



Obesity and Baseline Estradiol Levels Are Independent Predictors for Initiation of Anastrozole in Hypogonadal Men on Clomiphene Citrate

Sorena Keihani¹, Nathan J. Alder¹, Philip J. Cheng¹, Gregory J. Stoddard², Alexander W. Pastuszak¹, James M. Hotaling¹

¹Division of Urology, Department of Surgery, ²Division of Epidemiology, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA

Purpose: To assess the conversion rate from clomiphene citrate (CC) monotherapy to combination CC+anastrozole (AZ) therapy in hypogonadal men and the predictors associated with the initiation of AZ.

Materials and Methods: A retrospective review of records from hypogonadal men treated with CC in a single fertility center was performed from 2013 to 2018. Patient age, body mass index (BMI), blood pressure, and reproductive hormones were obtained at baseline. Obesity was defined as BMI \geq 30 kg/m². Cox proportional hazards models were used to identify predictors of switching to combination CC+AZ therapy.

Results: A total of 318 men on CC were included. Median (interquartile range) age was 34 years (30–39 years) and patients were followed for a median of 9 months (4–17 months). Of these, 97 (30.5%) were started on CC+AZ therapy. These patients had higher baseline BMI and estradiol, which in multivariable regression were significant predictors for switching to CC+AZ therapy. A threshold of 18.5 pg/mL for baseline estradiol provided the highest accuracy for predicting the addition of AZ after adjusting for baseline BMI and total testosterone levels.

Conclusions: In our practice, following CC monotherapy, 30% of men were initiated on CC+AZ. Obesity (BMI \geq 30 kg/m²) and baseline estradiol \geq 18.5 pg/mL can predict the conversion to combination therapy with addition of AZ. This information can be used to counsel patients and also help to identify patients who can be started on combination therapy upfront.

Keywords: Anastrozole; Clomiphene; Hypogonadism; Infertility, male; Testosterone

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INTRODUCTION

Male hypogonadism commonly affects older men;

however, low testosterone levels are diagnosed in 3% to 8% of men 20 to 45 years old [1]. Alternatives to testosterone therapy can be used to treat hypogonadism

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Correspondence to: Sorena Keihani <https://orcid.org/0000-0001-9006-5809>

Division of Urology, Department of Surgery, University of Utah School of Medicine, 30 North 1900 East, Salt Lake City, UT 84132, USA.

Tel: +1-801-213-2700, **Fax:** +1-801-213-2700, **E-mail:** sorena.keihani@hsc.utah.edu

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while preserving fertility in younger men [2]. Selective estrogen receptor modulators such as clomiphene citrate (CC) and aromatase inhibitors (AI) such as anastrozole (AZ), as well as human chorionic gonadotropin are commonly used for this purpose [3,4].

Initially developed to treat female infertility, CC blocks estrogen feedback and increases gonadotropin production in the hypothalamus and pituitary gland. In males, this can stimulate endogenous testosterone production [5] and a rising prevalence of CC usage in men has been reported in the USA [6]. Growing evidence suggests that CC is safe and effective for treating hypogonadism, particularly in young men [4,5]. However, CC treatment can cause increases in estradiol levels that may require the addition of AI in some patients [7-10].

The frequency of hyperestrogenemia and the factors predicting the need for AI therapy in the setting of CC monotherapy are unknown. Obesity is a risk factor for hypogonadism [11] and CC has been successfully used to increase testosterone levels in obese men but estrogen levels also increase [7,12]. Although the association between obesity and elevated estradiol levels seems intuitive given the presence of aromatase in adipose tissue, the evidence is inconsistent across studies [13]. Given that a large proportion of young hypogonadal men are also obese, a knowledge gap exists in the link between obesity and estradiol levels and also how these levels respond to CC therapy in obese men.

We hypothesized that obesity and hormone values at baseline can be used to identify the patients who will require AI therapy after starting CC treatment. We aimed to study the rate of initiation of combination CC+AZ therapy in our practice and also to identify the predictors for this change in a cohort of young men treated for hypogonadism.

MATERIALS AND METHODS

We retrospectively identified all patients who visited our fertility clinic and were prescribed CC for male hypogonadism from 2013 to 2018. Exclusion criteria included: (1) history of sex chromosome disorders, (2) recent treatment with exogenous testosterone or hormonal therapy, and (3) lack of follow-up after CC initiation. All patients were seen and treated by a single fellowship-trained urologist with expertise in male infertility.

Data on patient age, body mass index (BMI) and systolic blood pressure (SBP) at baseline were obtained. The following laboratory values were extracted prior to CC initiation: luteinizing hormone, follicle stimulating hormone, total testosterone (TT), bioavailable testosterone (BT), estradiol, sex hormone binding globulin (SHBG), albumin, and testosterone to estradiol (T/E) ratio. All hormone levels were based on early morning blood draws. Follow-up records were reviewed to identify patients who were switched to combination therapy with AZ. Time from initial CC order to AZ initiation or last follow-up on CC was recorded for each patient.

1. Definitions

Hypogonadism was defined as the presence of a TT<300 ng/dL or BT<155 ng/dL combined with signs and/or symptoms of low testosterone [3]. Baseline hypogonadal symptoms and sexual function were assessed using the validated Androgen Deficiency in Aging Male (ADAM) and Sexual Health Inventory for Men (SHIM) questionnaires, respectively. Any of the following was considered a hypogonadal symptom: (i) positive ADAM questionnaire (a 'yes' answer to questions on decreased libido [Q1] or erectile dysfunction [Q7], or any other three questions); (ii) erectile dysfunction as SHIM score <22; or (iii) a chief complaint of decreased libido or erectile dysfunction if ADAM/SHIM questionnaires were not completed. No men were treated for low TT levels in the absence of hypogonadal symptoms as defined above. BT was calculated according to the Vermeulen formula [14]. Biochemical hyperestrogenemia was defined as estradiol >50 pg/mL or a T/E ratio of <10. Obesity was defined as BMI \geq 30 kg/m².

2. Treatment and follow-up protocol

CC dose varied from 25 to 100 mg either daily or every other day and was titrated based on patients' clinical and hormonal response to treatment; 68% and 23% of patients were started on a 50 mg every other day and 50 mg daily regimen, respectively. AZ was added to CC for biochemical hyperestrogenemia +/- hyperestrogenemic symptoms such as flushing, gynecomastia, or breast/nipple tenderness. AZ was usually started at 1mg one to three times weekly and was titrated based on clinical and biochemical response.

We usually base our starting dose frequency upon severity of symptoms, patient BMI, testosterone levels, and BT when available, and will consider a dose in-

crease if BT is <250 ng/dL at first follow-up. Our biochemical treatment goal is usually a TT between 600 to 900 ng/dL, and we usually try to keep TT levels <1,000 ng/dL with dose adjustments as needed. Similarly, for AZ, we usually start with 1 mg twice weekly but base our decisions upon patient BMI, as well as testosterone and estradiol levels with adjustments made based on response to treatment.

Patients were followed-up with measurement of TT, BT and estradiol levels 3 to 4 weeks after initiation of CC therapy to assess initial response to treatment and then every 3 to 6 months. PSA and hematocrit were monitored only for high-risk patients or those who remained on CC therapy for >6 months. For patients on AZ, bone density was assessed only if patients received treatment for >12 months.

3. Statistical analysis

Values are presented as median (25th–75th percentile interquartile range [IQR]), mean±standard deviation, or mean±standard error as appropriate. Independent sample t-test or Wilcoxon rank-sum test were used to compare baseline characteristics and hormone values between the two groups. Scatter plots, Pearson correlation, and curvilinear correlation (quadratic fit) were used to explore the associations between baseline BMI and hormone values. Changes in hormone values from baseline to the last follow-up before initiation of AZ (for the combination therapy group) or to the last follow-up on CC (for the CC monotherapy group) were calculated and are presented as mean changes (95% confidence interval [CI]). Paired-sample t-test was used to compare the changes from baseline within each group. Independent t-test was used to compare the mean hormone changes between the two groups.

Cox regression analysis was used to explore the associations between baseline variables as predictors, and the addition of AZ to CC monotherapy as the outcome. Hazard ratios (HR) with 95% CIs from uni- and multivariable models are reported. For multivariable analyses, a multiple imputation approach was used to address missing hormone data. A multivariable model was developed by choosing the variables with a $p < 0.1$ from the univariable analyses and entering them in a stepwise regression model with backward variable selection (with $p > 0.1$ as significance level for removal from the model).

Time-dependent receiver operating curve analysis [15]

was used to identify the threshold estradiol level and BMI predictive for initiation of AZ within 24 months of starting CC with the highest accuracy. The optimal threshold was chosen based upon the highest Youden's index and the area under the curve (AUC) [16,17].

Survival analysis and Kaplan–Meier curves were used to graph the differences in outcome based upon categorical predictors for obesity and the calculated baseline estradiol level. As the number of patients and events were small beyond 24 months of follow-up, a truncated survival analysis at 24 months was used to calculate better estimates. Both unadjusted and adjusted (for age, BMI, SBP, baseline TT, estradiol, and albumin) Kaplan–Meier curves were developed.

4. Ethics statement

The study protocol was approved by the Institutional Review Board (IRB) of the University of Utah (IRB# 00073166). Informed consent was not necessary given the retrospective design and use of a Health Insurance Portability and Accountability Act compliant database.

RESULTS

We included 318 men who were initially started on CC. Baseline cohort characteristics and hormone values are summarized in Table 1. Median (IQR) age at first visit was 34 years (30–39 years) and patients were followed for a median of 9 months (4–17 months). Baseline BMI was positively correlated with baseline estradiol level and negatively correlated with TT, BT, T/E ratio, and albumin levels. The correlation between BMI and SHBG was curvilinear with a negative correlation for $BMI < 45 \text{ kg/m}^2$ (Supplement Fig. 1).

Overall, 29 patients (9.1%) experienced side effects while on CC including mood changes/irritability ($n=12$; 3.8%), fatigue ($n=4$; 1.3%), paradoxical TT response ($n=4$, 1.3%), asymptomatic increase in hematocrit >54% ($n=4$, 1.3%), headaches ($n=3$; 0.9%), and decreased libido/erectile dysfunction ($n=2$, 0.6%). Ninety-seven patients (30.5%) had AZ added to their regimen at a median of 2 months (1–4 months) after CC initiation. None of the patients had biochemical hyperestrogenemia (estradiol >50 pg/mL) at baseline. Overall, 50% of all patients were obese, and the obesity rate was higher in those who switched to combination therapy (65% *vs.* 43%, $p < 0.001$). Patients in combination therapy group had higher BMI and estradiol levels and lower TT levels

Table 1. Univariable comparisons of baseline patient characteristics and laboratory data separated by the follow-up need for combination therapy

Variable	Was combination therapy started in follow-up?			p-value
	Total (n=318) ^a	No (n=221)	Yes (n=97)	
Age (y)	34 (30–39)	35 (31–39)	34 (30–39)	0.4
BMI (kg/m ²)	29.9 (26.4–34.9)	29.1 (26.1–33.5)	32.8 (29.3–41.1)	<0.001
SBP (mmHg)	130 (120–140)	130 (119–138)	135 (122–144)	0.01
SHIM score	23 (19–25)	24 (20–25)	22 (19–24)	0.35
ADAM score	3 (1–6)	3 (1–6)	4 (2–7)	0.12
LH (IU/L)	4.5 (3.0–6.3)	4.4 (3.0–6.2)	4.5 (3.1–6.5)	0.59
FSH (IU/L)	4.4 (2.8–8.1)	4.8 (2.9–8.3)	4.1 (2.4–6.7)	0.09
TT (ng/dL)	247 (202–299)	256 (203–305)	232 (197–273)	0.03
BT (ng/dL)	160 (127–278)	140 (113–169)	130 (108–151)	0.07
Estradiol (pg/mL)	16.9 (13.5–22.5)	15.8 (12.8–20.3)	20.0 (15.7–28.0)	<0.001
T/E ratio	14.1 (10.5–19.0)	15.3 (11.5–19.7)	11.4 (8.3–15.5)	<0.001
SHBG (nmol/L)	24 (18–31)	24 (18–31)	23 (18–31)	0.65
Albumin (g/dL)	4.5 (4.2–4.7)	4.5 (4.3–4.7)	4.4 (4.1–4.6)	0.01

Values are presented as median (25th–75th interquartile range).

BMI: body mass index, SBP: systolic blood pressure, SHIM: Sexual Health Inventory for Men, ADAM: Androgen Deficiency in Aging Male, LH: luteinizing hormone, FSH: follicle stimulating hormone, TT: total testosterone, BT: bioavailable testosterone, T/E: testosterone to estradiol, SHBG: sex hormone binding globulin.

^aActual sample size for each variable might be different from total due to missing data for some: Age and TT (n=318), BMI and SBP and SHBG and albumin (n=300), LH and FSH and estradiol (n=283), ADAM and SHIM (n=230), BT (n=238).

Table 2. Baseline and follow-up laboratory values and corresponding changes while on clomiphene citrate for patients who did and did not switch to combination therapy with anastrozole

Variable	Number ^a	Baseline	Follow-up ^b	Change from baseline	p-value ^c
Combination therapy group	97				
TT (ng/dL)	94	236.1±7.4	665.0±18.7	+428.9 (+392.7 to +465.0)*	<0.001
BT (ng/dL)	51	129.3±5.1	372.4±18.9	+243.1 (+207.2 to +279.0)*	<0.001
Estradiol (pg/mL)	81	21.7±0.9	62.3±1.9	+40.6 (+36.7 to +44.4)*	<0.001
T:E ratio	81	12.3±0.6	11.1±0.3	-1.2 (-2.4 to -0.98)*	0.03
CC monotherapy group	221				
TT (ng/dL)	176	259.7±6.1	593.8±16.7	+334.13 (+304.0 to +364.3)*	<0.001
BT (ng/dL)	84	139.6±4.3	311.6±12.8	+172.0 (+148.1 to +195.9)*	<0.001
Estradiol (pg/mL)	152	17.1±0.6	35.1±1.9	+18.0 (+14.3 to +21.6)*	<0.001
T:E ratio	150	16.5±0.6	18.8±0.7	+2.4 (+0.9 to +3.9)*	<0.001

Values are presented as number only, mean±standard error, or mean (95% confidence interval). Values are reported only for those patients who had both baseline and pre-combination therapy hormone levels available.

TT: total testosterone, BT: bioavailable testosterone, T/E: testosterone to estradiol, CC: clomiphene citrate.

^aDifference in sample sizes is due to missing values for each of hormones and because not all patients had all the hormones measured both at baseline and follow-up for pairwise comparison.

^bFor patients who needed combination therapy (combo therapy=yes), follow-up values are from the last visit before starting combination therapy with anastrozole.

^cComparisons are made using paired t-test between baseline and pre-combination therapy hormones levels. p<0.5 is considered statistically significant.

*p<0.01 for comparisons of changes from baseline between the two groups. Comparisons made using independent samples t-test between combination therapy yes vs. no.

and T/E ratio at baseline (Table 1). Both patient groups had significant increases in TT, BT, and estradiol levels on CC treatment. Patients who were started on com-

bination therapy had a greater increase in estradiol levels before initiating AZ compared to patients who remained on CC monotherapy (mean estradiol increase

of 40.6 vs. 18.0 pg/mL, $p < 0.01$). They also had a mean of 1.2-point drop in T/E ratio compared to a 2.4-point average increase in T/E ratio for patients who remained on CC monotherapy (Table 2).

In univariable analysis, higher BMI and estradiol levels, and lower TT and albumin levels at baseline, were significant predictors for the initiation of AZ. After entering baseline age, BMI, SBP, TT, estradiol, and albumin in a multivariable Cox regression model, only BMI, TT, and estradiol remained in the final model with baseline BMI (HR=1.04, 95% CI=1.01–1.07, $p=0.003$) and baseline estradiol (HR=1.05, 95% CI=1.02–1.08, $p < 0.001$) as statistically significant predictors for switching to combination therapy.

A threshold value of 18.5 pg/mL for baseline estradiol levels provided the highest accuracy for predicting the

addition of AZ after adjusting for baseline BMI and TT (AUC=0.73, 95% CI=0.66–0.80). A threshold value of 29.0 kg/m² for baseline BMI provided the highest accuracy for predicting the addition of AZ after adjusting for baseline estradiol and TT (AUC=0.70, 95% CI=0.63–0.78) (Supplement Fig. 2). As this threshold was close to the widely accepted BMI cut-off of 30 kg/m² for obesity, we chose to categorize BMI at 30 kg/m². Fig. 1 depicts the crude and adjusted Kaplan–Meier curves for baseline obesity and estradiol ≥ 18.5 pg/mL for prediction of switching to combination therapy. In the adjusted model, obesity and baseline estradiol ≥ 18.5 pg/mL were associated with 1.7-fold (95% CI=1.1–2.8) and 2.6-fold (95% CI=1.6–4.3) increases in the probability of combination therapy within 24 months of starting CC, respectively.

Table 3 summarizes the 6-, 12-, and 24-month prob-

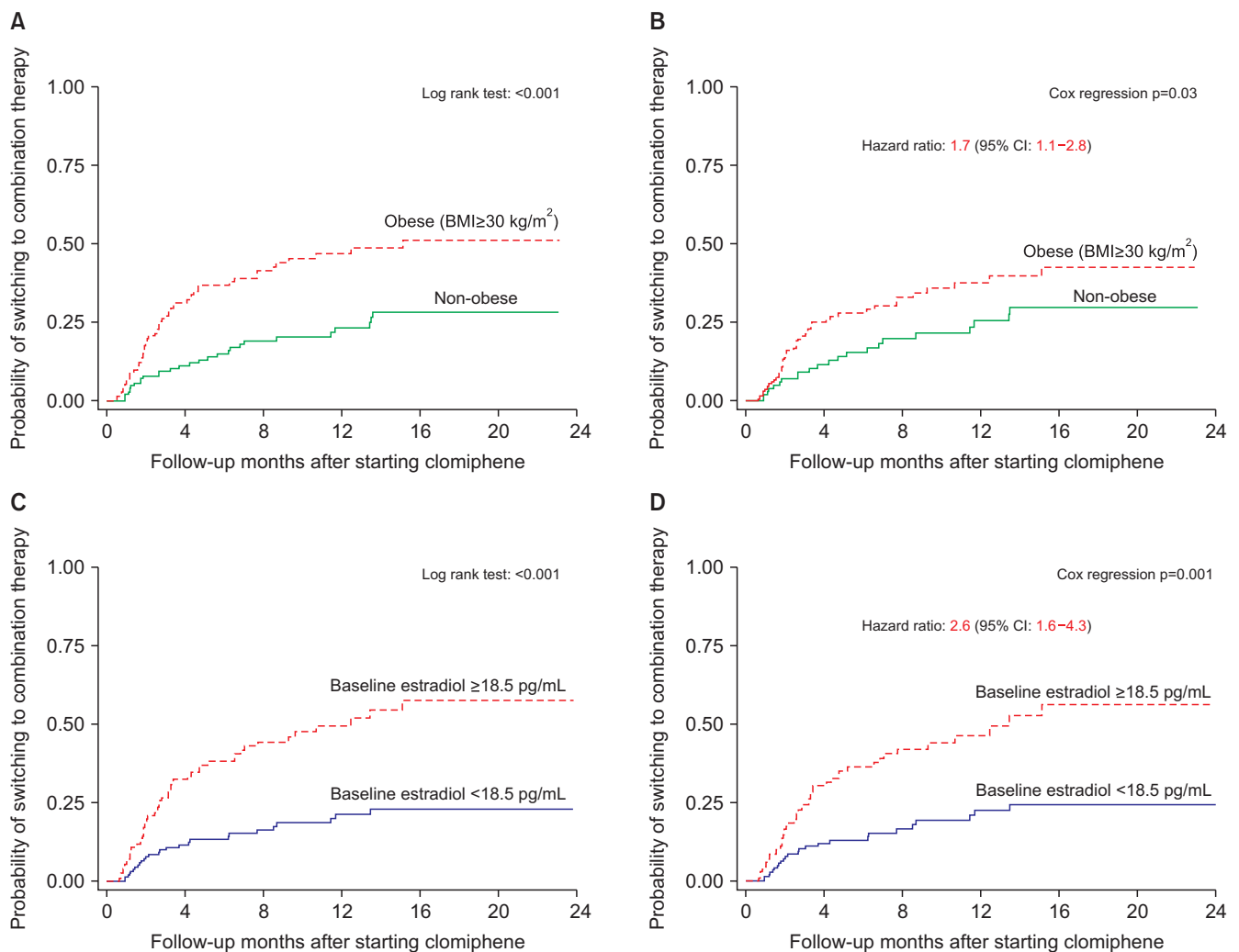


Fig. 1. Kaplan–Meier curves for baseline obesity (A, B) and estradiol ≥ 18.5 pg/mL (C, D) for prediction of switching to combination clomiphene+anastrozole therapy. (A, C) These graphs are unadjusted curves. (B, D) These graphs are adjusted for baseline age, systolic blood pressure, total testosterone, albumin, and estradiol (for B) or body mass index (BMI) (for D).

Table 3. Univariable Kaplan–Meier probability of switching to combination therapy according to baseline obesity and estradiol level

Baseline status	6-month probability	12-month probability	24-month probability
Body mass index < 30 kg/m ²	15% (10%–22%)	23% (16%–33%)	28% (20%–39%)
Body mass index ≥ 30 kg/m ² (obese)	37% (29%–46%)	47% (38%–57%)	51% (41%–62%)
Estradiol < 18.5 pg/mL	13% (9%–20%)	21% (15%–30%)	23% (16%–32%)
Estradiol ≥ 18.5 pg/mL	38% (30%–48%)	49% (40%–60%)	63% (49%–77%)
Obese+estradiol ≥ 18.5 pg/mL	51% (39%–64%)	62% (49%–76%)	75% (57%–89%)

abilities of the addition of AZ to CC monotherapy according to baseline obesity and estradiol status. For patients who were both obese and had baseline estradiol ≥ 18.5 pg/mL, 51% were switched to combination therapy within 6 months and the rate increased to 75% within 24 months (Table 3).

DISCUSSION

This study demonstrates that approximately 30% of hypogonadal men who are started on CC monotherapy will require the addition of AZ at a median CC treatment duration of 2 months due to increases in estradiol levels above the upper limit of normal. Obesity and higher estradiol levels were identified as independent predictors of this change in treatment.

CC is a safe and effective treatment for male hypogonadism particularly in younger men and when fertility preservation is desired. In a randomized controlled trial, CC was superior to AZ in raising testosterone levels although it was also associated with increased estradiol levels (from 27.6±0.9 to 50.0±4.2 pg/mL at three months) [9]. A recent placebo-controlled trial on obese men, also showed beneficial effects of CC in increasing gonadotropins and testosterone levels, as well as improvements in body composition; however, estradiol levels increased from 32.5±12.6 to 89.4±47.8 pg/mL within three months of starting CC [7]. These findings show that CC treatment, although effective in increasing testosterone levels, can be associated with an unwanted increase in estradiol and hyperestrogenemic symptoms [7-10,18,19]. AI such as AZ are often employed to correct elevations in estradiol levels or low T/E ratios that can be associated with CC treatment [20].

The true rate of conversion from CC monotherapy to CC+AZ combination therapy is unknown. In a recent study by Krzastek et al [21], 20% of patients who were receiving CC and had pre- and post-treatment estradiol levels required addition of AZ. These rates were 15%

and 37% for those who were followed-up for less than or more than three years, respectively. These patients had higher estradiol levels at baseline [21]. Nicholson et al [22] reported that 17% of patients who were started on CC needed combination therapy; these patients had higher average BMI at baseline (35.1 vs. 29.6 kg/m²). In our study, the rate of switching to combination therapy was higher (30%) despite the shorter follow-up. This might be due to differences in patient characteristics, stricter inclusion criteria (e.g., exclusion of genetic cases and patients on exogenous hormones), and variations in clinical practice. Regardless, we similarly found that patients who required combination therapy had higher baseline BMI (32.8 vs. 29.1 kg/m²). Additionally, higher baseline estradiol and lower testosterone levels and T/E ratios in these patients suggest that these men might represent a patient population with potentially higher adipose and/or testicular aromatase activity resulting in increased peripheral aromatization of testosterone. Interestingly, although the estradiol levels were normal at baseline (median=20.0 pg/mL) and none of the patients had levels >50 pg/mL, these patients had an average of 40 pg/mL surge in their estradiol after starting CC. Similarly, the T/E ratio decreased in this group after starting CC, indicating that although both testosterone and estradiol levels increased with CC treatment, the increase in estradiol levels outpaced the increases in testosterone.

Obesity has detrimental effects on male fertility and can cause hypothalamic-pituitary-testicular axis dysfunction through the effects of estradiol, leptin, and pro-inflammatory cytokines [11]. Although the specific effects of obesity on semen parameters and male reproductive hormones are not completely defined [13,23], increased BMI is consistently associated with lower testosterone and SHBG levels [13]. The association between BMI and estradiol levels, however, has been inconsistent between studies. In a 2010 meta-analysis, only 4 of 10 of the included studies reported a positive

correlation between BMI and estradiol [13]; however, subsequent studies suggested a more consistent association between higher BMI and lower T/E ratio [24-26]. Our results are in line with these findings as we found positive correlation between baseline BMI and estradiol levels as well as negative correlations between BMI and testosterone and T/E in our patient population.

Estrogen is required for optimal male reproductive function [27]. A complex homeostasis of estradiol, testosterone, and aromatase controls normal sexual function and spermatogenesis. Adipose tissue plays an important role in peripheral aromatization and conversion of androgens to estrogen in men [28,29]. Thus, a positive correlation between BMI and estradiol levels is biologically plausible [13]. However, in reality this interaction is more complex as lower testosterone levels in obese men limits the amount of substrate available to aromatase and can also decrease aromatase expression in adipose tissues as a potential negative feedback mechanism to preserve testosterone levels [11].

Both low and high estradiol levels can be associated with decreased libido [27] and relative excess of estrogen to testosterone (*e.g.*, low T/E ratio) has been proposed as a treatable endocrinopathy [29,30]. Thus, off-label use of AI provides a rational option to mitigate the detrimental effects of high circulating estradiol levels especially in obese hypogonadal men. Our results suggest that both obesity and estradiol levels ≥ 18.5 pg/mL at baseline are independent predictors for unfavorable changes in estradiol or T/E ratio after starting CC. Notably, our calculated BMI threshold to predict AZ addition was very close to the widely accepted BMI cut-off of 30 kg/m^2 for obesity, which reinforces adhering to the common obesity definition for this purpose. We believe this provides important information at baseline to decide the course of treatment and possibly start with combination therapy in some patients to avoid surges in estradiol levels.

This study has a number of strengths and limitations. This is the first report on rates and predictors of combination therapy in patients started on CC treatment. Availability of consistent baseline and follow-up data allowed us to use each patient as his own control to assess hormonal changes from baseline. However, retrospective design, homogenous patient population, and differences in clinical practice limit the external validity of our findings. Furthermore, the effect of different dose regimens and adjustments on hormonal

changes cannot be eliminated; however, given the off-label use of CC and AZ, there is no universal dosing recommendation and frequency of treatment is usually tailored based on patient response and achieving clinical and hormonal targets. Last, we used biochemical hyperestrogenemia as an indication for combination therapy, which might lead to overtreatment of some patients who have not yet developed hyperestrogenemic symptoms and might overestimate the need for combination therapy in our practice.

CONCLUSIONS

In our practice, following CC monotherapy, approximately 30% of men required combination therapy with CC+AZ for elevated estradiol levels. Higher baseline BMI and estradiol levels predict the conversion to combination therapy. Obese patients with baseline estradiol ≥ 18.5 pg/mL are more likely to need combination therapy with 50% requiring AZ by one year and 75% by two years. These results can be used to counsel patients and also help identifying patients who can be started on combination therapy upfront.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: SK, JMH. Data curation: SK, NJA, PJC, JMH. Formal analysis: SK, GJS. Methodology: SK, JMH, AWP. Supervision: AWP, JMH. Writing – original draft: SK. Writing – review & editing: SK, AWP, JMH.

Supplementary Materials

Supplementary materials can be found *via* <https://doi.org/10.5534/wjmh.190160>.

Data Sharing Statement

The data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study.

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