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ORIGINAL ARTICLE

Male Health

# Association of subcutaneous testosterone pellet therapy with developing secondary polycythemia

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**A variety of methods for testosterone replacement therapy (TRT) exist, and the major potential risks of TRT have been well established. The risk of developing polycythemia secondary to exogenous testosterone (T) has been reported to range from 0.4% to 40%. Implantable T pellets have been used since 1972, and secondary polycythemia has been reported to be as low as 0.4% with this administration modality. However, our experience has suggested a higher rate. We conducted an institutional review board-approved, single-institution, retrospective chart review (2009–2013) to determine the rate of secondary polycythemia in 228 men treated with subcutaneously implanted testosterone pellets. Kaplan–Meyer failure curves were used to estimate time until the development of polycythemia (hematocrit >50%). The mean number of pellets administered was 12 (range: 6–16). The mean follow-up was 566 days. The median time to development of polycythemia whereby 50% of patients developed polycythemia was 50 months. The estimated rate of polycythemia at 6 months was 10.4%, 12 months was 17.3%, and 24 months was 30.2%. We concluded that the incidence of secondary polycythemia while on T pellet therapy may be higher than previously established.**
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## INTRODUCTION

Clinical hypogonadism is a term used to define the combination of low serum testosterone (total testosterone [TT] <300 ng $dl^{-1}$), with symptoms associated with low testosterone. Low testosterone levels are found in approximately 24% of men aged >30 years old, while the prevalence of clinical hypogonadism is approximately 5%–6%.[1] Associated symptoms include sexual dysfunction, cognitive impairment, fatigue, depression, increased fat mass, decreased lean body mass, and decreased bone density.[1] The treatment of hypogonadism involves testosterone replacement therapy (TRT), for which a variety of products are available including injectable testosterone esters, transdermal testosterone gels, transdermal testosterone patches, buccal testosterone tablets, oral testosterone undecanoate (not available in the USA), and testosterone pellets. Testosterone replacement is a big business with the USA testosterone sales topping two billion dollars in 2012 according to consumer reports.[2] Choice of testosterone formulation involves consideration of pharmacokinetics, patient preference, cost, and potential formulation-specific adverse effects.[3] While many clinical trials have evaluated the effectiveness of the various testosterone therapies, there is little information on safety, particularly in the different formulations.[4]

Subcutaneous testosterone pellets have been available for use in the United States since 1972. At the current time, Testopel® is the only long-acting TRT approved by the USA Food and Drug Administration (FDA). Unlike other short-acting formulations, testosterone pellets can provide sustained increases in serum testosterone levels and can maintain these levels for up to 4–6 months.[5–7] Additional benefits of this form of administration include low drug transfer risk and potential increased patient compliance/convenience. However, limited data have existed regarding the side effect profile of this formulation.[8]

One significant side effect seen with all formulations of testosterone replacement is the development of secondary polycythemia. In fact, it is the single most frequent drug-related adverse event in published testosterone trials of middle-aged and older men.[3,9] Based on two meta-analyses, the administration of exogenous testosterone is felt to increase the risk of polycythemia (hematocrit [HCT] >50%) by 3.67 times.[10,11] The mechanism by which testosterone increases HCT levels is debated with theories including direct effects on bone marrow erythroblasts, improved red cell survival, and increased biological activity of erythropoietin and hepcidin.[12–14] The concern with elevations in HCT is that the increase in blood viscosity could exacerbate vascular disease in the coronary, cerebrovascular, or peripheral vascular circulation, leading to stroke, deep vein thrombosis, or cardiovascular events. The clinical consequences have not been clarified, and a critical threshold for HCT level has not been determined. Large epidemiologic studies have shown increased HCT levels to be associated with increased risk of cardiovascular events but meta-analyses of testosterone trials have failed to show significant increases in neuro-occlusive events.[10,11,15,16] However, the most recent FDA recommendations require manufacturers to add information to the labeling about a possible increased risk of heart attacks and stroke in patients taking testosterone.

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Rates of polycythemia following testosterone pellet administration have been cited as low as 0.4%–5.1% in the few studies that have looked at this end point.[8,17] Others have gone so far as to state that they have not "seen clinically significant cases" in their patient population receiving subcutaneously implanted pellet therapy.[5,18] Studies have used variable cutoffs for polycythemia ranging from HCT >50% to >55%. Both the Endocrine Society and the European Association of Urology (EAU) have listed HCT >50% as a contraindication to the administration of testosterone.[15,19] The EAU also recommended discontinuation of testosterone therapy if HCT >54%. We chose a cutoff of HCT >50% based on previous studies but also evaluated our data with the more stringent levels of HCT >52% and >54%. In our single-center experience, rates of polycythemia (HCT >50%) were felt to be substantially higher than those previously cited following administration of testosterone pellet therapy. We sought to determine the rates of polycythemia at our institution over time.

## MATERIALS AND METHODS

After Lifespan institutional review board approval, a retrospective chart review was undertaken of patients receiving subcutaneous testosterone pellet therapy at our single institution (the Men's Health Center at the Miriam Hospital in Providence, RI, USA). Two hundred and thirty-eight men who had received pellet treatment between 2009 and 2013 were identified.

Pretreatment serum HCT, TT, bioavailable testosterone (BT), and prostate-specific antigen (PSA) values were recorded. After each implantation, patients were asked to obtain repeated HCT, TT, and BT levels at 1 and 3 months. Previous forms of TRT used, the number of pellets implanted per treatment, and time until treatment switch from pellet implantation to other forms of TRT were also recorded. Finally, biometrics such as age, body mass index (BMI), and smoking history were also evaluated.

At our institution, the number of pellets implanted is based on clinician judgment (generally 10–12 pellets initially) and is adjusted based on testosterone levels to achieve testosterone within the desired range. For patients receiving testosterone pellet therapy, post-treatment laboratory values were obtained at 1 (early) and 3 (late) months postimplantation with a goal of keeping the TT levels within the range of 400–700 ng $dl^{-1}$. Any patient who developed a HCT >50% was advised to obtain phlebotomy. Since many patients obtained phlebotomy outside of the institution (e.g., RedCross), it was not possible to reliably document if phlebotomy had taken place. However, once a patient developed polycythemia, this was considered as an event and he was no longer included in the time-to-event analysis.

All analyses were conducted using SAS Software 9.4 (SAS Inc., Cary, NC, USA). Kaplan–Meyer estimation was used to examine time until the development of polycythemia for HCT >50% (HCT >52% and HCT >54% were also considered) using the LIFETEST procedure. The start date utilized was the 1st day of pellet treatment and the end date utilized was the last known follow-up date. Once a patient developed polycythemia, he was no longer included in the further analysis. Predictors of polycythemia were assessed using Cox Proportional Hazard regression with the PHREG procedure. Differences between maximum TT and BT were examined using a two-sample Wilcoxon rank-sum test. Statistical significance was established at the 0.05 level, and all interval estimates were calculated for 95% confidence.

## RESULTS

A total of 228 men received pellet treatment over the study period and were followed up for a mean of 566 days. The median age was 57 (lower quartile [Q1]: 50, upper quartile [Q3]: 64; range: 27–79) years and median BMI was 31 (Q1: 27, Q3: 35; range: 21–53) kg $m^{-2}$. The median age and median BMI were not observed to be different between those patients who did and did not go on to develop polycythemia (**Table 1**). The median baseline HCT level prior to treatment was 44% (Q1: 31%, Q3: 55%; range: 47.8%–55.0%). On treatment, the median TT was 598.5 (Q1: 487.0, Q3: 783.5) ng $dl^{-1}$ and median BT was 297.1 (Q1: 216.0, Q3: 430.6) ng $dl^{-1}$. The median number of pellets administered was 12 (Q1: 11, Q3: 13; range: 6–18).

The median time until the development of polycythemia (defined as HCT >50%) was 49.9 months (95% confidential interval [CI]: 36.4–143.5; **Figure 1**). The estimated rates of polycythemia at 6, 12, 18, 24, and 36 months were 10.4%, 17.3%, 23.7%, 30.2%, and 41.8%, respectively (**Table 2**). For every one-unit increase in BMI, the rate of polycythemia increased by 4.4% (hazard ratio [HR]: 1.044; 95% CI: 1.001–1.085, $P = 0.02$). However, no relationship was found for smoking ($P = 0.52$), age ($P = 0.50$), and prior treatment ($P = 0.92$).

Maximum TT and BT values were not statistically different for those who developed polycythemia relative to those who did not.

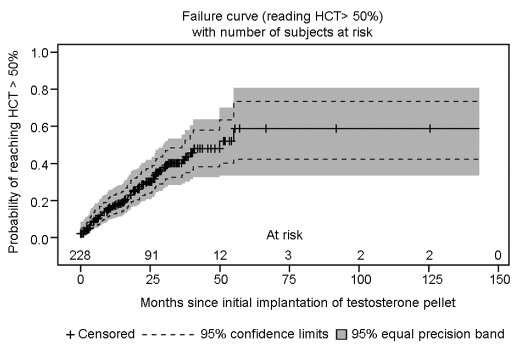


**Figure 1:** Failure curve (reaching HCT >50%). Failure curve represents time until the development of polycythemia defined as HCT >50%. As can be seen, the estimated rate of polycythemia at 6 months is 10.4%, at 12 months is 17.3%, at 18 months is 23.7%, and at 24 months is 30.2%. As patients are censored, or removed from analysis after achieving HCT >50%, the numbers above the X-axis represent the remaining cohort being analyzed at each time point. HCT: hematocrit.

**Table 1: Demographics for patients who did and did not develop polycythemia**

| *Variable* | *Developed polycythemia* | |
|---|---|---|
| | *Yes (n=79)* | *No (n=153)* |
| Age (year, median with Q1, Q3, and range in the parentheses) | 56 (50, 62; [36–77]) | 58 (51, 65; [27–79]) |
| BMI (kg $m^{-2}$, median with Q1, Q3, and range in the parentheses) | 32.0 (28.0, 37.0; [22.0–53.0]) | 30.0 (27.0, 34.0; [20.5–52.0]) |

BMI: body mass index; Q1: lower quartile; Q3: upper quartile

The median maximum TT for those who developed polycythemia was 900.0 ng dl$^{-1}$, compared to 850.5 ng dl$^{-1}$ for those who did not ($P$ = 0.1138), and the median maximum BT was 451.0 ng dl$^{-1}$, compared to 460.8 ng dl$^{-1}$ ($P$ = 0.43) (**Figure 2** and **3**). Those who had received prior testosterone treatment had significantly higher TT levels (median: 880.0 ng dl$^{-1}$) relative to those who did not (median: 664.5 ng dl$^{-1}$, $P$ = 0.003). However, as stated above, they did not have differences in the rates of polycythemia development. No significant difference was found in BT between those two groups ($P$ = 0.28). The median time between pellet administration and measurement of patient's peak TT level was 38 days (95% CI: 36.0–40.0). Days between pellet administration and highest TT and BT were not significantly different between those who did and did not develop polycythemia ($P$ = 0.14 and $P$ = 0.19, respectively).

As a secondary and exploratory analysis, we examined polycythemia as defined by HCT >52% and >54% (**Table 2**). Of note, patients were advised to obtain phlebotomy at HCT >50%. The survival curves for HCT >52% and >54% suffered from significant censoring as it was not possible to control for patients who had underwent phlebotomy once reaching HCT levels >50%. Therefore, the estimates made for HCT >52% and HCT >54% are based on a much smaller number of events occurring.

## DISCUSSION

In our single-institution retrospective review, estimated rates of polycythemia (HCT >50%) reached 25% by about 18 months and as high as 39% by 30 months of continuous administration of testosterone pellets (mean insertion of 12 pellets). Previous studies have reported rates of polycythemia following pellet administration that range from 0.4% to 5.1%.[8,17] The rates demonstrated in this series are clearly much higher than that in previous studies. These differences could be attributable to lower cutoff value for elevated HCT (>50%), higher number of pellets administered (mean: 12), longer follow-up period (mean: 566 days), or closer monitoring of HCT level. In the two previously published studies evaluating erythrocytosis as an end point, the cutoff values for HCT were >54% and >50%, respectively. In one of these studies, the number of pellets administered was not published, and in the other, a small portion of patients received 6–9 pellets,[17] while the vast majority received between 10 and 12 pellets.[8] Patient characteristics including baseline HCT levels, age, and smoking status were not found to be significantly associated with increased polycythemia rates in our study. BMI was associated with increased polycythemia rates. It is widely accepted that, in the obese population, there is an increase in the peripheral conversion of testosterone to estradiol by excess adipose tissue.[20] We postulate that these higher levels of estrogen or lower testosterone to estradiol ratio may explain the higher rates of polycythemia in this obese population, but further research is required to clarify this association. Unfortunately, as regular estradiol screening was not a part of the protocol at our center throughout the study period, estradiol levels or ratios were not able to be included.

Examination using higher cutoff values for HCT still found rates of polycythemia higher than previously published studies. However, these data have limited utility given the inability to control for patients who

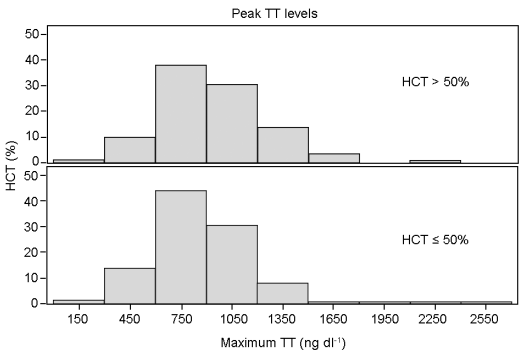


**Figure 2:** Peak total testosterone levels. Bar graph representing highest TT value achieved for patients who did and did not develop polycythemia defined as HCT >50%. The highest TT values were not statistically significantly different for those who did and did not develop polycythemia. HCT: hematocrit; TT: total testosterone.

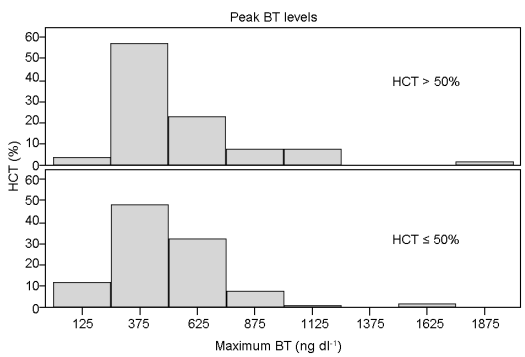


**Figure 3:** Peak bioavailable testosterone levels. Bar graph representing highest BT value achieved for patients who did and did not develop polycythemia defined as HCT >50%. The highest BT values were not statistically significantly different for those who did and did not develop polycythemia. BT: bioavailable testosterone; HCT: hematocrit.

**Table 2: Estimated cumulative probabilities of development of polycythemia based on Kaplan-Meyer survival curves at various time points for polycythemia cutoffs of HCT >50%, HCT >52%, and HCT >54%**

| *Time point (months)* | *HCT >50%* | | *HCT >52%* | | *HCT >54%* | |
|---|---|---|---|---|---|---|
| | *Probability (%)* | *s.e.* | *Probability (%)* | *s.e.* | *Probability (%)* | *s.e.* |
| 6 | 10.4 | 0.0206 | 4.2 | 0.0135 | 1.4 | 0.00804 |
| 12 | 17.3 | 0.0259 | 7.6 | 0.0182 | | |
| 18 | 23.7 | 0.0302 | 12.9 | 0.0244 | 3.5 | 0.0130 |
| 24 | 30.2 | 0.0340 | 15.0 | 0.0266 | | |
| 30 | 39.0 | 0.0397 | 20.6 | 0.0333 | 6.9 | 0.0235 |
| 36 | 41.8 | 0.0426 | 23.5 | 0.0381 | 9.3 | 0.0329 |

Of note, due to significant censoring, the values for HCT >52% and HCT >54% are based on smaller numbers. Estimates were not able to be determined for HCT >54% at 12 months and 24 months due to these small numbers. HCT: hematocrit; s.e.: standard error

received phlebotomy prior to achieving these values and the significant censoring of the patient numbers.

Multiple mechanisms for secondary polycythemia following testosterone administration have been postulated, but none have been proven. Rates of polycythemia have been shown to increase in a dose-dependent manner, with increasing doses of testosterone.[21] Rates have also been shown to differ according to formulation with injections having higher rates than gels or patches.[21–24] This difference has been postulated to be associated with supra-physiologic levels of bioavailable testosterone which are more frequent in intramuscular injections of testosterone.[22] In our series, no statistically significant difference in peak TT or BT levels was found among those who did and did not develop polycythemia.

Our study provides evidence that rates of polycythemia with pellet therapy may be higher than previously published and that polycythemia continues to develop with prolonged administration of pellet therapy. As no widely accepted guidelines exist for monitoring on testosterone therapy, practitioners are left to monitor in any way they see fit. This study supports the recommendations of the Endocrine Society Clinical Practice Guidelines that hemoglobin and HCT should be monitored in androgen-deficient men receiving testosterone therapy. It adds further evidence to suggest that close monitoring of HCT for patients specifically on testosterone pellet therapy should occur despite previous publications suggesting that rates were very low or negligible. It also suggests that patients should continue to be monitored for polycythemia even after prolonged administration, given that cases developed even after 2 years of consistent administration. Cardiovascular, cerebrovascular, and peripheral vascular events were not recorded in this sample and therefore the correlations of these clinical outcomes with the increased rates of polycythemia are impossible to make. Further research is still necessary to determine if rates of thromboembolic events are increased among those patients on TRT who develop polycythemia as this has yet to be shown.

A weakness in our study is its retrospective nature. Thus, a prospective randomized controlled trial examining the side effects of pellet therapy is suggested. At our institution, over the study period, five separate providers administered pellet therapy. Indications for all providers included low serum testosterone on two separate morning laboratory draws (<270 ng $dl^{-1}$ for our laboratory) and symptoms. However, slight variation in dosing and postadministration laboratory testing protocols existed. In addition, the average number of pellets administered in our study is higher than the recommended dosing by the company but were necessary to achieve reasonable physiologic levels of testosterone. A significant portion of patients had used other formulations of testosterone in the past. This is not unexpected given that it is rare in clinical practice to start a testosterone-naïve patient on a long-term formulation like Testopel®. Finally, the fact that the receipt of phlebotomy was not reliably recorded in this sample limited our ability to determine rates at higher cutoff values of 52% and 54% due to significant censoring but did not affect our main analysis.

## CONCLUSIONS

Rates of secondary polycythemia among patients receiving implantable pellet therapy for hypogonadism may be far higher than previously reported. Close monitoring in this population, even after prolonged administration, is necessary to prevent significant polycythemia.

## AUTHOR CONTRIBUTIONS

KLR participated in data collection, coordination, and helped to draft the manuscript. BN and MA participated in data collection. GLB performed the statistical analysis. MS and MMM participated in study design and helped to draft the manuscript. KH conceived of the study, participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

## COMPETING INTERESTS

All authors declare no competing interests.

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