaks and the age at which it starts declining. Some studies suggest that testosterone levels peak in men at around 30 and then slowly decline by an average of 2% per year. For some men this will be even faster, i.e., highest in the early twenties. The optimal level for men is in the upper one third of the normal range for his age. When a man is at these levels of Testosterone, he performs better physically, mentally, and sexually.[13] While other studies suggest that testosterone levels in men begin to decline in the late third or early fourth decade and diminish at a constant rate thereafter.[14-16]

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Studies in the 1940's showed the average testosterone level to be at 700 ng/dl; 400 ng/dl higher than for men today. In the past, a drop in testosterone levels to 250 ng/dl was rarely reported before men were 80 years of age. Yet today, it is not an uncommon value for middle aged men. The decrease in serum levels is now occurring at an even earlier age. Up to 50% of all men at 40 years now have testosterone levels below what was considered the normal range of 450 ng/dl.[17]

To solve this problem which exists in literature we designed this study to determine the age at which testosterone starts decreasing in male subjects from 18-25 years of age. Since 25 years was the highest age in these subjects so we could be able to say if testosterone decreases before 30 years i.e., in mid twenties.

METHODOLOGY

This was a cross sectional study having 155 subjects. Group 1 included 75 subjects having an age of 22 – 25 years, while group 2 included 80 subjects having an age of 18 – 21 years.. Subjects having history of hypogonadism, hyperthyroidism, hypothyroidism, mental illness like depression were all excluded.

Informed consent was taken from all subjects (patients and controls) and data was recorded in a questionnaire designed with the help of a biostatistician. 5 ml of venous blood was taken from each subject between about 7.00 to 9.00 am due to diurnal variation. The samples are then transported to the RIA Laboratory of Institute of Radiotherapy and Nuclear Medicine (IRNUM) on ice. Serum was separated by centrifugation at the rate of 1500-2000 revolution/sec for 10 min. The serum was tipped out with micropipette into sterile plastic tubes labeled with corresponding data which were properly sealed and stored at – 20 °C till analysis for serum Testosterone.

The data was recorded and processed on SPSS software version 13.0. The mean and SD of serum T for the two groups was calculated & the desirable comparison was done using t-test (Independent sample t-test).

RESULTS

In this study we had subjects of two age groups. **Group 1** (n=80) had subjects with an age range of 18-21 years and **Group 2** (n=75) had subjects with age ranging from 22 -25 years.

Testosterone level was >12 ng/ml in 22.5% (n=18/80) cases in group 1 and in 8% (n=6/75) cases in group 2. It was <7 ng/ml in 18.75% (n=15/80) cases of group 1 and 37.3% (n=28/75) cases in group 2 (table 1).

Group 1 had a mean testosterone level of 9.40±2.986 ng/ml (table 2). In this group the maximum testosterone level recorded was 16.9ng/ml, while minimum level was to be 3.1 ng/ml. Group 2 had a mean testosterone level of 7.89±2.891ng/ml. In this group, the highest value of testosterone was 13.4 ng/ml, while the lowest level was 3.1 ng/ml. Applying independent sample t-test the P-value came out to be 0.002 showing a significant difference between the serum testosterone levels of the two age groups.

DISTRIBUTION OF TESTOSTERONE AMONGST THE TWO GROUPS

Testosterone Level	Group # 1 (Age: 18-21years) (n = 80)	Group #2 (Age: 22-25years) (n = 75)
>12 ng/ml	18 (22.5%)	6(8%)
7-12ng/ml	47 (58.75%)	41(54.6%)
<7 ng/ml	15 (18.75%)	28(37.3%)

Table I

COMPARISON OF TESTOSTERONE LEVEL BETWEEN SUBJECTS OF AGE 18-21 YEARS & THOSE OF AGE 22-25 YEARS

	Testosterone level in ng/ml		t- Test
	Mean	SD	
Group # 1 (Age: 18-21years) (n = 80)	9.40	2.986	0.002
Group #2 (Age: 22-25years) (n = 75)	7.89	2.891	

Table II

DISCUSSION

In this study there was significant difference in the Testosterone level between two groups of male subjects having an age of 18-21 years (mean T level=9.40±2.9 ng/ml) and 22-25 years (mean T level=7.89±2.8ng/ml) respectively. It means that decline in testosterone level starts at or around mid-twenties, a finding which is consistent with the finding of Mazur, A et al[18] showing that T levels peak in the late teens and early 20s, and then usually decline slowly throughout adult life in men. There are similar age trends for male libido, aggressiveness and antisocial deviance, all being highest among teenagers and men in their early twenties, then diminishing.[18] Gapstur, SM showed that the decline in T level starts in thirties.[19]

Although the age-related decrease in blood testosterone has been well documented, yet the mechanism responsible for this decrease is not clear. Multiple mechanisms are suggested for the age-related decline in testosterone like the decrease in the number of Leydig cells, diminished testicular response to pituitary signals such as luteinizing hormone (LH), age-related increase in sex hormone binding globulin (SHBG) which tightly binds testosterone thus decreasing its bio available fraction.[20]

The recent findings describe a novel mechanism involving increased cyclooxygenase-2 (COX2) and its tonic inhibition of steroidogenic acute regulatory (*StAR*) gene expression and testosterone production in aging Leydig cells. Luitinizing hormone (LH) binds to its receptors on the Leydig cells of the testis and not only induce the synthesis of cAMP but also releases the arachidonic acid (AA) from the membrane lipids through G-protein mediated activation of phospholipase A_2 (PLA_2).[21,22] The cAMP causes the activation of protein kinase A (PKA) in PKA phosphorylation pathway leading to the stimulation of StAR gene expression and increased steroid hormone biosynthesis. While the AA is acted upon by two enzymes cyclooxygenase (COX) and lipoxygenase (LOX), the products of which transduce signals to the nucleus. The AA metabolites produced by lipoxygenase activities enhanced steroidogenesis.[23,24] COX has two isozymes i.e. COX-1 and COX-2. An earlier study reported that prostaglandin PGF_{2}, an AA metabolite produced by COX2, inhibited *StAR* gene expression by inducing a negative transcription factor that binds to the *StAR* promoter to depress *StAR* gene transcription and this is called tonic inhibition of StAR gene.[25] It has been reported that COX2 expression is up-regulated during the aging process in various tissues,[26,27] and, importantly, that COX2 mRNA level increased in aged Leydig cells.[28] Recently, levels of COX2 protein, StAR protein and testosterone production were analyzed in Leydig cells isolated from male Brown Norway rats that were 3, 20 and 30 months of age.[29] The results showed that the levels of COX2 protein in Leydig cells increased with age, an increase inversely related to decreases in StAR protein, blood testosterone concentrations and testosterone biosynthesis. These studies indicate that a COX2-dependent tonic inhibition of *StAR* gene expression is enhanced during the course of male aging and reduces the sensitivity of Leydig cells to LH or cAMP stimulation. Consequently, the increased COX2 expression results in decreased testosterone biosynthesis. These observations were corroborated by results from in vitro experiments with isolated aged Leydig cells and in vivo experiments with aged rats.[29] Inhibition of COX2 activity increased cAMP-stimulated StAR protein and testosterone biosynthesis in Leydig cells isolated from 24-month-old Brown Norway rats. Strikingly, subsequent dietary supplementation with the selective COX2 inhibitor, DFU, increased blood testosterone concentrations and StAR protein in the Leydig cells in a dose-dependent manner.

The studies of COX2 inhibition indicated the decreased production of PGF which released the tonic inhibition. Reduction of this tonic inhibition dramatically increased the sensitivity of Leydig cells to cAMP stimulation, with sub-threshold levels of cAMP or PKA activity resulting in maximal levels of *StAR* gene expression and steroid hormone production in Leydig cells.[30] Now, more current studies suggest that inhibition of COX2 activity may result in the reduction of COX2-generated AA metabolites that inhibit *StAR* gene expression and also increase 5-lipoxygenase-generated AA metabolites that enhance *StAR* gene expression, resulting in a significant increase in testosterone production in Leydig cells.

There is an increase in the anxiety and stress with the increase in the age of men. Stress and other conditions that elevate circulating adrenocorticotropine hormone (ACTH) and cortisol levels lead to depressed testosterone levels in animals and in men.[31,32] Excessive exposure to cortisol initiates apoptosis in rat Leydig cells, potentially contributing to the suppression of testosterone levels.[33]

The increase in reactive oxygen species is also associated with increase in age. ROS produced by endogenous cellular processes either physically disrupts membrane lipids or inappropriately activates the cellular desensitization machinery, resulting in attenuation of LH receptor signaling to adenylyl cyclase with concomitant decreases in maximal levels of cAMP. This attenuation of cAMP production has short-term effects on the intracellular transfer of cholesterol to the mitochondria and longer-term effects on the metabolism of cholesterol to testosterone.[34]

CONCLUSIONS

In this study we have observed the testosterone level in male subject is significantly lowered at 22–25 years of age as compared to 18–21 years of age. It means that now-a-days the testosterone decreases at an earlier age as compared to the previously studies in the past. As there could be a possible correlation between low testosterone levels and increased risk of cerebrovascular and cardiovascular diseases, osteoporosis and hip fracture at an earlier age, well planned and large scale studies are required to address the issue in detail and to find out the causes of early decline of the testosterone level in young male subjects.

Also there is a trend of late marriages in many families in our society, so they should also consider this earlier decrease in testosterone levels, occurring now-a-days, while doing arrangements for a marriage.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

UUR: Conception and design; acquisition, analysis and interpretation of data; Final approval of the version to be published

NH, Ub & NA: Acquisition of data, Drafting the manuscript & Final approval of the version to be published

MS & MT: Drafting the manuscript & Final approval of the version to be published

JUR: Critical Revision & Final approval of the version to be published

CONFLICT OF INTEREST

Authors declare no conflict of interest

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NONE DECLARED

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