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ORIGINAL RESEARCH

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Controlling the polycythemia effect associated with TRT

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Abstract

The goal of this study was to determine how to minimize the secondary polycythemia effect observed in patients on testosterone replacement therapy (TRT). Patient hemoglobin, estradiol (E2) and total testosterone (TT) levels were used in this study to determine when a patient became "stable" on treatment. Stability was defined in this study as the point at which a patient's symptoms have resolved, secondary polycythemia has stopped, and testosterone cypionate (TC) dosage has remained consistent for at least three months. Currently, secondary polycythemia associated with TRT is commonly being controlled by frequent blood donations, or therapeutic phlebotomies. However, this study shows that it is possible to minimize fluctuations in TT and E2 levels, which then minimizes side effects including secondary polycythemia. In this study, we found that the patients stabilized at TT levels between 605–1051 ng/dL. The effects of stable TC dosing were tracked and discussed in terms of total cholesterol, Prostate Specific Antigen (PSA) and A1c levels as well. These were not necessarily the focus of the study, but significant trends were noted once data was collected to warrant their inclusion in the study.

Keywords

Testosterone replacement therapy; Total testosterone; Testosterone cypionate; Estradiol; Stabilization

1. Introduction

1.1 Background

Several total testosterone (TT) normal ranges can be found in the literature [1–3]. For example, the National Endocrine Society identifies the normal range for TT levels in males to be 264–916 ng/dL [1, 2]. However, LabCorp Diagnostics used the previously accepted normal range of 348–1197 ng/dL until 2017 and Quest Diagnostics uses a reference range of 250–1110 ng/dL [2, 3].

Over the past 15–20 years, TT levels have decreased across the United States [4, 5]. The factors tracked in this study that seemed to contribute to this decline in TT levels included, but are not limited to, irregular work schedules, processed food intake and stress. The most common professions of patients who qualified to participate in this study were police officers, firefighters, medical professionals and business owners. This may be attributed to the high stress levels and irregular work schedules associated with their careers. Recent advances in technology have created a fast-paced culture, which appears to have increased the prevalence of stress and anxiety. The decline in TT levels has correlated with this change, and has led to a significant increase in patients treated with testosterone replacement therapy (TRT). Many clinics embraced the new treatment. However, the majority of these clinics are non-medically owned, suggesting that they have minimal incentive to improve therapy. The association of TRT with these non-medically owned clinics has caused the medical field to avoid TRT, likely due to a lack of data for therapy and risk of thrombosis. Several forms of TRT are currently available including oral pills, creams, pellets and injections. This study focused on intramuscular testosterone cypionate (TC) injections. The injectable route of administration was used due to the well-known half-life and elimination time of the medication. TC has a half-life of 7–8 days and is eliminated from the body in approximately 30 days when injected intramuscularly [6, 7]. Injections were administered once weekly, and TT levels were measured after 4 consecutive injections, or once patients reached steady state concentrations. Side effects include, but are not limited to, acne, elevated estradiol (E2) levels, secondary polycythemia, hair loss, decreased High Density Lipoprotein (HDL), increased Low Density Lipoprotein (LDL) levels, negative feedback of the hypothalamic-pituitary axis (luteinizing hormone and follicle stimulating hormone decrease), and aggression [4–8]. The goal of this study was to minimize the polycythemia effect associated with TRT while maximizing benefits of treatment. To accomplish this, both quantitative and qualitative data of patients' responses to TC injections administered every seven days were tracked. Incidental findings were also recorded from the start of treatment compared to stability, including total cholesterol, A1c and PSA levels.

1.2 Objectives

Find a total testosterone range that maximizes benefits to the patient while minimizing side effects. Offer an alternative normal range for testosterone levels in males based on the elimination of the polycythemia effect. Establish an appropriate TC starting dosage with an appropriate dosing range.

2. Methods

2.1 General approach

One of the most worrisome side effects associated with TRT is an increasing hemoglobin level, or secondary polycythemia (hereafter referred to as "polycythemia") [6, 8–11]. Polycythemia increases the risk of thrombosis, including stroke or heart attack. This has been a significant source of concern for most providers and has caused them to avoid treatment for fear of putting their patients at risk for thrombosis. However, the data provided in this study suggest that most of the patients experiencing the polycythemia effect were either being overdosed or incorrectly dosed during treatment. The data also suggest that the timing of injections, as well as sufficient control of fluctuations in testosterone and estrogen levels, are necessary to control the polycythemia. These data suggest that correctly timing the administration of TC injections and dosing of anastrozole, if necessary, decreases the overall fluctuation of both TT and E2 levels in the blood. Consistency of both TT and E2 levels needed to be achieved before the patients were able to reach a point of stabilization with their treatment. In previous trials, patients were treated with either daily topical testosterone or TC injections with dosing regimens ranging from 50 mg weekly to 300 mg every other week [6, 12]. However, in this trial, TC injections were administered every seven days, and blood samples were collected seven days post-TC injection and after at least four consecutive weeks of injections for accuracy. These parameters were set based on the half-life (7–8 days) and elimination time (approximately 1 month) of TC. Blood samples were sent to an outsourced laboratory (LabTech Diagnostics). Fasting blood samples were collected at the patients' initial visit, after their first four consecutive TC injections, after three months of treatment, and at three-month intervals thereafter. TT, E2 and hemoglobin levels were measured in every blood sample. PSA and cholesterol levels were measured every three months. A1c levels were checked with initial blood work and then once per year if A1c was within normal limits (WNL) or every three months if A1c was >5.6%.

Stable/stabilization/stability—point at which a patient's symptoms have resolved, secondary polycythemia has stopped, and testosterone cypionate dosage has remained consistent for at least three months.

The primary goal was to determine a stabilization point at which the patient achieved maximum benefit with minimal side effects (*e.g.*, elimination of polycythemia) on treatment. The challenge was to identify the TC dose at which the patient's hemoglobin level stopped increasing. Hemoglobin levels appeared to be the most specific metric that indicated the point at which the patient's treatment stabilized. Patients were advised to start 81 mg aspirin daily if their hemoglobin levels increased to >16 g/dL during treatment. Starting aspirin, which acted as a minor blood thinner, helped either decrease hemoglobin levels or slow the rate of increase in hemoglobin levels during treatment. TC dosage adjustments were made in 20 mg (0.1 mL) increments. Assessment of new dosages was not performed until after four consecutive injections of the new dose. After data analysis, there were notable trends in the TT, E2 and hemoglobin levels once stable on treatment. There were also differences between patients previously on TRT and those never on TRT. The most noticeable difference was that patients previously on TRT took longer to reach stability than those never on TRT.

2.2 Two cohorts studied

The two cohorts studied were males who had previously been on TRT and males who had never been on any form of TRT. The patients selected for this study were selected from a pool of about 7000 patients that were tracked over a 7-year span. Patients were selected and relevant data was recorded for those who were able to reach stability in treatment. There were only 60 patients that met this criterion, so further application of the findings from this study was needed to verify the results (**Supplementary material**). Since completion of the study, data collected has served as a guideline to help other patients reach stability. Blood work was collected from all patients at their initial visit, after 1 month of treatment, after three months of treatment, and then at six months, nine months, 12 months and so on. The 1-month draw was to ensure that patients were on the appropriate TC dosing. Data was only accurate after 4 consecutive injections, since the first 4 injections had an additive effect. Three-month intervals were used due to the lifespan of red blood cells, which is about 90 days. Data were collected for each cohort including the length of time that it took to reach stability on treatment and the average dosage injected weekly at stabilization. Age, weight, and height were also tracked in this study, but did not appear to affect the results of treatment.

3. Results

The chief complaints and symptoms identified by the patients during their initial office visits are listed below. All of these complaints/symptoms were reported by the patient to be well controlled once stable on treatment.

Fatigue—98.3% [9, 13, 14];
Poor motivation—78.3% [9, 13, 14];
Poor sleep quality—46.7% [9, 14];
Decreased libido—45% [9, 13, 14];
Weight gain—33.3% [9, 13–15];
Mental fogginess—26.7% [9, 13];
Moodiness—20% [9, 13, 14];
Depression—15% [9, 13, 14];
Loss of muscle mass—15% [9, 13–15];
Erectile dysfunction—8.3% [9, 13, 14].

All patients reported significant improvement, if not full resolution, of symptoms once stable compared to prior to treatment. Notable clinical changes were also seen. These included improved affect, improved social interactions, and increased

motivation to advance their personal relationships and careers. Partners of patients also reported better relationships. Physical changes reported by patients included increased strength and muscle definition/mass [16]. On treatment, patients gained muscle mass starting in the chest and shoulders. Fat loss was then noted in these areas, followed by fat loss most notable around the waistline. Patients also became much more motivated to maintain consistency with treatment once stable because they would experience a return of symptoms when inconsistent.

4. Discussion

Analysis of the data (Table 1) revealed significant similarities in TT, E2 and hemoglobin levels once patients reached stabilization on treatment. Free testosterone levels were not tracked during this study. While Sex Hormone Binding Globulin (SHBG) and free testosterone levels were initially tracked in the study, it was noted that total testosterone levels and free testosterone levels had similar correlations with hemoglobin levels. Ultimately, running SHBG levels became an unnecessary expense for the patients, as it did not add any additional pertinent data, and was ultimately eliminated from testing in the study. While this study initially started with 60 patients who no longer experienced the polycythemia effect, controlling the polycythemia effect ultimately led to suggest a more refined range for TT. The most notable trend of the study was that reaching, and ultimately maintaining, certain ranges of TT and E2 levels, allowed patients to minimize or even eliminate the polycythemia effect. Patients who were inconsistent with either their TC injections or anastrozole doses had difficulty achieving and maintaining stability. This suggests that maintaining consistency of both TT and E2 levels allows for better hemoglobin control with TRT.

There were noticeable differences between patients who had been on TRT in the past and those who started treatment with our protocols. The most notable difference was stabilization time, as patients who had previously been on TRT in any form needed an average of 9.7 months longer to stabilize than those who had never been on TRT.

Based on the data gathered during this study, the recommended starting TC dosage is 140–150 mg every seven days. This was the average dosage administered to the patients at the point of stabilization. The TT range for patients in the study that reached stabilization was 605–1051 ng/dL. Ninety percent (54/60) of patients treated in this study needed to take anastrozole, an aromatase inhibitor, three days after their TC dosage. Anastrozole prevented the conversion of TC to E2 when timed correctly, allowing patients to achieve a higher TT level with a lower TC dose. The half-life of anastrozole in human ranges from 30 to 60 hours [17], and the conversion of TC to E2 occurs at 48–72 hours post-TC injection [18]. Therefore, in patients who were taking their anastrozole on the day of their injection, the medication was ineffective because it was eliminated from the body before conversion occurred. Patients experienced fewer side effects when they remained consistent with the timing and dosage of TC and anastrozole. Patients frequently experienced acne, mood swings, and elevated hemoglobin levels when they were not consistent with both TC and anastrozole dosing. This reinforced the theory that fluctuations in either testosterone or estradiol levels can cause unwanted side effects, including secondary polycythemia, commonly experienced with TRT.

TABLE 1. Previously treated *vs.* no prior treatment.

All data are averages	Patients previously on TRT	Patients who have never been on TRT
Starting TT dose	167.3 mg	138.7 mg
TC Dosage once stable	147.0 mg	149.3 mg
Starting TT level	479.83 ng/dL (21 pts)	347.77 ng/dL
TT at week 5	805.90 ng/dL	705.43 ng/dL
TT once stable	780.10 ng/dL	794.53 ng/dL
Initial Hemoglobin level	15.78 g/dL	15.06 g/dL
Hemoglobin at 5 weeks	16.22 g/dL	15.33 g/dL
Hemoglobin at stabilization	15.70 g/dL	15.79 g/dL
E2 level at stabilization	17.5 pg/mL	18.2 pg/mL
Anastrozole dose at stabilization	0.90 mg	0.75 mg
Initial A1c	5.66% (24 pts)	5.99% (23 pts)
A1c at stabilization	5.52% (24 pts)	5.60% (23 pts)
Initial total cholesterol level	207.93 (28 pts)	195.78 (27 pts)
Total cholesterol at stabilization	195.86 (28 pts)	186.11 (27 pts)
Initial PSA level	1.017 ng/mL	0.859 ng/mL
PSA level at stabilization	1.163 ng/mL (14.36% increase)	1.090 ng/mL (26.89% increase)

TRT: testosterone replacement therapy; TT: total testosterone; TC: testosterone cypionate; E2: estradiol; PSA: prostate specific antigen.

Estrogen control was a vital component of hemoglobin stabilization in this study. Patients who started anastrozole generally saw an increase in their total testosterone level, allowing them to remain at lower TC doses overall. This was expected because TC conversion to E2 was inhibited. The average E2 level at stabilization was 17.50 pg/mL for patients previously on TRT and 18.21 pg/mL for patients never on TRT. The average anastrozole dosage at stabilization was 0.90 mg for patients previously on TRT and 0.75 mg for patients never on TRT. However, when patients were started on anastrozole at the beginning of treatment they frequently experienced side effects including hot flashes and joint pain, as their E2 levels dropped too low. Therefore, it is suggested that anastrozole should only be started if patients begin experiencing symptoms of elevated estrogen, such as bloating, or their E2 level increases to >35 pg/mL.

In this study, patients' TT levels stabilized between 605–1051 ng/dL. The majority of patients were still experiencing symptoms of testicular hypofunction when their TT level was <605. Additionally, the side effects started to outweigh the benefits of treatment when TT levels were >1051. The side effects observed at higher TT levels included acne, aggression, erectile dysfunction, difficulty losing weight, elevated E2 levels, hair loss and increased body hair. Hair loss with TRT did not occur with appropriate dosing and management unless the patients had a family history of hair loss. In these cases, hair loss tended to accelerate, following their family history of male pattern baldness. Similarly, patients were more likely to experience acne if they had a personal history of acne or naturally oily skin. Regardless, maintaining relatively consistent and appropriate TT and E2 levels minimized all side effects and helped patients achieve the best results on treatment. Therefore, the data collected in this study suggest that the ideal range for a patient's total testosterone level, drawn after four consecutive weeks of injections and exactly seven days after the previous injection, is 605–1051 ng/dL. Note that this is a much narrower range than the currently suggested ranges, including 348–1197 ng/dL [1].

Additional trends noted in patients who reached stability in this study included:

— An average decrease of 0.14% in A1c for patients previously on TRT and 0.39% decrease in A1c for patients never on TRT.

— Elimination of the common increase in total cholesterol levels observed with excessive TC dosing [13].

— An average weight loss of 1.03 lbs (0.44%) for patients never on TRT.

— However, those previously on TRT showed a slight increase (1.40 lbs or 0.64%) in average weight.

Further studies are needed to investigate the mechanisms of action associated with the above trends.

Finally, as expected, PSA levels increased once patients reached stability [19]. There was a 14.36% increase in PSA on average from the start of treatment to stabilization in those previously on TRT and a 26.89% increase in PSA for patients never on TRT. This was likely attributable to TC acting on androgen receptors present on the prostate.

PSA levels were tracked every 3 months while on treatment. Out of about 7000 patients tracked over 7 years, 3 patients developed prostate cancer. Two of these patients saw an immediate increase in PSA levels after 3 months of treatment, strongly suggesting they had prostate cancer prior to treatment. The third was a firefighter who had occupational exposure to carcinogens. All 3 were successfully treated for their prostate cancer.

5. Conclusions

Based on the data collected from sixty total patients who reached stabilization on TRT (30 previously on TRT and 30 never on TRT), the average TC weekly dosage at stabilization for those previously on TRT was 147 mg, and the average weekly TC dosage at stabilization for those never on TRT was 149.3 mg. Therefore, it is recommended to start patients with 140–150 mg TC injections weekly (ideally every seven days) for the first four weeks of treatment (accounting for the thirty-day elimination time). Testosterone levels should then be re-measured at the half-life (seven days post-injection) for accuracy. We recommend that dosing adjustments be made in 10–20 mg increments, and only after four consecutive injections of the same TC dose. TT levels stabilized at 780.1 ng/dL on average (range: 605–1020 ng/dL) for those previously on TRT and 794.53 ng/dL on average (range: 641–1051 ng/dL) for those never on TRT. The range of 605–1051 ng/dL was then used to create a testosterone treatment flowchart, and when tested for accuracy held true. Based on these results, the recommended target range for a total testosterone level is 605–1051 ng/dL.

E2 levels at stabilization averaged 17.50 pg/mL (range: 5–37 pg/mL) for patients previously on TRT and 18.21 pg/mL (range: 5–39 pg/mL) for patients never on TRT. Patients previously on TRT were on an average anastrozole dosage of 0.90 mg weekly at the time of stabilization and those never on TRT averaged 0.75 mg weekly at the time of stabilization. Some patients in this study had E2 levels of 5 pg/mL. However, with further investigation these patients were experiencing hot flashes and joint pains, which were then eliminated by decreasing their anastrozole dose and subsequently increasing the E2 level to 7 pg/mL or greater. Therefore, it is recommended to start anastrozole dosing at 1 mg weekly, approximately 48–72 hours after TC injections, and decrease the anastrozole dose if patients experience symptoms of low E2 or have an E2 level of <7. Although E2 antagonizes the stimulating effect of erythropoietin [20, 21], the effectiveness of this mechanism was only seen if the E2 level was well-controlled. Only six patients (10%) in this study were able to stabilize their hemoglobin level without anastrozole, suggesting that most patients will require an aromatase inhibitor (regardless of dosing) to reach stability.

A significant finding of this study was that hemoglobin stabilization was vital to the stabilization of treatment. Based on this finding, it is recommended that patients start 81 mg aspirin daily if their hemoglobin level approaches the upper portion of normal range (17.1 g/dL) and maintain adequate hydration to minimize the polycythemia. If hemoglobin levels increase to >17 g/dL despite preventative measures, it is suggested that a therapeutic phlebotomy (about 1 pint of blood) be performed to avoid the risk of thrombosis. Patients

with familial erythrocytosis whose hemoglobin level starts at or above 17 g/dL are encouraged to start 81 mg aspirin daily at the beginning of treatment. In this study, taking 81 mg aspirin daily helped minimize the need for therapeutic phlebotomy. This procedure, when performed too frequently, can lead to iron deficiency and return of fatigue. Therapeutic phlebotomy can also result in erythropoiesis, which can further increase hemoglobin levels. Therefore, minimizing the need for this procedure in this study allowed for better control of the polycythemia effect.

Following completion of the study it was possible to create a Testosterone Treatment Flowchart (Figs. 1,2). The flowchart was then used to test for repeatability, and 124 patients have since reached stability (**Supplementary material**). Ultimately, achieving and maintaining a TT level of 605–1051 ng/dL and an E2 level of 7–35 pg/mL greatly reduced the polycythemia effect. This suggests that maintaining TT and E2 levels in these ranges, regardless of the route of administration of both testosterone (any derivative) and an aromatase inhibitor, will ultimately minimize the polycythemia effect associated with TRT.

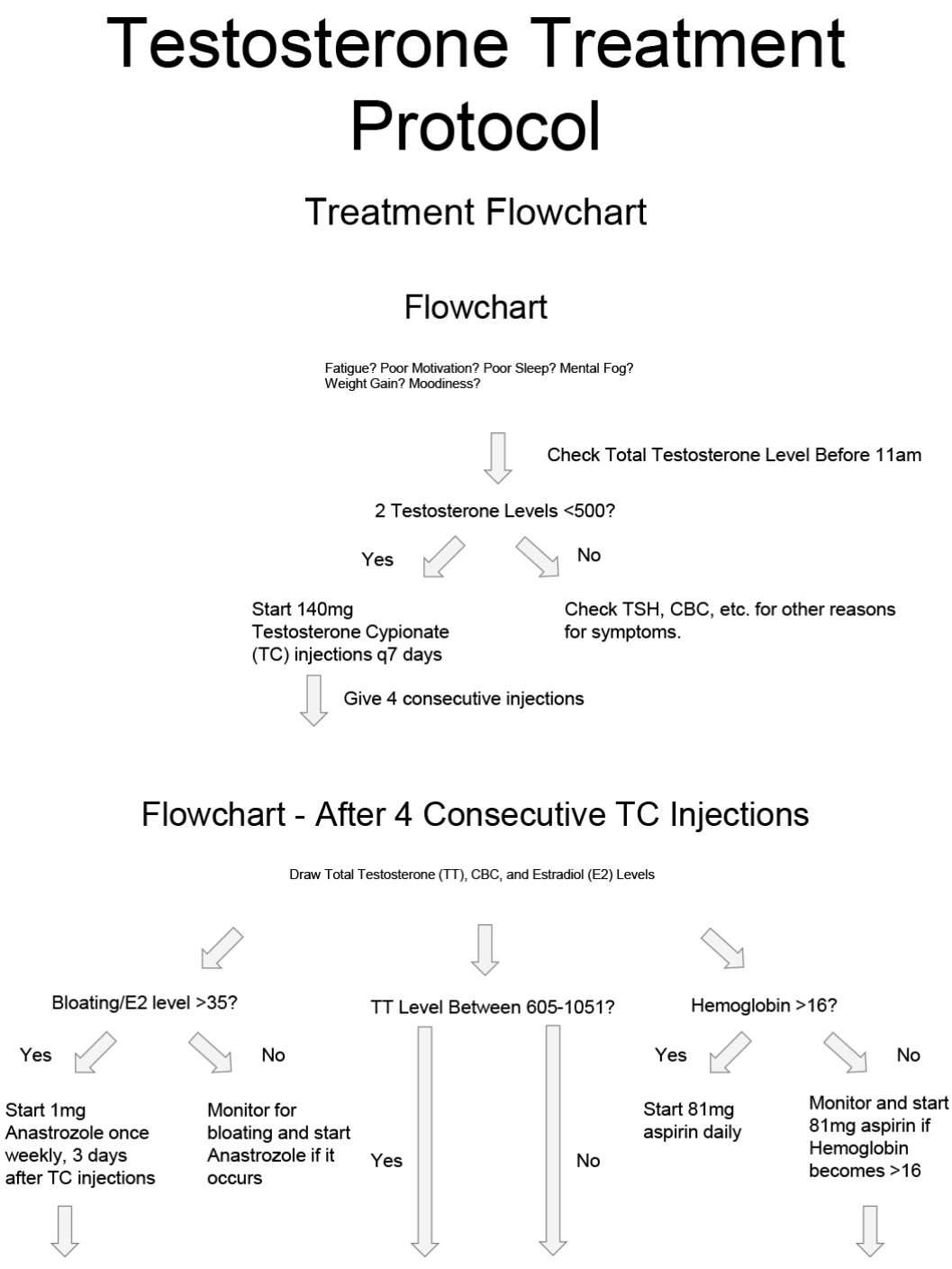

FIGURE 1. Testosterone Treatment Flowchart. TC: testosterone cypionate; TSH: Thyroid Stimulating Hormone; CBC: Complete Blood Count.

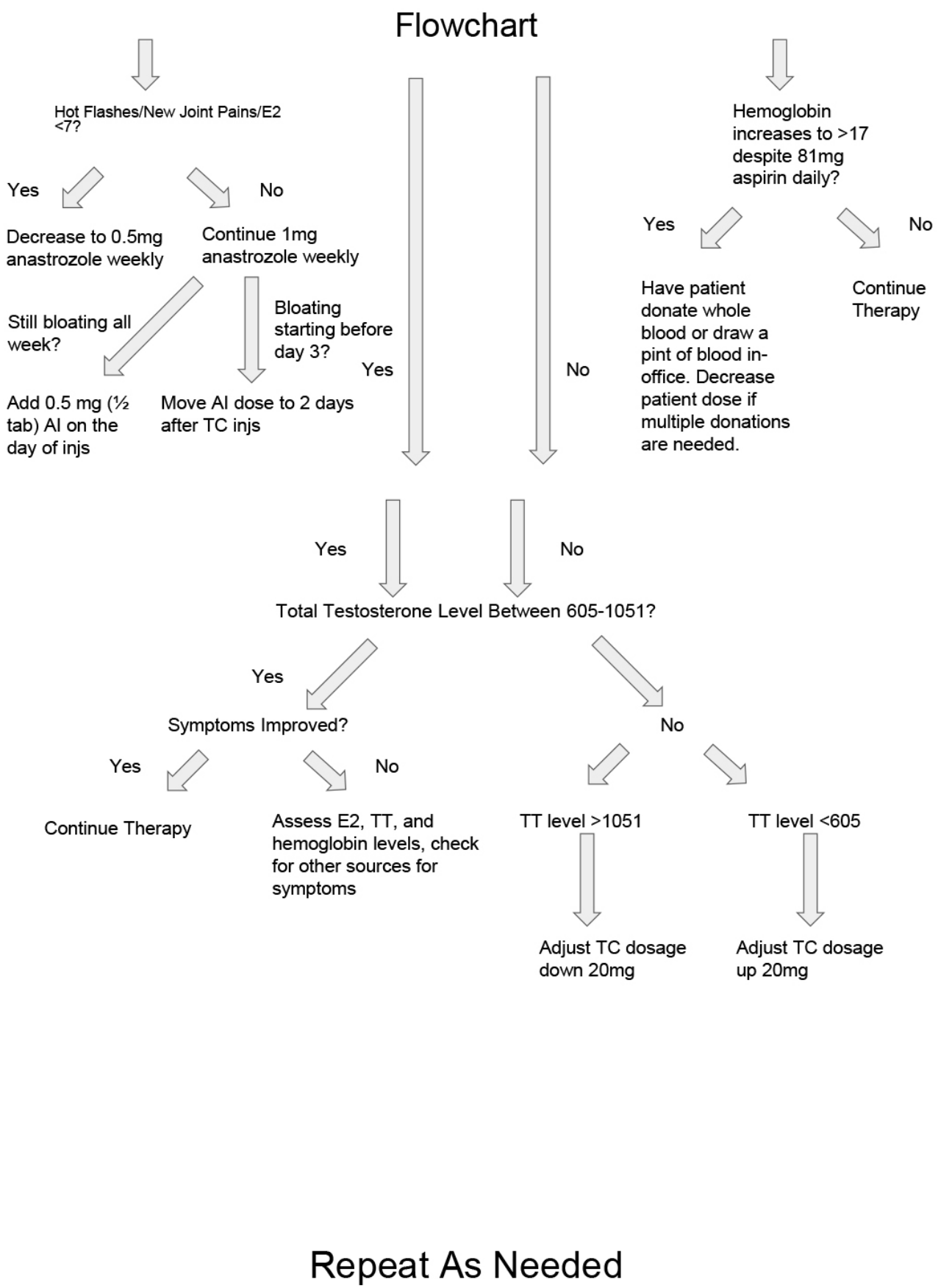

FIGURE 2. Testosterone Treatment Flowchart. TC: testosterone cypionate.

ABBREVIATIONS

E2, estradiol; TC, testosterone cypionate; TT, total testosterone; TRT, testosterone replacement therapy; WNL, within normal limits.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article (and supplementary material).

AUTHOR CONTRIBUTIONS

SMK—designed the research study; performed the research; analyzed the data; wrote the manuscript; contributed to editorial changes in the manuscript; read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval obtained from Dr. Randall Phillips, DO, FAOCO: "The information contained in the submitted article is a simple data review analysis of lab metrics for statistical comparison. This is done without revealing any review subject information and for the sole purpose of supporting the findings presented and any included conclusions/recommendations. As such it is considered appropriate for this ethics approval waiver.". All participants provided written informed consent prior to starting testosterone replacement therapy. All patient data were collected in accordance with the currently accepted protocol for TRT. This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jomh.org/files/article/1752214762603593728/attachment/Supplementary%20material.xlsx.

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