



Testosterone replacement therapy and hospitalization rates in men with COPD

Chronic Respiratory Disease
Volume 16: 1–9
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DOI: 10.1177/1479972318793004
journals.sagepub.com/home/crd


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Abstract

Testosterone deficiency is common in men with chronic obstructive pulmonary disease (COPD) and may exacerbate their condition. Research suggests that testosterone replacement therapy (TRT) may have a beneficial effect on respiratory outcomes in men with COPD. To date, however, no large-scale nationally representative studies have examined this association. The objective of the study was to assess whether TRT reduced the risk of respiratory hospitalizations in middle-aged and older men with COPD. We conducted two retrospective cohort studies. First, using the Clinformatics Data Mart—a database of one of the largest commercially insured populations in the United States—we examined 450 men, aged 40–63 years, with COPD who initiated TRT between 2005 and 2014. Second, using the national 5% Medicare database, we examined 253 men, aged ≥ 66 years, with COPD who initiated TRT between 2008 and 2013. We used difference-in-differences (DID) statistical modeling to compare pre- versus post-respiratory hospitalization rates in TRT users versus matched TRT nonusers over a parallel time period. DID analyses showed that TRT users had a greater relative decrease in respiratory hospitalizations compared with nonusers. Specifically, middle-aged TRT users had a 4.2% greater decrease in respiratory hospitalizations compared with nonusers (–2.4 decrease vs. 1.8 increase; $p = 0.03$); and older TRT users had a 9.1% greater decrease in respiratory hospitalizations compared with nonusers (–0.8 decrease vs. 8.3 increase; $p = 0.04$). These findings suggest that TRT may slow disease progression in patients with COPD. Future studies should examine this association in larger cohorts of patients, with particular attention to specific biological pathways.

Keywords

Testosterone replacement therapy, chronic obstructive pulmonary disease, hospitalization, androgen therapy

Date received: 12 December 2017; accepted: 13 June 2018

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality internationally, and is predicted to be the third leading cause of death by 2030.¹ Men with COPD often have hypoxemia, multiple comorbidities, and prolonged glucocorticoid exposure,² all of which increase their risk for hypogonadism.^{2,3} It is biologically plausible

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that testosterone deficiency exacerbates COPD symptoms, either directly—via an impact on respiratory muscle—or indirectly—by diminishing overall strength and exercise capacity.^{2,3} Several observational studies have shown that low levels of circulating testosterone levels are associated with adverse respiratory outcomes, including reduced forced expiratory volume in one second (FEV-1) and forced vitality capacity (FVC).^{4–8}

Over the last several years, there has been a growing interest in the potential use of testosterone replacement therapy (TRT) to treat the physical and functional outcomes in patients with COPD. Several randomized controlled trials (RCTs) suggest that TRT is associated with improved body composition, skeletal muscle strength, and exercise capacity in COPD patients.^{9–12} It is hypothesized that TRT may also have a beneficial effect on respiratory outcomes, via either a direct effect on respiratory muscle or an indirect effect, through improvements in overall strength and exercise capacity.^{7,8,13} Evidence regarding improvements in pulmonary function and respiratory muscle strength, however, is inconsistent; and beneficial effects have been reported only when testosterone supplementation has been combined with other interventions such as standardized pulmonary rehabilitation, nutritional support, or resistance training.^{10–12,14–17} To date, no large-scale nationally representative studies have examined the effect of TRT on respiratory outcomes in men with COPD. The purpose of this investigation was to assess whether TRT is associated with a reduced risk of respiratory hospitalizations in nationally representative cohorts of middle-aged and older males with COPD.

Methods

Design and data sources

We conducted retrospective cohort studies of men with COPD using two administrative databases: (1) Clinformatics Data MartTM (CDM) (Optum Insight, Eden Prairie, Minnesota, USA), a database of one of the nation's largest national commercial health insurance programs,^{18–20} and (2) the national 5% national Medicare database.

From the CDM database, data were obtained from a member file which included information on demographic factors, region of residence, and insurance enrollment date; a medical file which included all inpatient and outpatient encounter information; and a pharmacy file which included medication name,

date of fill, formulation, dose, quantity, and days of supply. From the Medicare database, data were obtained from the Medicare beneficiary summary file which included the beneficiary's demographic and enrollment data; the Medicare provider analysis and review files which included inpatient data; the outpatient standard analytic file which included outpatient facility data; the Part D file which included pharmacy data; the carrier claim file which included physician services information; and the durable medical equipment file which included medical equipment supply information. This study was approved by the Institutional Review Board at the University of Texas Medical Branch at Galveston.

Study cohorts

In the CDM cohort, we identified 450 men aged 40–63 years who were diagnosed with COPD between January 1, 2004 and December 31, 2013, who initiated TRT in the 12 months after their first COPD diagnosis date, and who had complete enrollment at least 12 months before and 12 months after their testosterone initiation date. Patients with ≤ 60 days TRT in the year following their index testosterone prescription were excluded from the study cohort. In the Medicare cohort, we identified 253 men who met the same criteria as the CDM cohort except they were aged ≥ 66 years at COPD diagnosis, and diagnosed between January 1, 2007 and December 31, 2012.

Patients who met any of the following criteria were classified as having COPD: (1) at least two outpatient or consultation visits (Evaluation and Management (E&M) codes 99201–99205 and 99211–99215), each with a diagnosis of COPD at least 30 days apart within 12 months; or (2) one acute care hospitalization with a primary discharge diagnosis of COPD based on the following International Classification of Diseases, 9th revision (ICD-9) codes: 491.x (chronic bronchitis), 492.x (emphysema), or 496 (chronic airway obstruction); or (3) hospitalization for respiratory failure (ICD-9 codes 518.81, 518.82, and 518.84) listed as the primary diagnosis at hospital discharge and COPD listed as the secondary diagnosis at hospital discharge.

The following codes were used to identify TRT. National Drug Code (NDC) related to therapeutic class code in 6808010090, 6808010050, and 6808010025; and Healthcare Common Procedure Coding System (HCPCS) code in J1060, J1070, J1080, J1090, J3120, J3130, J3140, and J3150. We included all doses and routes of administration of

TRT in our analyses, using NDC numbers for topical gel, transdermal patch, and oral formulations and HCPCS codes for injectable routes of administration. We included, in this definition, pharmacy fill dates of 30, 60, or 90 days. All injections of TRT were treated as the equivalent of a 30-day supply of a prescription testosterone.

Covariates

For both cohorts, geographic region was divided into four Census Bureau regions, the Elixhauser comorbidity index was identified from both outpatient and inpatients claims to generate the number of comorbidities for beneficiaries as an index score (0, 1, 2, ≥ 3).²¹

COPD complexity was categorized as low, moderate, and high as described in previous studies.²² For the Medicare cohort, sociodemographic characteristics—including age at TRT initiation (66–74, 75–84, and ≥ 85 years), race, and ethnicity (White, Black, or other)—were obtained from Medicare enrollment files. Low socioeconomic status was identified by either a patient's eligibility for state buy in coverage provided by the Medicare program or a patient's receipt of a low-income subsidy for the Medicare Part D program. For the CDM cohort, age at TRT initiation was classified as 40–49, 50–59, and 60–63 years.

Receipt of COPD medication—in either the pre-TRT or post-TRT period—was defined as having received at least one prescription for any of the following: long-acting beta agonists (LABAs), long-acting muscarinic agonists (LAMAs), inhaled corticosteroids (ICSs), fixed-dose LABA/ICS combinations, short-acting beta2 agonists (SABAs), and short-acting muscarinic agonists (SAMAs). No information on race or socioeconomic status was available for the CDM cohort.

COPD complexity

A classification of COPD complexity, based on administrative claims data, was created to serve as an indicator of COPD severity. Comorbid respiratory conditions and medical procedures at any time during the study period served as a basis for assigning patients to one of three COPD complexity levels (high, moderate, or low), as described in previous studies.²² High complexity conditions included cor pulmonale, tuberculosis, or malignant neoplasm; moderate complexity conditions included pneumonia, cyanosis, bronchoscopy, or dependence on supplemental oxygen. All COPD patients who did not have

high or moderate complexity conditions were classified as low complexity.

Outcomes

Our primary outcome was the hospitalization rate for respiratory conditions (ICD-9-CM = 460.xx-519.xx) in the 12 months before versus the 12 months after initiation of >60 days of TRT. As a control outcome, we examined the hospitalization rate for all non-respiratory conditions over the same time period.

Statistical analysis

The study cohort characteristics were expressed as mean \pm standard deviation for continuous variables and as percentages for categorical variables. The percentage of patients with hospitalizations for respiratory disease conditions in 1 year pre- versus 1 year post-initiation of TRT, for >60 days, was compared using the McNemar test. Second, we conducted difference-in-differences (DID) analyses using logistic regression to compare the differences in respiratory hospitalizations among TRT users, pre- versus post-TRT, to the differences among non-TRT users over the same time period. DID is the interaction term between a categorical variable denoting the time period (pre vs. post) and the group (users vs. nonusers) in the logistic regression model. TRT users and nonusers were matched according to TRT initiation date/index date, age (± 1 year), COPD complexity and COPD medication use in the previous year. Matching criteria also included socioeconomic status in the older cohort. Nonusers were required to have had 12 months of continuous coverage both prior to and following their index date. This period corresponded to the pre- versus post-periods of the matched TRT user.

We then conducted sensitivity analyses in which we restricted our analyses to COPD patients who received >90 days of TRT, >120 days of TRT, and >30 days of TRT in the first 6 months and second 6 months of the look-forward period. All analyses were performed using SAS version 9.4 (SAS Inc., Cary, North Carolina, USA).

Results

We identified 450 men with COPD, aged 40–63 years, from the CDM database who were new users of TRT between January 1, 2005 and December 31, 2014 and 253 men with COPD, aged ≥ 65 years, from

Table 1. Flowchart showing cohort selection.

Middle-Aged Men (Clinformatics Data Mart)		Older Men (Medicare)	
Men diagnosed with COPD during 2004-2013	N=117,809	Men diagnosed with COPD during 2007-2012	N=71,004
Initiated TRT within 12 month after COPD diagnosis date (2005-2014)	N=2,416	Initiated TRT within 12 month after COPD diagnosis date (2008-2013)	N=1,351
Had continuous enrollment for 12 months before and 12 months after TRT initiation date.	N=1,546	Had continuous enrollment for 12 months before and 12 months after TRT initiation date.	N=510
Was not in a nursing facility in the 12 months before and the 12 months after testosterone initiation	N=1,121	Was not in a nursing facility in the 12 months before and the 12 months after testosterone initiation	N=440
Aged 40 to 63 at TRT initiation	N=753	Age \geq 66 at TRT initiation	N=440
>60 days testosterone prescription in one year period after testosterone initiation	N=450	>60 days testosterone prescription in one year period after testosterone initiation	N=253

the Medicare database who were new users of TRT between January 1, 2008 and December 31, 2013 (Table 1). The baseline characteristics of the study cohorts are presented in Table 2. For the middle-aged cohort, the mean age at initiation of TRT was 55.8 years; 65.3% had at least one comorbidity and 36.2% had ≥ 2 comorbidities. Only 6.7% of patients experienced COPD that was defined as high complexity; 59.6% received COPD medication in the year before initiating TRT and 56.0% received COPD medication in the year after initiating TRT. For the older cohort, the mean age at initiation of TRT was 74.5 years; 93.7% were White; 90.8% had at least one comorbidity and 71.9% had ≥ 2 comorbidities. Approximately 10.7% of these patients experienced COPD that was defined as high complexity; 71.5% received COPD medication in the year before TRT and 74.7% received COPD medication in the year after TRT.

Table 3 presents all hospitalizations for respiratory conditions in the 12 months before versus the 12 months after initiation of >60 days of TRT for both study cohorts. Hospitalizations for respiratory conditions were significantly lower in the 12 months after versus the 12 before initiation of TRT in the middle-aged cohort (4.0% vs. 6.4%, $p = 0.04$) but not in the older cohort (8.7% vs. 9.5%, $p = 0.72$). Among older men, the absence of a statistically significant association persisted across all of the sensitivity analyses. Among middle-aged men, the beneficial effect of TRT persisted in two sensitivity analyses (restricted to >120 days of TRT and excluding high complexity COPD) but not in the analysis restricted to >90 days. We also

examined all non-respiratory conditions as a control outcome. Hospitalizations for this outcome were not significantly different in the post- versus pre-period in either the middle-aged (14.4% vs. 15.6%, $p = 0.61$) or older (21.0% vs. 21.7%, $p = 0.82$). These findings persisted across all sensitivity analyses.

A DID analysis (Table 3) showed that—in comparison with non-TRT users examined over the same time period—TRT users in both age groups had a greater relative decrease of respiratory hospitalizations over time. Among the middle-aged cohort, TRT users had a 4.2% greater decrease in respiratory hospitalizations compared with their non-TRT counterparts (−2.4 decrease vs. 1.8 increase; $p = 0.03$). In the older cohort, TRT users had a 9.1% greater decrease in respiratory hospitalizations compared with the non-TRT cohort (−0.8 decrease vs. 8.3 increase; $p = 0.04$). In both cohorts, these findings persisted in only the first, least restrictive (60 days) of the four TRT dose-based sensitivity analyses. In each of the more restrictive analyses—with successively smaller sample sizes—the DIDs failed to reach statistical significance.

Discussion

In this study of two nationally representative cohorts of men with COPD—450 middle-aged commercial insurance enrollees and 253 older Medicare beneficiaries—we found that initiation of TRT reduced the risk of hospitalizations for respiratory conditions in middle-aged men but not in older men. Our comparison of TRT users with matched nonusers,

Table 2. Baseline characteristics of middle-aged and older men with COPD who received TRT (>60 days).

Characteristic	Middle-aged men (Clinformatics Data Mart)		Older men (Medicare)			
	N	%	N	%		
Overall	450	100	253	100		
Year of TRT						
2005	6	1.3	—	—		
2006	24	5.3	—	—		
2007	23	5.1	—	—		
2008	34	7.6	6	2.3		
2009	53	11.8	27	10.7		
2010	62	13.8	43	17.0		
2011	62	13.8	44	17.4		
2012	76	16.9	63	24.9		
2013	68	15.1	70	27.7		
2014	42	9.3	—	—		
Age group	55.8 ± 5.5		74.5 ± 5.7			
	(40–49)	67	14.9	(66–74)	143	56.5
	(50–59)	244	54.2	(75–84)	94	37.2
	(60–63)	139	30.9	(≥85)	16	6.3
Race						
White	—	—	237	93.7		
Black	—	—	9	3.6		
Other	—	—	7	2.7		
Low socioeconomic status ^a						
No	—	—	195	77.1		
Yes	—	—	58	22.9		
Region						
North East	28	6.2	20	7.1		
Middle West	89	19.8	48	19.0		
South	285	63.3	132	52.2		
West	48	11.0	53	21.0		
Number of comorbidities ^b						
0	156	34.7	23	9.1		
1	131	29.1	48	18.9		
2	82	18.2	56	22.1		
≥3	81	18.0	126	49.8		
COPD complexity						
High	30	6.7	27	10.7		
Moderate	112	24.9	106	41.9		
Low	308	68.4	120	47.4		
COPD medication 1 year before index TRT						
Yes	268	59.6	181	71.5		
PDC ^c (mean ± standard deviation, median, Q1–3)	51.5 ± 33.2, 53.3, 18.7–81.6		54.5 ± 31.7, 57.3, 26.2–83.6			
COPD medication 1 year after index TRT						
Yes	252	56.0	189	74.7		
PDC (mean ± standard deviation, median, Q1–3)	52.7 ± 32.7, 55.2, 21.3–83.7		52.6 ± 31.5, 49.3, 24.7–83.8			

TRT: testosterone replacement therapy; COPD: chronic obstructive pulmonary disease; PDC: proportion of days covered.

^aLow socioeconomic status was identified by either a patient's eligibility for state by in coverage provided by the Medicare program or a patient's receipt of a low-income subsidy for the Medicare Part D program.

^bElixhauser comorbidity index was identified from both outpatient and inpatients claims to generate the number of comorbidities for beneficiaries as an index score.

^cPatient had medication available.

Table 3. Observed DID in respiratory hospitalizations among COPD patients who received TRT versus those who did not.

	<i>n</i>	Pre (%)	Post (%)	Difference	<i>P</i> ^a	Difference-in-differences	<i>P</i> ^b
Middle-aged men (Clinformatics Data Mart)							
60 days of TRT	450	6.4	4.0	−2.4	0.04	−4.2	0.03
Matched comparison group (no TRT)	450	5.3	7.1	1.8	0.25		
60 days of TRT, excluding high complexity COPD	420	5.7	3.1	−2.6	0.02	−5.6	0.003
Matched comparison group (no TRT)	420	4.1	7.1	3	0.04		
90 days of TRT	353	6.5	4.3	−2.2	0.10	−2.7	0.18
Matched comparison group (no TRT)	353	5.7	6.2	0.5	0.74		
120 days of TRT	278	6.8	3.2	−3.6	0.03	−3.6	0.10
Matched comparison group (no TRT)	278	6.5	6.5	0	1		
30 days in first 6 months and second 6 months	259	6.2	3.1	−3.1	0.06	−3.9	0.11
Matched comparison group (no TRT)	259	5.4	6.2	0.8	0.71		
Older men (Medicare)							
60 days of TRT	253	9.5	8.7	−0.8	0.72	−9.1	0.04
Matched comparison group (no TRT)	253	13	21.3	8.3	0.01		
60 days of TRT, excluding high complexity COPD	226	9.7	7.1	−2.6	0.22	−9.6	0.02
Matched comparison group (no TRT)	226	12	19	7	0.02		
90 days of TRT	199	9.1	9.6	0.5	0.83	−8.5	0.10
Matched comparison group (no TRT)	199	12.1	21.1	9	0.01		
120 days of TRT	164	8.5	9.2	0.7	0.81	−6.6	0.28
Matched comparison group (no TRT)	164	13.4	20.7	7.3	0.05		
30 days in first 6 months and second 6 months	147	6.8	8.8	2	0.41	−3.4	0.82
Matched comparison group (no TRT)	147	14.3	19.7	5.4	0.17		

TRT: testosterone replacement therapy; COPD: chronic obstructive pulmonary disease; DID: difference-in-differences.

^a Percentages compared using McNemar's test.

^b A DID analytic approach using logistic regression to compare pre- versus post-respiratory hospitalization rates in TRT users versus matched nonusers.

using a DID analytic approach, showed that, in both age groups, TRT users had a greater relative decrease in respiratory hospitalizations after initiation of treatment compared with nonusers over a parallel time period. The DID results among the older cohort appear to be largely attributable to an increased hospitalization rate in the non-TRT group, rather than to a reduced hospitalization rate in the TRT group. Taken together, these findings suggest that TRT may slow the progression of disease in men with COPD. To our knowledge, this is the first study to examine this association in nationally representative population-based cohorts of real-world COPD patients.

Many studies have shown that men with COPD are at increased risk for developing hypogonadism, reported to range from 22% to 69% prevalence.^{2,3,23,24} The mechanisms that underlie this risk include systemic inflammation, chronic illness, and long-term exposure to glucocorticoids.² It is biologically plausible that testosterone deficiency exacerbates COPD symptoms directly—via an impact on respiratory muscles—or indirectly—by diminishing overall strength and exercise capacity. Animal studies have shown that circulating testosterone is positively associated with measures of respiratory function.^{4,5} Likewise, human observational studies have shown a

protective effect of circulating testosterone levels on several respiratory outcomes including FEV-1 and FVC.^{6–8}

Several RCTs suggest that testosterone supplementation is associated with improved body composition, skeletal muscle strength, and exercise capacity in COPD patients.^{9–13} However, evidence regarding improvements in pulmonary function and respiratory muscle strength is equivocal. Some clinical trials have reported beneficial effects of TRT on COPD outcomes when it has been combined with other interventions such as standardized pulmonary rehabilitation, nutritional support, or resistance training.^{10,11} In their study of 47 men with COPD, Casaburi et al.¹¹ reported that men receiving TRT and resistance training had small but statistically significant increases in peak oxygen uptake. Likewise, in their RCT of 70 older adults with congestive heart failure, Caminiti et al.¹⁴ reported that TRT was associated with improvements in peak oxygen consumption. Other studies, however, have failed to show such a therapeutic effect of TRT in COPD patients.^{12,15–17}

While considerable physiological differences exist between respiratory and peripheral limb muscles, further research is needed to explain the potential differential effect of TRT on respiratory versus other skeletal muscle types.¹⁷ Based on current evidence, a cardiorespiratory benefit associated with testosterone supplementation seems to manifest itself either when testosterone is complemented by other supporting interventions—such as nutrition, pulmonary rehabilitation, or resistance training—or through improvements in overall skeletal muscle strength, lean muscle mass, and exercise capacity.

Our findings suggest that, in the older cohort, the severity of COPD increased at a more accelerated rate over the 24-month follow-up period, compared with the middle-aged cohort. It is possible that age-associated changes in lung parenchyma and vasculature²⁵ contribute to this acceleration in older adults. It will be important for future studies to consider these time-related biases when examining the absolute effect of TRT in older adults with COPD.

The results of our study may have been influenced by several limitations. First, all diagnoses were based on ICD-9-CM codes, which may be inaccurate or incomplete.²⁶ It is possible that some of the cases we identified may have been based on misclassified data. Second, the pharmacy plans used by both study cohorts did not cover over-the-counter medications. Our database, therefore, did not include information on coadministration of these drugs; some of them,

such as n-acetylcysteine, may influence the risk of respiratory outcomes. Third, the claims data used in this study did not permit examination of certain potential confounding factors such as diet, alcohol use, and other health-related behaviors. Fourth, our study cohorts were relatively small and may have lacked adequate statistical power and precision. Finally, our data included the date the prescription was filled but not the date it was obtained by the patient. In view of this, some of the drug exposure periods may have been misclassified.

Despite these limitations, this investigation has a number of strengths including nationally representative cohorts and a broad range of clinically and socioeconomically diverse patients treated in real-world settings. In conclusion, our investigation suggests that TRT may reduce the risk of respiratory hospitalizations in middle-aged men. It will be important for future studies—both RCTs and observational studies—to examine this association in larger samples of patients, with particular attention to specific biological pathways. Reliable information on the effectiveness and safety of TRT will help COPD patients and their providers make informed risk–benefit assessments about treatment options.

Authors' note

JB is the manuscript's guarantor and affirms that the manuscript is an honest and transparent account of the study that is being reported. JB, YFK, and WZ had full access to the data and take full responsibility for the accuracy of the reported analysis. JB, RJU, WZ, MFZ, ZJ, MSM, YFK, and GS contributed to the review of literature, study design, analysis, and interpretation of results.

Declaration of conflicting interests


The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: JB has received payment, for consulting, from AbbVie, Endo Pharmaceuticals, GlaxoSmithKline Pharmaceuticals, and Auxilium Pharmaceuticals. The funding organizations had no role in the design or conduct of the study; in the collection, analysis, or interpretation of data; or in the preparation, review, or approval of the manuscript.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was conducted with the support of the Institute for Translational Sciences at the University of Texas Medical Branch, supported in part by a Clinical

and Translational Science Award (UL1TR001439) from the National Center for Advancing Translational Sciences, National Institutes of Health.

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