Effect of Opioids on Testosterone Levels:
Cross-Sectional Study using NHANES

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take responsibility for the work.

Abstract

Objective. Opioids can suppress gonadal hormone
production, which may result in low testosterone lev-
el. To date, there have been no large-scale popula-
tion-based studies examining the extent to which
opioid use may contribute to changes in testosterone
levels.

Design. Cross-sectional study.

Setting. 2011–2012 National Health and Nutrition
Examination Survey.

Subjects. Participants 17 years and older who had
data on prescription medication usage and serum tes-
tosterone levels available. Participants were divided
in two groups, opioid exposed and unexposed.

Methods. Testosterone levels of participants who
responded that they had been exposed (n = 320) to
prescription opioids in the past 30 days were compared with those who were unexposed (n = 4909). The number of participants with low testosterone levels was calculated and unadjusted and adjusted analyses were performed.

Results. Participants on opioids had higher odds of having low testosterone levels than those unexposed, odd ratio (OR) = 1.40, 95% confidence interval (CI) (1.07–1.84). After controlling for opioid exposure, as the age and the number of comorbidities increased, the odds of having low testosterone levels significantly increased in all categories. Compared with participants between 17 and 45 years of age, participants >70 years had OR = 1.70, 95% CI (1.16–2.50). Compared with participants with no comorbidities, participants with >2 comorbidities had OR = 1.69 95% CI (1.24–2.30).

Conclusion. When assessing the impact of opioids on testosterone, the effects of age and medical conditions should be considered.

Key Words. Opioids; Testosterone; Age; Comorbidities; National Health and Nutrition Examination Survey

Introduction

Opioids exert their analgesic effect primarily through their activity on mu opioid receptors in the central nervous system. In addition to the analgesic effect, mu opioid agonism may affect the neuroendocrine system, suppressing the hypothalamic-pituitary-gonadal axis and the secretion of gonadotropin-releasing hormone [1,2], resulting in reduced testosterone synthesis and lower testosterone plasma levels [3,4]. Decreased levels of testosterone can lead to reduced libido, fatigue, decreased muscle mass, and osteopenia [5]. This syndrome is often referred to as opioid induced androgen deficiency (OPIAD).

Previous studies that have assessed the effect of opioids on testosterone levels evaluated small numbers of patients (<54 patients) [3,6–9] and focused on specific populations [e.g., heroin addicts [10], opioid prescription medication addicts [11], patients receiving opioids intrathecally [12–14], or patients with cancer [9]], thus, making the findings difficult to generalize. Studies in patients using intrathecal opioid administration and in methadone maintenance therapy have showed high incidences of androgen deficiency [5,11]. Studies in patients on oral opioids for the treatment of pain also reported a link between reduced testosterone levels and opioid use [3,6–9,15]. Determining the association between opioids and testosterone levels in a larger study of the general population will assist in understanding opioid effects and guiding the clinical management of patients on opioid therapies.

The National Health and Nutrition Examination Survey (NHANES) offers an excellent opportunity to determine the association between opioids and testosterone levels in a representative sample of the US population. NHANES is a program that continually collects information about the health and nutrition of the US population through the use of interviews and medical examinations. NHANES includes questions about usage of prescription medications and, for the first time in the 2011–2012 period, the survey also measured testosterone levels in participants 6 years and older. The use of the NHANES data offers many advantages: 1) it is a representative sample of the US population that assures coverage of individuals often excluded from studies, such as minorities or low income citizens. 2) The study findings can be generalized to the US population. 3) The data are of high quality due to strict quality control and quality assurance protocols. 4) The use of standardized analyses of lab results decreases variability of results. 5) The survey offers transparency as the NHANES data are made publicly available.

Using the 2011–2012 NHANES results, we conducted a cross-sectional study to assess the association of testosterone levels with opioid use in a larger representative sample of the general US population.

Methods

Data Source and Study Population

In 2011–2012, 13,431 persons were selected for participation in NHANES from 30 different study locations across the United States [16]. Of those selected, 9,756 completed the interview and 9,338 were examined. NHANES selection of participants for the survey was intended to represent the US civilian population. To produce reliable estimates, NHANES oversampled persons 60 years and older, African Americans, Hispanics, and low income whites. The NHANES interview included demographic and health-related questions, such as self-report of medical conditions and medications. The examination component consisted of medical examinations as well as laboratory tests. NHANES was designed to facilitate and encourage participation. Transportation was provided to and from the mobile center where the health examination and laboratory tests took place. The NHANES sites that administered laboratory tests were open 5 days per week. Participants were randomly assigned to exams in the morning, afternoon, or evening sessions. Participants received compensation, and a report of medical findings was given to each participant [16].

Inclusion Criteria

We included in this study participants 17 years and older who had data on prescription medication usage...
and serum testosterone levels available. Participants were divided into two groups, opioid exposed and unexposed. Exposed were those who responded that they were taking opioid analgesics when asked: “In the past 30 days, have you used or taken medication for which a prescription is needed?” Unexposed were those responders who did not report taking opioid analgesics.

The following procedure was used to capture prescription medications in NHANES: If the survey participants answered “yes” to the question above, they were asked to show the interviewer the medication containers of all the products used. For each medication reported, the interviewer entered the product’s complete name from the container into a computer. If no container is available, the interviewer asked the participant to verbally report the name of the medication. NHANES used a proprietary database that contained all prescriptions drug products available in the US drug market. NHANES uploaded the files to a laptop computer and incorporated them into a search engine for use by the interviewers. When the interviewer entered the medication name into the computer, the name was automatically matched to a prescription drug in the database to identify an exact match or similar text matches. If an exact match of the medication could not be found, the interviewer was instructed to select “drug not found on list.” Participants were also asked how long they had been taking the medication [16].

**Testosterone Measurement**

To measure total serum testosterone, NHANES used a validated isotope dilution liquid chromatography tandem mass spectrometry method. This method used liquid–liquid extractions of serum to isolate the steroid and stable isotope-labeled testosterone as an internal standard to correct for sample recovery. Assay imprecision was 5% [17].

**Opioid Exposure**

We assessed opioid exposure as a yes/no variable. We also measured the duration of opioid exposure and created three categories: no exposure, up to 1 month, or >1 month of exposure.

**Effect of Age and Comorbidities**

Age and presence of comorbidities are variables that can significantly affect testosterone levels [18–21]. Age was measured as a continuous and categorical variable. We grouped participants into four different categories: 17–45, 46–60, 61–70, and >70 years of age.

In NHANES, participants self-report the presence of health conditions and respond to questions such as: “Has a doctor or other health professional ever told you that you had a stroke?” The medical conditions were grouped into the following comorbidity categories: anemia, arthritis (including any arthritis and gout), asthma, cancer, cardiovascular disease (including acute myocardial infarction, angina, congestive heart failure, and cerebral ischemia), chronic bronchitis (including emphysema), diabetes, hypertension (including risk factors such as hyperlipidemia and overweight), liver disorders, and miscellaneous (thyroid problems and celiac disease). The number of comorbidity categories was counted, and participants were divided into 4: no comorbidities, 1, 2, and >2 comorbidities.

**Outcomes**

We calculated the number of participants who had levels of testosterone that were considered low for each group. In men those levels were: <300 ng/dL [22] and in women, <30 ng/dL [23], independent of age. We also assessed the testosterone levels as a continuous variable.

**Measuring the Association of Testosterone Levels with Opioid Exposure**

To assess the association of opioid exposure with testosterone levels, we conducted unadjusted and adjusted analyses using logistic and linear regression models. In the logistic regression, the outcome was low vs normal levels of testosterone. In the linear regression, the outcome was the testosterone levels. We also report the unadjusted and adjusted association of age, gender, and comorbidities on testosterone levels.

**Univariate and Multivariate Logistic Regression**

In the logistic regression analyses, both men and women were included because the cutoffs for defining low levels of testosterone were based on the sex of the participant and because the interaction between opioid exposure and sex, which assessed whether the effect of opioids on testosterone would change depending on sex, was not statistically significant OR = 1 (0.97) (P = 0.9).

In the unadjusted analyses, the outcome was low vs normal levels of testosterone and the risk factor was opioid exposure as a yes/no variable. We also built a model that used duration of opioid exposure.

In the adjusted analyses, the outcome was low vs normal levels of testosterone and the risk factors, in addition to opioid exposure, included age categories, number of comorbidities, and sex. To assess whether the effect of opioids on testosterone levels changed depending on the age of the participant, we tested the interaction of the age categories with opioid exposure. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported.
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Univariate and Multivariate Linear Regression

We reported the results of linear regression only in men because testosterone levels in women on opioids were similar to those observed in women unexposed to opioids.

For the adjusted analysis, the outcome was levels of testosterone and the risk factors included were opioid exposure along with age categories and number of comorbidities. To assess whether the effect of opioids on testosterone levels changed depending on the age of the participant, we tested the interaction of the age categories with opioid exposure.

To obtain estimates representative of the US population and to avoid overstating statistically significant associations, we correctly accounted for the complex survey design [24]. We used in all the analyses the Primary Sampling Unit variable (sdmvpsu) as the stratification variable (sdmvstra) and the mobile examination center (MEC) exam variable (wtmec2yr) as the weight variable. STATA version 12.1 was used to conduct the analyses.

Results

Among the 6,007 participants 17 years and older who completed the interview, 778 had missing testosterone data. Therefore, a total of 5,229 participants met the inclusion criteria and 6.4% of those reported being exposed to opioids in the last 30 days. Participants who made up the opioid-exposed group were older, more likely to be women, and had more comorbidities compared with those in the unexposed group (Table 1). The time of venipuncture was similar in opioid-exposed and unexposed participants.

In terms of duration of opioid exposure, 29.3% of those participants exposed to opioids were exposed up to a month and 70.7% for more than a month. Of the participants who were exposed for more than a month, 34.4% reported being exposed for more than 3 years. The most commonly used opioids were hydrocodone, oxycodone, and tramadol, and 11.1% of participants reported being on more than one opioid (Table 2).

The proportion of participants who had low testosterone levels was higher in the opioid-exposed groups for both men and women (Table 1). Participants who had taken opioids had higher odds of having low levels of testosterone than those who were unexposed to opioids, unadjusted OR = 1.40, 95% CI (1.07–1.84; Table 3). When opioid exposure was categorized according to duration (no exposure, up to 1 month, or >1 month of exposure), participants with >1 month of exposure had higher odds of having low levels of testosterone than those who were unexposed, OR = 1.40, 95% CI (1.01–1.96). Participants with up to 1 month of opioid exposure also had higher odds of having low levels of testosterone than those who were unexposed, but this finding did not reach statistical significance, OR = 1.44, 95% CI (0.8–42.47).

After controlling for age, comorbidities, and sex, the OR for low testosterone levels due to opioid exposure decreased from 1.40 to 1.15, 95% CI (0.76–1.74). The changes in OR estimates after adjusting for age, comorbidities, and sex are presented in Table 3. We did not detect a significant interaction between effect of opioid exposure on testosterone levels and age (P values ranged from 0.24 to 0.7).

Age and presence of comorbidities affected testosterone levels even after controlling for opioid exposure. As the age and the number of comorbidities increased, the odds of having low testosterone levels significantly increased in all categories. Compared with participants between 17 and 45 years of age, participants >70 years had OR = 1.70, 95% CI (1.16–2.50). Compared with participants with no comorbidities, participants with >2 comorbidities had OR = 1.69 95% CI (1.24–2.30), Table 4.

The testosterone levels in men exposed to opioids were numerically lower than those observed in the unexposed group, with the exception of the 46–60 year old age group. The lowest numerical testosterone levels in both the exposed and unexposed groups occurred in men over the age of 70.

The distribution of the levels of testosterone was not too far from normal with a skewness of 1.3. The unadjusted linear regression analysis in men showed that the levels of testosterone were 37 ng/dL lower in participants exposed to opioids than those who were unexposed, 95% CI (−80.72 to 5.67). After controlling for age and presence of comorbidities, men on opioids had average levels of testosterone that were numerically lower than those in the unexposed group, 20.02 ng/dL, 95% CI (−72.70 to 32.65), although this difference did not reach significance. We did not detect a significant interaction between the effect of opioid exposure on testosterone levels and age (P values ranged from 0.14 to 0.61).

The levels of testosterone decreased an average of 1.1 ng/dL per year of age, 95% CI (−1.7 to −0.5). After controlling for opioid exposure and age as the number of comorbidities increased, the levels of testosterone increased. Men with >2 comorbidities had levels of testosterone that were 83.925 ng/dL lower, 95% CI (−128.36 to −39.48) than men with no comorbidities, Table 4.

Discussion

In a representative sample of the US population aged 17 years and older, 6.4% had used opioid medications in the last 30 days based on NHANES 2011–2012 data. Participants on opioids were older, had more comorbidities, and were also more likely to have lower levels of testosterone than those not on opioids. The two methods that were used to assess the association of opioids
and testosterone levels, comparing participants with low levels of testosterone to participants with normal levels and analyzing the levels of testosterone as a continuous variable, yielded complementary results.

The study findings suggest that the association of opioids and testosterone was similar in men and women, consistent with other studies [5,7]. This was confirmed by including men and women in the analysis, using thresholds that were sex-specific to define low levels of testosterone, and testing the interaction between sex and opioid exposure in the regression model. The advantage of this approach over having one model for men and one for women is that using a combined sample we improve the statistical ability to detect the opioid association—we are not losing statistical

### Table 1  Characteristics and testosterone levels of participants exposed and unexposed to opioids

| Variables                                      | No, Opioid* | Yes, Opioid* |
|------------------------------------------------|-------------|--------------|
| Participants 17 years or older with testosterone level data (N = 5229), n (%) | 4909 (93.6) | 320 (6.4)    |
| Age in years, mean (SE)                        | 45.7 ± 0.8  | 49.1 ± 1.1   |
| Sex, n (%)                                      |             |              |
| Men                                            | 2459 (48.9) | 146 (44.6)   |
| Women                                          | 2450 (51.1) | 174 (55.4)   |
| Comorbidity, n (%)                             |             |              |
| None                                           | 1484 (29.5) | 30 (11.5)    |
| ≥1                                             | 3425 (70.5) | 290 (88.5)   |
| Testosterone levels (ng/dL) ± SE by age (in years) |             |              |
| group in men                                    |             |              |
| 17–45 (n)                                      | 423.2 ± 8.6 (1248) | 345.9 ± 26.6 (45) |
| 46–60 (n)                                      | 391.1 ± 7.5 (544) | 425.5 ± 33.1 (53) |
| 61–70 (n)                                      | 453.4 ± 22.0 (354) | 331.3 ± 54.9 (29) |
| >70 (n)                                        | 356.5 ± 14.2 (313) | 222.3 ± 38.4 (19) |
| Testosterone levels (ng/dL) ± SE by age (in years) |             |              |
| group in women                                  |             |              |
| 17–45 (n)                                      | 28.9 ± 1.0 (1238) | 33.2 ± 9.2 (66) |
| 46–60 (n)                                      | 20.0 ± 1.0 (580) | 15.1 ± 1.5 (43) |
| 61–70 (n)                                      | 19.5 ± 0.9 (341) | 25.3 ± 8.6 (38) |
| >70 (n)                                        | 19.7 ± 1.0 (291) | 18.1 ± 2.6 (27) |
| Number of participants with low testosterone levels† (%) | 2588 (53.2) | 198 (61.4)   |
| Number of women with low testosterone levels† (%) of total women | 1873 (77.0) | 141 (82.6)   |
| Number of men with low testosterone levels† (%) of total men | 715 (28.3) | 57 (35.1)    |
| Number of participants with low testosterone levels† and no comorbidities, (%) | 649 (12.8) | 11 (3.5)     |
| Number of participants with low testosterone levels† and at least one comorbidity, (%) | 1939 (40.4) | 187 (57.9)   |
| In each age group, number of participants with low testosterone levels† and at least one comorbidity (%) | 3425 (70.5) | 290 (88.5)   |
| 17–45 (# cases/total participants)             | 654/1304 (51.0) | 53/86 (67.9) |
| 46–60 (# cases/total participants)             | 578/894 (61.9) | 56/91 (59.3) |
| 61–70 (# cases/total participants)             | 356/641 (56.4) | 40/67 (65.1) |
| >70 (# cases/total participants)               | 351/586 (63.7) | 38/46 (82.5) |
| Time of venipuncture, n (%)                    |             |              |
| Morning                                        | 2444 (50.3) | 144 (47.6)   |
| Afternoon                                      | 1768 (33.9) | 123 (35.2)   |
| Evening                                        | 697 (15.9)  | 53 (17.2)    |

* Results reflect the complex survey design (see Methods section).
† Low levels of testosterone were: in men <300 ng/dL and in women <30 ng/dL.
Adjusted only by sex 1.39 (0.98–1.97)
Adjusted by age, number of comorbidities, and sex 1.15 (0.76–1.74)

* For odds ratio (OR) >1, opioid exposure increased the odds of having low levels of testosterone.
† Results reflect the complex survey design (see Methods section).

We tested whether the effect of opioids on testosterone levels was more pronounced in some age groups, but none of the interactions were statistically significant. However, there were only 19 participants in the 70 years and older group, the age group in which the decrease in testosterone levels was numerically largest; therefore, a differential effect of opioids on testosterone levels in specific age groups cannot be ruled out.

We found that testosterone levels in men exposed to opioids were on average, 20.02 ng/dL lower than in unexposed men after controlling for the effects of comorbidities and age (although this difference was not statistically significant). This estimate is much smaller than the estimates reported in the literature [3,7–9]. In contrast to these studies, which had smaller sample sizes or were conducted in specific populations, our study examined the opioid effect on testosterone levels in a larger sample of the general population. However, it has been reported that analyses of cross-sectional studies tend to underestimate the effect of age on testosterone when compared with analyses of longitudinal studies (when subjects are followed over time) [20,21]. Similarly, the lack of longitudinal measurements could mean that the association of opioids and testosterone may be underestimated in this study.

This study showed that having low levels of testosterone is prevalent in the US general population in both women and men. The cutoffs that we used are the ones recommended by the National Institutes of Health: 300 ng/dL for men and 30 ng/dL in women [22,23]. Opioid exposure was not the only factor that affected testosterone levels. We found that age and comorbidities strongly influenced testosterone levels, confirming previously reported studies [18–20]. We also observed a statistically significant decrease in testosterone levels per each year of age, equivalent to a 0.24% decrease in testosterone levels per year. This decrease is of similar magnitude to the cross-sectional assessment of the Massachusetts male aging study that included men between 40 and 70 years of age [21]. Several medical conditions have been associated with decreased testosterone levels, notably obesity, diabetes, chronic obstructive pulmonary disease, and hypertension [15,19,25]. We found that as the number of comorbidities increased, testosterone levels decreased, and the odds of having low levels of testosterone were higher.

One of the strengths of this cross-sectional study is that it was based on NHANES, which uses a complex, multistage, probability sampling design to select participants representative of the US population. For that reason, our study findings may be generalized to the larger US population. However, this study was limited in that it assessed the exposure (opioid exposure) and the
outcome (testosterone levels) simultaneously. Therefore, the association between lower levels of testosterone in participants exposed to opioids does not necessarily imply causality. As mentioned above, cross-sectional studies tend to underestimate the effect of age on testosterone levels; therefore, the effect of opioids on testosterone could be underestimated in this study. An additional limitation is that in this study, we could not assess the impact of pain intensity or the type of pain syndrome on testosterone levels.

In our study, the effect of opioids was assessed as a class, but mechanistically not all opioids are the same [15]. Variations in opioid receptor binding or in the affinity for the different opioid receptors could affect how opioids influence testosterone levels, as the effect of opioids on the neuroendocrine system is mediated through opioid receptors. In addition, some of the non-opioid actions of the opioids could have affected testosterone levels. For example, opioids whose mechanism of action involves inhibition of norepinephrine reuptake may have a lower impact on testosterone levels than opioids whose analgesic effect is only through activation of opioid receptors [26]. Another shortcoming is that the daily dose of opioids taken by the participants was not known, so the effect of opioid dose was not assessed. Not accounting for opioid dose could result in an underestimation or overestimation of the association of opioids and testosterone levels as the higher the opioid dose, the more likely it is to have lower levels of testosterone [11,15].

In summary, participants on opioids were more likely to have low levels of testosterone. Increasing age and presence of medical conditions are important risk factors that are also associated with low levels of testosterone. When assessing the impact of opioids on testosterone levels, prospective studies need to account for the effect of these risk factors in the study design or in the analysis.

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**Table 4** Association of opioid, age, and comorbidities with testosterone: adjusted and unadjusted results*

|                  | Univariate Logistic Analysis OR (95% CI)† | Multivariate Logistic Regression OR (95% CI)† | Univariate Linear Analysis in Male (Mean Change in Testosterone Levels Compared with the Reference) (95% CI)‡ | Multivariate Linear Regression in Males (Mean Change in Testosterone Levels Compared with the Reference) (95% CI)‡ |
|------------------|------------------------------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| **Opioid**       | 1.40 (1.07 to 1.84)                      | 1.15 (0.76 to 1.74)                         | −37.52 (−80.72 to 5.67)                                                                          | −20.02 (−72.70 to 32.65)                                                                         |
| **Age in years** |                                           |                                              |-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| 17–45 Reference  |                                           |                                              |                                                                                                |                                                                                                |
| 46–60 1.80 (1.52 to 2.13) 1.87 (1.51 to 2.33) | Reference                                  | Reference                                  | Reference                                                                                       | Reference                                                                                       |
| 61–70 1.64 (1.30 to 2.07) 1.40 (1.01 to 1.94) | Reference                                  | Reference                                  | Reference                                                                                       | Reference                                                                                       |
| >70 2.07 (1.61 to 2.68) 1.70 (1.16 to 2.50) | Reference                                  | Reference                                  | Reference                                                                                       | Reference                                                                                       |
| **Female**       | 0.12 (0.10 to 0.13)                      | 0.11 (0.10 to 0.13)                         | Results are for men                                                                             | Results are for men                                                                             |
| **Males**        |                                           |                                              |                                                                                                |                                                                                                |
|                  |                                           |                                              |                                                                                                |                                                                                                |
| **Number of conditions** |                                           |                                              |                                                                                                |                                                                                                |
| 0 Reference      | 1.45 (1.16 to 1.83)                      | 1.34 (1.04 to 1.72)                         | −48.55 (−72.40 to −24.70)                                                                       | −51.17 (−73.63 to −28.71)                                                                       |
| 1 1.88 (1.49 to 2.37) 1.53 (1.10 to 2.13) | Reference                                  | Reference                                  | Reference                                                                                       | Reference                                                                                       |
| 2 2.47 (2.04 to 3.00) 1.69 (1.24 to 2.30) | Reference                                  | Reference                                  | Reference                                                                                       | Reference                                                                                       |
| >2 2.80 (2.37 to 3.23) 1.69 (1.21 to 2.17) | Reference                                  | Reference                                  | −38.60 (−114.04 to −46.67)                                                                      | −83.92 (−128.36 to −39.48)                                                                      |

* Results reflect the complex survey design (see Methods section).

† For odds ratio (OR) > 1, opioid exposure increased the odds of having low levels of testosterone.

‡ Negative values indicate lower testosterone levels than the reference category.
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