

## Testosterone levels in men with chronic migraine

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### Abstract

Chronic migraine is a frequent and debilitating condition affecting 14% of the general population. This prospective observational pilot study investigated whether men with chronic migraine have lower than expected total serum testosterone levels. We identified 14 men ages 26-51 at our Institution who fulfilled the ICHD-3b criteria for chronic migraine and obtained serum total testosterone levels. The mean total testosterone level in our 14 patients was 322 ng/dL (range: 120-542 ng/dL) which is in the lower 5% of the reference range for our laboratory (300-1080 ng/dL). Men with chronic migraine had lower total testosterone levels compared to published age-matched normative median values by a median difference of 62 ng/dL ( $P=0.0494$ ). This finding suggests that hypothalamic regulation is altered in patients with chronic migraine. Further studies are warranted to determine whether testosterone supplementation in men with chronic migraine reduces the number of headaches or the associated symptoms of hypogonadism.

### Introduction

Migraine is a common, multifactorial, disabling primary headache disorder.<sup>1,2</sup> According to the International Classification of Headache Disorders, 3<sup>rd</sup> edition (beta version), chronic migraine refers to a headache occurring on 15 or more days per month for more than 3 months which has the features of migraine on at least 8 days per month.<sup>2</sup> According to the National Health Interview Survey in 2012, the overall prevalence of migraine or severe headache is 14.2% in the United States, with 19.1% of females and 9.0% of males affected with substantial variations depending on age.<sup>3</sup> Migraine ranked as the third most common cause of disability worldwide in individuals under 50 as reported by the Global Burden of Disease

Survey 2015.<sup>4</sup> Migraines are considered to involve the hypothalamus, brainstem, and cortex which regulates autonomic, affective, cognitive, and sensory functions.<sup>1</sup> Chronic migraine may affect hypothalamic hormonal secretion. Many men with chronic migraine exhibit symptoms that are frequently seen with hypogonadism (depressed mood, reduced energy, difficulty concentrating).

Positron emission tomography (PET) has shown hypothalamic activation in spontaneous migraine attacks which persists after headache relief by sumatriptan.<sup>5,6</sup> Attention has focused on the function of the hypothalamus in circadian rhythms, pain control coordinating the activity of the sympathetic and parasympathetic nervous systems, and in maintaining homeostasis.<sup>1,5,7</sup> In addition, the hypothalamus is integrally involved with the body's responses to stress.<sup>7</sup> The hypothalamus secretes gonadotropin-releasing hormone (GnRH) which stimulates the anterior pituitary gland to release luteinizing hormone (LH) from the gonadotrophs.<sup>8</sup> The receptors for LH are located on Leydig cells in the testis which synthesize testosterone following LH stimulation.<sup>8</sup> Figure 1 depicts the hypothalamic regulation of testosterone.

There are no reports known to the authors on the effect that chronic migraine may have on testosterone levels in men. We investigated whether men with chronic migraine have lower than expected total serum testosterone levels. In this prospective pilot study, we present our findings pertaining to the interaction between chronic migraine and testosterone levels. We also discuss the impact of chronic migraine on the regulation of the hypothalamo-pituitary-gonadal axis.

### Materials and Methods

#### Patient population

Under an institutional review board (IRB) approved protocol, we prospectively identified 14 men who fulfilled the ICHD-3b criteria for chronic migraine without opioid or barbiturate overuse at our Institution. These patients were evaluated by a neurologist at our Institution's outpatient clinic in a metropolitan community. All men obtained serum total testosterone levels. These values were compared to the local laboratory normal values and to published age-matched controls.<sup>9</sup>

#### Statistical analysis

Data are presented in listings and summarized as either mean (SD) or median

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Key words: Neurology, Migraine, Testosterone, Hypothalamus, Hypogonadism.

Acknowledgements: the authors acknowledge Norton Healthcare for their continued support. They also acknowledge Douglas John Lorenz, Ph.D., Andrew J. Shearer, B.S., and Lauren A. Shelton, for their contributions to this work (data management and data checks for quality).

Contributions: LS made substantial contributions to the conception and design, analyzed and interpreted the data, performed the literature search, and was the major contributor in the writing of the manuscript. TS and BP made substantial contributions to the conception and design, analyzed and interpreted the data, and revised the draft critically for important intellectual content. BS is the statistician who performed the statistical analysis in this work and also contributed to the conception and design, analyzed and interpreted the data, and revised the draft critically for important intellectual content.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Conference Presentation: Presented as a poster at the 57<sup>th</sup> Annual Scientific Meeting of the American Headache Society, June 18-21, 2015, Washington, D.C. U.S.A.

Received for publication: 21 February 2019.  
Revision received: 14 April 2019.  
Accepted for publication: 14 April 2019.

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Neurology International 2019; 11:8079  
doi:10.4081/ni.2019.8079

(interquartile range: 25<sup>th</sup> %-tile & 75<sup>th</sup> %-tile). To test whether the testosterone distribution amongst those men with migraines differed from a control population distribution, the median testosterone from a published age-specific control population was matched to the age-specific testosterone level for the 14 migraine subjects.<sup>9</sup> To assess whether these age-matched groups differed, Wilcoxon Signed Rank test was

used to test for the testosterone distribution difference. An a-priori two-sided significance level of 5% was used to interrogate any observed difference.

## Results

A total of 14 men fulfilled the criteria for inclusion. The mean age was 36.1 years (range: 26-51 years). The local laboratory normal range for total testosterone was 300-1080 ng/dL. Table 1 illustrates the total testosterone levels of migraine patients compared to published age-matched controls. The mean total testosterone level in the 14 patients with chronic migraine was 322 ng/dL (range: 120-542 ng/dL).

For published age-matched controls, the mean total testosterone level was 384 ng/dL (SD=10.3). Six males (43%) had testosterone levels below the minimum of the normal local laboratory range. Men with chronic migraine had lower total testosterone levels compared to published age-matched controls by a median difference of 62.0 ng/dL (interquartile range of 0.34 to 130). The Wilcoxon Signed rank statistic revealed a statistically significant difference between the two distributions ( $P=0.0494$ ).

## Discussion

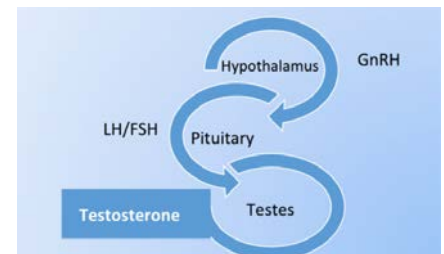
In our pilot study, men with chronic migraine had statistically significant lower total testosterone levels compared to an age-matched normative population, suggesting that hypothalamic regula-

tion is altered in patients with chronic migraine. We propose that the suppression of the hypothalamic pituitary axis as a result of chronic migraine inhibits the release of GnRH resulting in secondary hypogonadism. A host of studies have investigated the pathophysiology of the hypothalamus in both cluster headache<sup>10</sup> and chronic migraine,<sup>1,5-7,11</sup> however, a paucity of studies have explored the interaction between testosterone levels and chronic migraine, tension type headache (TTH), and cluster headache.<sup>12,13</sup> It has been suggested that both male and female sex hormones could influence the course of primary headaches, specifically, tension-type headache, migraine, and cluster headache.<sup>14</sup> Romiti and colleagues studied plasma testosterone levels in cluster headache and non-cluster headache controls.<sup>13</sup> Plasma testosterone levels were significantly lower during the cluster attack and were within the reference limits in the remission period of episodic cluster headache.<sup>13</sup> These authors suggest that a decrease of plasma testosterone levels in episodic cluster headache should be considered in relation to disordered rapid eye movement (REM) sleep in cluster headache.

The present study and that of Romiti *et al.* highlighted testosterone levels in migraine and cluster headache, respectively.<sup>13</sup> Both studies reported that testosterone levels were significantly lower in the headache disorder group compared to controls. We demonstrated that men with chronic migraine had lower total testosterone levels compared to their age-matched control by a median difference of 62 ng/dL (interquartile range of 0.34 to

130). In addition, there was a statistically significant difference between the two distributions ( $P=0.0494$ ). Six males (43%) had testosterone levels below the minimum of the normal local laboratory range. Of note, the mean total testosterone level in our 14 patients with chronic migraine was 322 ng/dL which is in the lower 5% of the reference range for our laboratory (300-1080 ng/dL). This finding supports that testosterone levels are very low in migraine patients. Abnormality of the hypothalamus-pituitary-gonadal axis is believed to be involved in the pathogenesis of migraine.<sup>15</sup> In Li and colleagues' study of the levels of HPG axis hormones serum FSH, LH, estradiol, progesterone, testosterone, prolactin, and GnRH, they reported that these hormones were abnormal in migraineurs and were associated with migraine-related clinical characteristics.<sup>15</sup>

Hypogonadism refers to "a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and a normal



**Figure 1. Hypothalamic regulation of testosterone.**

**Table 1. Total testosterone levels of migraine patients compared to published age-matched controls.**

| Age | Total testosterone of migraine patients (ng/dL) | Normal for reference lab (1=yes;0=no) | Total testosterone of published age-matched controls (ng/dL)* |
|-----|---|---------------------------------------|---|
| 26  | 406   | 1                                     | 406   |
| 27  | 428   | 1                                     | 403   |
| 30  | 120   | 0                                     | 392   |
| 32  | 434   | 1                                     | 386   |
| 33  | 270   | 0                                     | 383   |
| 33  | 324   | 1                                     | 383   |
| 34  | 378   | 1                                     | 383   |
| 35  | 268   | 0                                     | 380   |
| 37  | 542   | 1                                     | 378   |
| 38  | 360   | 1                                     | 378   |
| 40  | 230   | 0                                     | 375   |
| 42  | 310   | 1                                     | 375   |
| 48  | 196   | 0                                     | 375   |
| 51  | 245   | 0                                     | 375   |

Normal Testosterone Range (Local Reference Lab): 300-1080 ng/dL. \*See Kelsey *et al.* 2014.<sup>9</sup>

number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-testicular axis".<sup>16</sup> Hypogonadal symptoms include diminished libido, fatigue, poor concentration, erectile dysfunction, and depressed mood in the setting of low serum testosterone levels.<sup>17</sup> Many men with chronic migraine exhibit symptoms that are frequently seen with hypogonadism, specifically, depressed mood, reduced energy, and difficulty concentrating. Testosterone supplementation has been shown to be beneficial in improving both hypogonadal symptoms and serum total testosterone levels.<sup>16,17</sup> Testosterone therapy in hypogonadal men has been shown to be highly effective and safe for improving lower urinary tract symptoms, cardiometabolic risk, and major adverse cardiovascular events<sup>18</sup> as well as urinary and sexual function and quality of life.<sup>19</sup> Testosterone serves as a neuroprotective agent,<sup>20</sup> suggesting a valuable role in the treatment of chronic migraine. Continuous testosterone has also been reported as beneficial in reducing the severity of migraines in both pre- and post-menopausal women.<sup>21</sup> These studies demonstrate that testosterone effectively treats migraine headaches in both men and women and that low testosterone is likely causal and not the result of migraines.

The strength of the present study is the prospective evaluation of the possible role of testosterone in migraine headaches as it is far less studied than estrogen/progesterone. Our study is limited by its small sample size. Prospective, randomized studies with a larger sample size are warranted to permit generalizability of our results.

## Conclusions

In this pilot study, men with chronic migraine had statistically significant lower total testosterone levels compared to an age-matched normative population. Further investigation is necessary to determine whether testosterone supplementation in men with chronic migraine reduces either the number of headache days per month or

the accompanying symptoms of hypogonadism.

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