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Original Article

New Treatments for Adult Female Acne

Nuevos tratamientos para el acné en mujeres adultas

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ABSTRACT

Introduction: Adult female acne is a common dermatological condition whose management is challenging because of its tendency toward chronicity, recurrence, and resistance to available treatments. The aim of this systematic review is to study the effectiveness, safety, and use profile of antiandrogenic treatments used as an alternative in women who present alterations in androgen hormones or receptors or who have a state of hyperandrogenism.
Material and methods: A search was conducted in the PubMed database including all types of epidemiological studies—clinical trials, retrospective, prospective, cohort, and case-series studies—published in the last 10 years and performed in humans that evaluated the effectiveness and safety of antiandrogenic treatments—spironolactone, metformin, and bicalutamide—in patients with acne.
Results: Thirteen articles met the inclusion criteria, evaluating a total of 1335 patients. Of these 13 articles, 4 (30.8%) addressed spironolactone and 9 (69.2%) addressed metformin. No studies were found evaluating the effectiveness and tolerability of bicalutamide for acne. Both drugs showed good results in reducing acne lesions, measured with different scales, and in terms of safety and tolerability. The most frequent adverse effects were menstrual irregularities in the case of spironolactone and gastrointestinal discomfort with the use of metformin. The latter also showed good results in improving the lipid profile, insulin resistance, and BMI, which should be taken into consideration in the management of acne associated with polycystic ovary syndrome.
Conclusion: Although antiandrogenic treatments such as spironolactone and metformin have shown promise as options for the management of acne in adult women, more controlled and randomized studies comparing these drugs with each other and with placebo are needed to evaluate their efficacy and tolerability with a higher level of evidence.

Introduction

Acne is an inflammatory skin disease that affects the pilosebaceous unit through a multifactorial process. It is mainly located on the face, chest, and back, the areas richest in sebaceous glands. It is characterized by the presence of different types of elementary dermatological lesions, such as comedones, papules, pustules, nodules, cysts, and scars. These lesions may have major psychological consequences in terms of patients' self-esteem and social relationships.[1]

Several factors influence the pathogenesis of acne and give rise to these follicular lesions. First, enlargement of the sebaceous gland leads to increased sebum production and changes in its composition, with an increased fatty-acid content.[2] This causes irritation of the follicular wall, resulting in desquamation of its keratinized cells and producing follicular hyperkeratosis, which leads to pore obstruction. In this setting, *Cutibacterium acnes* (*C. acnes*), a bacterium that colonizes the pore, proliferates, ultimately causing inflammation of the follicle.[3]

Therefore, the factors known to lead to lesion development are mainly hyperseborrhea, follicular hyperkeratosis, bacterial colonization, and inflammation. However, another factor that favors the initiation of the entire process should also be mentioned: hormonal influence[2] (Fig. 1).

This influence occurs mainly through dihydrotestosterone (DHT), the androgenic hormone capable of acting on the sebaceous gland by increasing sebum production and altering its composition. Its role in acne may be due either to increased androgen production, at both the ovarian and adrenal levels, as occurs in puberty, polycystic ovary syndrome (PCOS), or type 2 diabetes mellitus (T2DM), or

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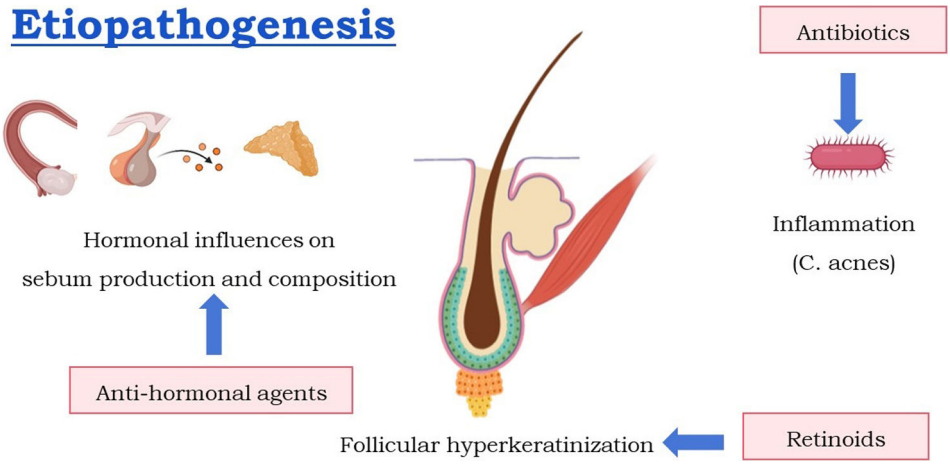

Fig. 1. Etiopathogenesis of acne.

to increased receptor sensitivity, which is the most frequent cause of adult female acne. DHT results from the action of the enzyme 5-α-reductase on circulating androgens, namely dehydroepiandrosterone (DHEA), dehydroepiandrosterone-5 (DHEA-5), free testosterone, and bound testosterone.[2]

Regarding acne treatment, there are several types of active ingredients aimed at targeting each of the pillars of its etiology. According to the European and American clinical guidelines,[4,5] acne has been classified into 4 stages according to severity: comedonal acne, mild or moderate papulopustular acne, severe papulopustular acne, and cystic or conglobate acne. Although there is no clear evidence regarding the effectiveness of available treatments, consensus has been reached on prescribing stepwise treatment according to lesion severity. For comedonal acne, topical retinoids are recommended with a moderate recommendation grade; for mild and moderate papulopustular acne, the combination of adapalene with benzoyl peroxide (BPO) or clindamycin with BPO is recommended with a high recommendation grade; and for severe papulopustular or cystic acne, isotretinoin is recommended. In these last 2 stages, the combination of oral antibiotics with adapalene or azelaic acid, or adapalene and BPO, may be used too.[4] Isotretinoin is currently the most effective drug for the management of moderate-to-severe acne, being first-line therapy for severe acne and second-line therapy for moderate acne that does not respond to other treatments.[4,5] However, it acts at all levels of acne etiopathogenesis except the hormonal level. Therefore, in acne caused by hormonal alterations, as in adult female acne, lesions very frequently recur once the drug has been completely eliminated from the body, since the hormonal influence continues to act.[4]

In these cases, although with a low recommendation grade, hormonal antiandrogens may be used for moderate-to-severe acne in adult women, together with systemic antibiotic therapy and topical treatment.[4]

Hormonal antiandrogens include oral contraceptives, which act on hormone synthesis, and spironolactone, metformin, and bicalutamide, which act on hormone receptors.[6] In the case of oral contraceptives, those containing ethinyl estradiol together with a preferably antiandrogenic progestogen, such as norgestimate, norethisterone acetate, or drospirenone, are recommended.[6] Spironolactone is a steroidal antiandrogen that nonselectively inhibits androgen receptors and is therefore useful in cases in which there is no increase in hormone production but rather greater receptor sensitivity.[7] Metformin is an antidiabetic drug whose mechanism of action consists of increasing the sensitivity of peripheral tissues to insulin, reducing insulin-like growth factor 1 (IGF-1) and androgen hormone levels, and reducing inflammation.[8] Bicalutamide is a nonsteroidal antiandrogen that selectively and competitively inhibits androgen binding to its receptor.[9]

Although evidence is lacking and there is a clear need for further research and for verification of the effectiveness and tolerability of these drugs for the treatment of adult female acne in controlled and randomized studies, this systematic review will focus on evaluating, through a review of the currently available literature, the effectiveness, safety, and use profile of hormonal antiandrogens that reduce androgen receptor sensitivity: spironolactone, metformin, and bicalutamide.

Material and methods

Design and search criteria

A systematic review of the literature was conducted to answer the following questions:

- What hormonal antiandrogenic treatments are currently available for the management of adult female acne?
- What is the effectiveness of these treatments?
- What adverse effects do these antiandrogenic drugs cause?

We conducted a bibliographic search in the PubMed database including all articles published from May 2013 to May 2023, following the PRISMA guidelines and using the search string: (ACNE) AND ((SPIRONOLACTONE) OR (METFORMIN) OR (BICALUTAMIDE) OR (ANTIANDROGENS)).

Inclusion and exclusion criteria

The search was limited to studies conducted in humans in the past 10 years that evaluated the effectiveness and safety of antiandrogenic treatments—spironolactone, metformin, and bicalutamide—in patients with acne, and that were written in Spanish or English. All types of epidemiological studies were included: clinical trials, cohort studies, case-control studies, retrospective studies, observational studies, and cross-sectional studies, in which one of the outcomes studied was acne. The exclusion criteria were in vitro, ex vivo, or animal studies. Reviews, clinical guidelines, protocols, conference posters, and studies in patients with acne that did not evaluate drug efficacy were also excluded.

Study selection

Two investigators (MZV and TMV) independently reviewed the titles and abstracts obtained in the initial search to assess relevant studies. Articles that met the inclusion criteria were read in full, and their references were reviewed to identify additional sources. Articles considered relevant by both investigators were included in the review.

Disagreements regarding the inclusion or exclusion of some articles were discussed until consensus was reached; if consensus was not achieved, the article was discussed with a third investigator (SAS).

Variables

The variables evaluated in the studies included in the review were the type of study, year, author, drug evaluated, number of participants, age and sex of the patients, scales used to assess efficacy, and adverse effects caused by the treatments.

Results

The search yielded a total of 431 results (Fig. 2), whose titles and abstracts were reviewed. After this initial screening, 61 articles were selected for more detailed review; 24 of these were discarded, and 37 were considered relevant and read in full to confirm that they met all inclusion criteria. Articles whose results did not include evaluation of the effectiveness or tolerability of the drugs under study were excluded one by one. Finally, 13 articles were included in the review.

What hormonal antiandrogenic treatments are currently available for the management of adult female acne?

Currently, there are several types of drugs aimed at reducing the androgenic influence that causes the onset or recurrence of acne in adult women. These include drugs aimed at decreasing endogenous hormone synthesis, namely oral contraceptives (OCs), and those aimed at decreasing androgen receptor sensitivity, namely spironolactone, metformin, and bicalutamide. This systematic review will focus on the latter.

What is the effectiveness of these treatments?

Spironolactone (SPL)

After the bibliographic search, a total of 4 articles studying the effectiveness of spironolactone in women > 18 years with acne were included (Table 1). Of these 4 articles, only 1 (25%) was a randomized controlled clinical trial,[10] 2 (50%) were retrospective studies,[11,12] and 1 (25%) was a retrospective case series.[13]

The clinical trial[10] was conducted in 63 women aged between 25 and 45 years, who were divided into 3 groups receiving topical benzoyl peroxide plus spironolactone 50 mg (SPL 50), spironolactone 25 mg (SPL 25), or placebo. The main objective of the study was to assess the efficacy and tolerability profile of low-dose spironolactone (25–50 mg) for the treatment of adult female acne, with improvement assessed using the Adult Female Acne Scoring Tool for the face (AFAST-F scale) and total lesion count. The main result was a significantly greater improvement in acne in the SPL 50 group vs the placebo group (75% improvement vs 30%). This improvement was defined as achieving clear or almost clear skin, or at least improvement to grade 2 on the AFAST-F scale. Significant improvements were observed in all groups in total lesion count, inflammatory lesions, and comedonal lesions after 12 weeks of treatment, although in this case there were no significant differences among the 3 groups.

One of the retrospective studies[11] was conducted in 63 women with PCOS who took SPL 100 mg to treat hyperandrogenic symptoms: hirsutism, acne, and androgenetic alopecia. A 60% reduction in the Comprehensive Acne Severity Scale (CASS) score was observed in most patients. Eleven of the 43 (25.6%) patients who had acne reduced their score to 0, whereas only 5 (11.6%) patients in the total sample were not satisfied with the result. The 58 patients who were satisfied were followed to evaluate the long-term effects of SPL; 38 (65.5%) of them maintained the results after 33.7 months, whereas 20 (24.5%) relapsed 17.5 months after treatment discontinuation. Treatment duration was significantly longer in patients with classic-phenotype PCOS than in those with ovulatory PCOS (29.2 vs 18.2 months), and the duration of results was also longer in the former group (21.4 vs 8.2 months).

The other retrospective study[12] was conducted in 110 women with a median age of 27 years who took SPL (100–200 mg) to treat their acne. Improvement was measured with the CASS scale independently on the face, chest, and back. Of the 110 patients, 94 (85.5%) reduced their CASS score; 61 (55.5%) of them reached a CASS score of 0 on the face, chest, and back. The reduction in CASS score was 73.1%, 75.9%, and 77.6% on the face, chest, and back, respectively. Only 16 women (14.5%) did not improve or relapsed with treatment, whereas 86 (78.2%) improved within the first 4 months. The case-series study13 was conducted in the same way in 403 women and showed complete (CASS = 0) or almost complete reduction of acne on the face, chest, and back in 75.5%, 84%, and 80.2% of women, respectively. At the end of the follow-up period (>2 years), 96% of patients had achieved a CASS score of 0.

Treatment duration with spironolactone ranged from 12 weeks to 2 years. Acne-free survival after discontinuation varied across the articles. According to Sabbadin et al., 68.3% of women maintained the response after more than 33 months, whereas 31.7% of women relapsed at a mean of 18 months after treatment discontinuation. Conversely, Charny et al. found that 10.9% (12/110) of patients relapsed after discontinuation or dose reduction of SPL, without specifying the time to recurrence.

Metformin (MTF)

Nine articles studying the efficacy of metformin in patients with acne were included after the literature search (Table 2). Six of these (66.7%) were randomized controlled clinical trials,[14–19] 1 (11.1%) was a cohort study,[20] another was a cross-sectional study,[21] and another was a prospective observational study.[22] Two trials compared MTF with antibiotic treatment, another 2 with OCs, another with inositol, and another with rosiglitazone. Three of the 9 studies were conducted in women with PCOS.

The first clinical trial, by Robinson et al., [14] was conducted in 84 women (70.2%) and men divided into 2 groups, who received tetracyclines and benzoyl peroxide with or without the addition of MTF 850 mg. Acne improvement was measured with the total lesion count, the Cardiff Acne Disability Index (CADI scale), and the Investigator Global Assessment (IGA scale) to assess the treatment success rate. The main result was a greater improvement in the success rate in the group that received MTF (66.7% vs 43.2%, $P = .04$). This group also showed better results, although not significant, in inflammatory, noninflammatory, and total lesion counts; however, the CADI score was better in the control group, although the differences were likewise not significant. A reduction in body mass index (BMI; $P < .001$) and fasting blood glucose was also observed in the group that received MTF ($P = .007$). Another trial, by Sadati et al.,[15] compared the use of MTF 1000 mg vs doxycycline 100 mg in 40 patients aged 15–40 years, 87.5% of whom were women. The IGA, CADI, Global Acne Grading System (GAGS), total lesion count (TLC), and inflammatory and noninflammatory lesion counts were used to assess acne improvement. Both groups showed significant reductions in the scores of all scales ($P < .001$), although without differences between them, except for the GAGS score ($P = .007$) and inflammatory lesion count ($P = .046$), which decreased more in the doxycycline group.

The trial by Li et al.[16] divided 204 women with PCOS into 3 groups that received MTF (1500 mg), rosiglitazone (4 mg), and both drugs (MTF 1000 mg and rosiglitazone 4 mg), respectively, with acne improvement assessed using the GAGS scale. The main result was a decrease in menstrual irregularities, acne, and hirsutism in each group ($P < .001$), although with no differences among the 3 groups. Body weight, BMI, hip circumference, serum testosterone, and other metabolic parameters also decreased significantly, with no differences among groups. Group 1 (MTF alone) showed a greater reduction in BMI and body weight than the other groups ($P < .025$); group 2 (rosiglitazone alone) showed a smaller reduction in testosterone ($P < .025$) than the other groups;

Table 1
Articles reviewed on spironolactone.

Author, year	Design	*N*	Sex, age	Main outcome	Other outcomes	Adverse effects
Patiyasikunt M et al., 2020[10]	Clinical trial	63	Women, 25–45 y	Three groups were compared: topical benzoyl peroxide (BP) + SPL 50 mg, SPL 25 mg, or placebo. The scale used to assess improvement was the AFAST-F and total lesion count. The combination of SPL 50 mg and BP showed significantly higher success and improvement rates—defined as achieving clear or almost clear skin, or improvement to at least grade 2 on the AFAST scale—than the placebo group (75% vs 30%; $P = .01$).	Significant improvements were observed in total lesion count (placebo, 53.2 vs 11.4, $P < .001$; SPL 25, 45.4 vs 11.3, $P < .001$; SPL 50, 39.1 vs 9.9, $P < .001$), comedonal lesions (placebo, 43.7 vs 8.6, $P < .001$; SPL 25, 35.4 vs 8.3, $P < .001$; SPL 50, 33.8 vs 8.7, $P < .001$), and inflammatory lesions at the week-12 count (placebo, 9.4 vs 2.9, $P < .001$; SPL 25, 10.0 vs 3.0, $P < .001$; SPL 50, 5.3 vs 1.2, $P < .00$), although with no differences among the 3 groups (SPL 50, SPL 25, placebo).	Adverse effects were mild and well tolerated in both groups. Higher rates of menstrual irregularities (placebo, 5%; SPL 25, 0%; SPL 50, 30%; $P = .013$ [SPL 50 vs placebo]) and dizziness (placebo, 0%; SPL 25, 5%; SPL 50, 24%; $P = .039$ [SPL 50 vs placebo]) were observed in the SPL 50 mg group compared with the SPL 25 and placebo groups. Other adverse effects, such as breast tenderness (placebo, 5%; SPL 25, 5%; SPL 50, 20%), breast enlargement (placebo, 5%; SPL 25, 5%; SPL 50, 10%), fatigue (placebo, 0%; SPL 25, 0%; SPL 50, 5%), weight gain (placebo, 0%; SPL 25, 5%; SPL 50, 0%), and potassium and creatinine levels, showed no significant differences among groups.
Garg V et al., 2021[13]	Retrospective case series	403	Women, >18 y (median, 26 y)	A case-series study was conducted in 403 women who had taken SPL to treat acne between 2008 and 2019. Acne improvement was assessed using the CASS scale. SPL use almost or completely cleared acne (CASS score = 0) on the face, chest, and back of treated women: 75.5%, 84.0%, and 80.2% complete or almost complete acne reduction (CASS score of 0 or reduction in CASS score of ≥1 point), respectively, at the first follow-up visit at 3 months.	The CASS score decreased by a median of 0.8, 0.3, and 0.4 points on the face, chest, and back, respectively, at the first follow-up visit. Among patients with available follow-up data, 73 (20%) had completely clear skin (CASS 0) at 3–5.9 months, 125 (40%) at 6–8.9 months, and 152 (53%) at 9–11.9 months. At the end of follow-up (<2 years), a total of 217 patients (96%) had cleared all acne (CASS 0). This supports the idea that SPL reaches its maximum effect 4–6 months after treatment initiation. Mean drug survival until first discontinuation was 470 days.	Treatment was well tolerated, with only 21 patients—23% of patients with no loss to follow-up ($n = 227$)—discontinuing treatment because of adverse effects; 15 discontinued because of nonmenstrual adverse effects and 6 because of menstrual adverse effects. Nonmenstrual adverse effects included dizziness, headache, polyuria, fatigue, dry skin, anxiety, and abdominal pain.
Sabbadin C et al., 2022[11]	Retrospective study	63	Women, 20 ± 4.6 y	A retrospective study was conducted in 63 women with PCOS who took SPL 100 mg to treat cutaneous hyperandrogenic symptoms—hirsutism, acne, and female androgenetic alopecia—caused by this condition. Acne improvement was assessed using the CASS scale. Treatment with SPL showed significant improvement ($P < .0001$) in cutaneous hyperandrogenic symptoms derived from PCOS in most patients in the study. Only 5 patients (7.9%) were dissatisfied with the result and required another treatment (OCs). After treatment, the CASS score decreased by 60% (reduction of 1.5 ± 1.4 points), and 11 of the 43 patients with acne (25.6%) reduced their score to 0.	The 58 patients who were satisfied with treatment were followed to evaluate the long-term effects of SPL. Thirty-eight of them maintained the results after 33.7 months, whereas 20 had a relapse of cutaneous hyperandrogenic symptoms 17.5 months after treatment discontinuation. Mean treatment duration was 25.7 months, significantly longer in patients with classic-phenotype PCOS than in those with ovulatory-phenotype PCOS (29.2 vs 18.2 months, respectively; $P = .0194$). The long-term duration of results was significantly shorter in women with ovulatory-phenotype PCOS than in those with classic-phenotype PCOS (8.2 ± 3.6 months vs 21.4 ± 15.7 months, respectively; $P < .0001$); these patients were also treated for a shorter time.	SPL was well tolerated in all patients. The most frequent adverse effect was irregular menstrual bleeding (68.2% of patients), especially in the classic-phenotype PCOS group (81.4% vs 40.0% in the ovulatory phenotype; $P = .0028$). Six percent of patients reported orthostatic hypotension (orthostatic SBP < 100 mmHg) and mild hyperkalemia (K+, 4.5–5 mmol/L). No significant differences were observed in any group in hormonal, clinical, or metabolic profiles.

Table 1 (*Continued*)

Author, year	Design	*N*	Sex, age	Main outcome	Other outcomes	Adverse effects
Charny J et al., 2017[12]	Retrospective study	110	Women, median age 27 y	A retrospective study was conducted in 110 women who took SPL to treat acne. Improvement was assessed using the CASS scale. Of the 110 women treated, 94 reduced their CASS score, and 61 cleared acne completely (CASS = 0 on the face, chest, and back) at the end of follow-up. The reduction in CASS score from baseline to follow-up visits was 73.1% on the face (2.19 at baseline vs 0.59 after treatment), 75.9% on the chest (1.41 vs 0.34), and 77.6% on the back (1.65 vs 0.37).	Of the women treated, 16 did not improve with treatment: 4 discontinued it for this reason, 6 improved but subsequently relapsed, 3 relapsed after dose reduction because of a good initial response to treatment, 2 relapsed after completing treatment with good results, and 1 relapsed after receiving an injection of medroxyprogesterone acetate. Of the 108 patients with CASS > 0 for facial acne at baseline, 86 had a reduction in CASS at the first follow-up visit (4 months), 7 more at the second visit (7 months), and 1 more at the fourth visit (17 months).	Treatment was well tolerated in most patients. Fourteen patients discontinued treatment for several reasons, but only 6 did so because of adverse effects: excessive drowsiness, intermenstrual bleeding, increased urinary frequency and tachycardia, menstrual irregularities, diffuse pruritus, and anxiety. These 6 patients represented 11.7% of the 51 women who experienced adverse effects. Overall, 34 patients had menstrual adverse effects and 26 had nonmenstrual adverse effects.

SPL: spironolactone; OC: oral contraceptive; AFAST-F: Adult Female Acne Scoring Tool-Face; CASS: Comprehensive Acne Severity Scale scores.

Table 2
Articles reviewed on metformin.

Author	Type of study	*N*	Sex, age	Main outcome	Other outcomes	Adverse effects
Robinson S et al., 2019[14]	Clinical trial	84	25 men, 59 women (ratio, 1:2.36) 18–40 y	Two groups of patients were compared; both received tetracyclines and topical benzoyl peroxide, with or without MTF 850 mg, for the treatment of acne. Improvement was assessed using total lesion count, the CADI scale, and the IGA scale to evaluate treatment success rate. The addition of MTF to treatment showed a significant improvement in the treatment success rate—IGA scale—(66.7% vs 43.2%; $P = .04$). The MTF-treated group also showed a greater, although nonsignificant, reduction in inflammatory lesion count (44.9% vs 37.4%; $P = .445$), noninflammatory lesion count (83.1% vs 75.6%; $P = .064$), and total lesion count (71.4% vs 65.3%; $P = .278$) at week 12. However, the CADI score decreased by a mean of 2.46 ± 2.89 in the MTF group vs 2.65 ± 2.82 in the control group ($P = .776$) at week 6, and 4.82 ± 3.39 vs 4.22 ± 3.56 ($P = .451$) at week 12.	A reduction in BMI was observed in the MTF group, whereas an increase was observed in the control group (-0.26 ± 0.72 vs $+0.3 \pm 0.72$ kg/m^2; $P < .001$) at week 12. A significant reduction in fasting serum glucose was also observed in the MTF group and an increase in the control group (-0.15 ± 0.62 mmol/L vs 0.19 ± 0.45 mmol/L; $P = .007$) at week 12. BMI, IGF-1, serum insulin, and HOMA-R showed a positive correlation with lesion count at baseline, although this was not significant. There were no significant differences in CADI reduction when patients were separated into low- and high-BMI groups (-4.6 ± 3.15 vs -5.31 ± 3.92, respectively; $P = .533$).	Among subjects treated with metformin ($n = 41$), 0 patients experienced hypoglycemia. Among these 41 patients, only 13 (31.7%) experienced gastrointestinal adverse effects—nausea, vomiting, discomfort, and abdominal bloating—which did not last longer than 2 weeks. No serious adverse effects associated with metformin treatment were observed.
Albalat W et al., 2022[20]	Cohort study	50	17 men, 33 women (ratio, 1:1.94) 16–30 y	A cohort study was conducted in 50 patients diagnosed with acne who received MTF to evaluate changes in IGF-1 levels before and after treatment and their relationship with acne severity, whose changes were measured using the GAGS scale in addition to clinical assessment of lesions. In patients treated with metformin, there was a significant decrease in acne score, IGF-1, and BMI after treatment (25.2 ± 6.8, 45.4 ± 6.3, and 23.5 ± 1.8 vs 13.6 ± 4.5, 28.8 ± 8.2, and 22.3 ± 1.3, respectively; $P = .001$).	Furthermore, higher IGF-1 levels were observed in patients with acne; these were not significantly correlated with acne severity but were correlated with BMI ($P = .04$). IGF-1 levels decreased significantly in the treated group, supporting the idea that there is a relationship between this hormone, insulin levels and resistance, and acne.	Mild adverse effects were observed in few patients: GI adverse effects in 6 patients (12%) and hypoglycemia in 3 (6%).
Bahadur A et al., 2021[19]	Clinical trial	72	Women, 18–45 y	Two groups of women with PCOS were compared; they received MTF $\pm$ myo-inositol plus D-chiro-inositol to evaluate changes in clinical, metabolic, and hormonal parameters, including acne. The scale used for acne assessment was the Global Acne Score. Significant improvement was observed in the group treated with both drugs in acne score (4.41 ± 2.59 vs 2.80 ± 1.39; $P = .04$) and menstrual-cycle regulation (63.9% vs 38.9%; $P = .034$).	Moreover, significant differences were found between the control and treated groups in LH (9.09 ± 4.53 vs 6.06 ± 2.24; $P = .002$), the LH/FSH ratio (1.39 ± 0.43 vs 1.11 ± 0.44; $P = .007$), total cholesterol (146.75 ± 36.37 vs 131.58 ± 23.99; $P = .040$), HDL (41.53 ± 6.38 vs 47.25 ± 15.92; $P = .049$), LDL (106.16 ± 22.78 vs 85.89 ± 19.84; $P = .0001$), and postprandial insulin (57.82 ± 37.52 vs 35.30 ± 18.94; $P = .005$). There were no significant differences between the 2 groups in FSH, testosterone, DHEAS, triglycerides, postprandial and fasting blood glucose, or HOMA-IR ($P > .05$).	NS

Table 2 (*Continued*)

Author	Type of study	*N*	Sex, age	Main outcome	Other outcomes	Adverse effects
Mhao N et al., 2016[18]	Clinical trial	26	Women, 14–40 y	Two groups of patients with PCOS were compared; they received MTF and ethinyl estradiol-cyproterone acetate (OC), respectively. Improvements in acne—2 of 4 patients improved in the MTF group vs 4 of 5 in the OC group—and hirsutism—10.1 to 9.2 points in the MTF group vs 9.3 to 7.9 points in the OC group—associated with the hyperandrogenic state of these patients were greater in the second group than in the first. Acne improvement was assessed by lesion count. The infertility rate improved more in the MTF group—5 of 16 women became pregnant—than in the OC group—1 of 4 women became pregnant. Menstrual irregularities improved more in the OC group—6 of 8 patients achieved regular cycles vs 9 of 14 patients in the MTF group.	Group 1, which received MTF, showed a significant increase in HDL (39.78 ± 7.43 vs 35.36 ± 7.63 mg/dL; $P = .006$) and a decrease in triglycerides (110.36 ± 16.19 vs 95.72 ± 16.62 mg/dL; $P = .006$), VLDL (19.14 ± 12.52 vs 22.07 ± 11.23; $P = .006$), and serum testosterone (0.486 ± 0.291 vs 0.956 ± 0.309; $P = .038$), which was associated with improvement in oral glucose tolerance test (GTT) results and BMI. LDL and total cholesterol decreased, although not significantly. Group 2, which received the OC, showed a significant increase in triglycerides (92.86 ± 13.27 vs 90.86 ± 18.54 mg/dL; $P = .01$) and a decrease in LDL (98.00 ± 29.96 vs 115.14 ± 37.77 mg/dL; $P = .04$). BMI decreased more in group 1 (26.12 vs 27.22; $P = .000$) than in group 2 (29.58 vs 30.49; $P = .048$) at the end of treatment. Thus, the study showed improvement in lipid profile, glucose tolerance, fertility, serum testosterone, and BMI in group 1 (MTF), and improvement in the clinical manifestations of PCOS, such as hyperandrogenic status and menstrual-cycle regulation, in group 2 (OC).	NS
Kumar Y et al., 2018[17]	Clinical trial	90	Women, 18–40 y	Three groups of patients were treated with MTF ± OCs: group 1 with MTF, group 2 with OC, and group 3 with both. The combination of both drugs showed greater improvement in the reduction of inflammatory markers, insulin resistance, and body composition than either drug as monotherapy. The scale used to assess acne improvement was GAGS.	The group treated with MTF alone showed a significant decrease in hyperandrogenism, dyslipidemia, inflammation, and body fat ($P < .001$), whereas the group treated only with OC experienced a reduction in hirsutism and acne, and an increase in insulin resistance and body-fat percentage ($P < .001$). Combination therapy showed a greater reduction in inflammatory parameters—C-reactive protein, fibrinogen, and ferritin—than either monotherapy group ($P < .001$). Menstrual alterations and hirsutism improved significantly in all 3 groups ($P < .001$).	Adverse effects were very infrequent and mild. Two patients had transient GI intolerance with metformin, and 1 developed a self-limited rash with the OC.
Artani M et al., 2018[21]	Cross-sectional study	100	Women, 18–48 y	A cross-sectional study was conducted to evaluate the effects of MTF in women with PCOS. Patients treated with MTF showed significant improvement in acne and hirsutism—from 85% of patients to 58%; $P < .001$—mood changes—from 92% to 64%; $P < .001$—daily energy levels—from 54% to 37%; $P < .001$—and menstrual irregularities—from 100% to 69%; $P = .046$. Symptom improvements were clinically assessed using a questionnaire adapted from the WHO.	After MTF treatment, the study population showed no statistically significant differences in ability to conceive—from 34% to 24% of patients; $P = .096$—or in body weight—from 81% to 61% of patients; $P = .073$.	NS

Table 2 (*Continued*)

Author	Type of study	*N*	Sex, age	Main outcome	Other outcomes	Adverse effects
Li Y et al., 2019[16]	Clinical trial	204	Women	Patients were divided into 3 groups and received MTF, rosiglitazone, or both, respectively. The scale used to evaluate acne improvement was GAGS. A significant decrease was observed in menstrual irregularities—46.19 days vs 65.25 in group 1, 45.07 vs 65.04 in group 2, and 43.65 vs 67.48 in group 3; $P < .001$—acne—GAGS 0 vs 8 in group 1, 2 vs 8 in group 2, and 0 vs 9 in group 3; $P < .001$—and hirsutism—mFG 2 vs 3 in all 3 groups—after treatment in each group, although with no differences among the 3 groups ($P > .05$). Body weight, BMI, hip circumference, serum testosterone, and other metabolic parameters also decreased significantly, although with no differences among groups.	In group 1 (MTF alone), a significant improvement in BMI (−2.68 vs − 1.32 vs −1.38 kg/m2) and body weight (−6.81 vs −3.40 vs −3.54 kg) was observed compared with the other groups ($P < .025$). In group 2 (rosiglitazone alone), the reduction in serum testosterone levels was smaller than in the others (−0.161 vs −0.125 vs −0.187; $P < .025$). In groups 2 and 3 (both drugs), total cholesterol (−0.437 vs −0.520 vs −0.722) and triglyceride levels (−0.341 vs −0.524 vs −0.536) decreased significantly more than in group 1, although there were no differences in TC/HDL and LDL/HDL ratios among groups.	Adverse effects caused by MTF were gastrointestinal symptoms, whose severity increased with increasing dose. At 500 mg, they were mild; at 1000 mg, moderate; and at 1500 mg, more intense, although patients adapted within 1–5 weeks and only 1 had to reduce the dose. No adverse effects related to rosiglitazone were observed.
Kamboj P et al., 2023[22]	Observational study	30	Women	An observational study was conducted to evaluate the effectiveness of MTF treatment in women with acne who did not have PCOS. The scale used to assess acne improvement was GAGS. MTF monotherapy significantly reduced acne (GAGS 19.8 vs 13.89 after treatment; $P < .001$) in the patients studied in the first month. An increase in IGF-1 was observed (96.46 vs 109.5 ng/mL^{-1} after 3 months of treatment; $P = .03$).	A significant decrease in the free androgen index was observed (41 vs 22.75; $P < .001$) as a result of a significant increase in SHBG (15.07 vs 22.22 mmol/L^{-1}; $P < .001$), with a decrease in testosterone (NS, 6.49 vs 4.7 ng/mL^{-1}; $P = .31$). HOMA-IR and plasma insulin did not change significantly. FOXO1 protein expression was significantly reduced (0.99 vs 0.58; $P = .006$) at the mRNA level, without significant changes at the protein level ($P = .08$). Furthermore, expression of the lipogenic genes HMGCR (1.01 vs 0.23; $P < .001$), SQLE (1.02 vs 0.58; $P = .026$), and ACSL5 (0.95 vs 0.73; $P = .03$) was reduced.	No patient experienced adverse effects with MTF use.

Table 2 (*Continued*)

Author	Type of study	*N*	Sex, age	Main outcome	Other outcomes	Adverse effects
Sadati M et al., 2023[15]	Clinical trial	40	Men and women, 15–40 y	Two groups of patients were administered doxycycline 100 mg and MTF 1000 mg, respectively, to treat acne. The scales used to evaluate improvement were IGA, CADI, GAGS, TLC, and inflammatory and noninflammatory lesion counts. On the IGA scale, a significant reduction from 2.95 ± 0.22 to 1.45 ± 0.51 after treatment ($P < .001$) was observed in the MTF group (group 1), and from 3.00 ± 0.00 to 1.40 ± 0.50 ($P < .001$) in the doxycycline group (group 2), with no differences between groups ($P = .537$). On the CADI scale, the reduction was from 11.55 ± 1.95 to 5.95 ± 1.76 ($P < .001$) in group 1 and from 11.40 ± 1.31 to 5.00 ± 1.77 ($P < .001$) in group 2, with no differences between groups ($P = .659$). On the GAGS scale, the reduction was from 24.10 ± 6.93 to 13.45 ± 4.22 ($P < .001$) in group 1 and from 29.65 ± 11.72 to 14.7 ± 10.84 ($P < .001$) in group 2, with a greater reduction in group 2 ($P = .007$). In TLC, the reduction was from 40.15 ± 23.98 to 14.10 ± 10.57 ($P < .001$) in group 1 and from 47.50 ± 36.86 to 14.30 ± 13.90 ($P < .001$) in group 2, with no differences between groups ($P = .111$). In inflammatory lesions, the reduction was from 15.40 ± 11.13 to 5.05 ± 3.47 ($P < .001$) in group 1 and from 22.50 ± 18.70 to 6.40 ± 7.59 ($P < .001$) in group 2, with a slightly greater reduction in group 2 ($P = .046$). In noninflammatory lesions, the reduction was from 25.40 ± 20.55 to 10.35 ± 11.68 ($P < .001$) in group 1 and from 25.50 ± 31.23 to 7.90 ± 11.80 ($P = .002$) in group 2, with no differences between groups ($P = .523$).	Both groups showed significant reductions in acne scores on all scales, although there were no differences between the groups in any of them except GAGS and inflammatory lesion count, which decreased more in the doxycycline group.	One patient who took doxycycline reported mild photosensitivity during treatment, whereas 3 patients who took MTF reported mild-to-moderate gastrointestinal discomfort. No patient withdrew from the study because of these adverse effects.

MTF, metformin; OC, oral contraceptive; GAGS, Global Acne Grading System; IGA, Investigator Global Assessement for acne; CADI, Cardiff Acne Disability Index; TLC, Total Lesion Count; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; SHBG, Sex Hormone Binding Globulin; mf-g, modified ferryman galwey; NS, not specified; ns, not significant.

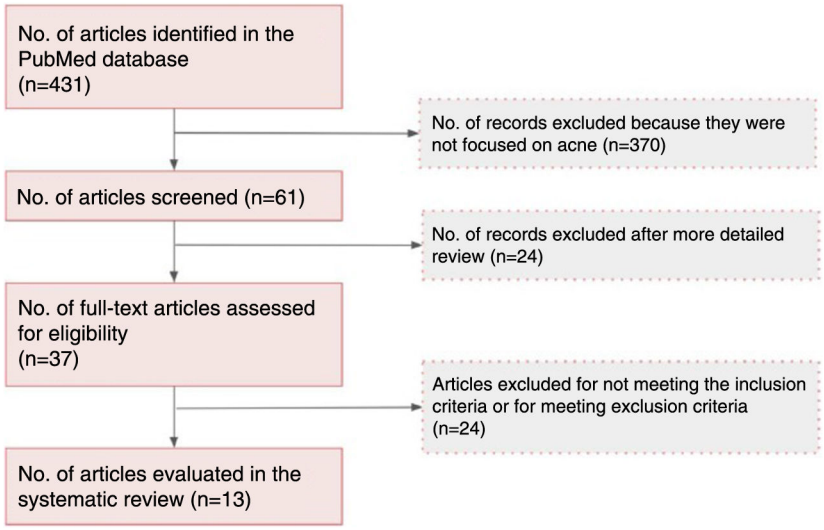

Fig. 2. Flowchart of the selected studied.

and groups 2 and 3 (both drugs) showed a greater reduction in total cholesterol and triglycerides than group 1.

Two trials compared MTF with an oral contraceptive. The first, by Kumar et al.,[17] divided 90 women with PCOS (age, 23.2 ± 4.4 years) into 3 groups that received MTF, OCs, or both, with acne improvement assessed using the GAGS scale. It showed that the combination of both drugs improved the reduction in inflammatory markers, insulin resistance, and body composition more than either drug as monotherapy. In the group treated with MTF alone, a decrease in hyperandrogenism, dyslipidemia, inflammation, and body fat was observed ($P < .001$), whereas the group treated only with OCs experienced a reduction in hirsutism and acne and an increase in insulin resistance and body fat percentage ($P < .001$). Combined therapy showed a greater reduction in inflammatory parameters—C-reactive protein, fibrinogen, and ferritin—than the other monotherapy groups ($P < .001$). Menstrual alterations and hirsutism improved in all 3 groups ($P < .001$). The other trial, by Mhao et al.,[18] divided 26 women with PCOS into 2 groups receiving MTF and OCs—ethinyl estradiol-cyproterone acetate—respectively. Acne was assessed by total lesion count and improved more in the OC group: 4 of 5 patients (80%) improved vs 2 of 4 (50%) in the MTF group; hirsutism and menstrual irregularities also improved more in the OC group, whereas the infertility rate improved more in the MTF group. Regarding laboratory and metabolic parameters, the MTF group showed improvement in HDL, triglycerides, VLDL, testosterone, oral glucose tolerance test results, and BMI. The OC group showed an increase in triglycerides and a decrease in LDL. Thus, the study showed improvement in the lipid and hormonal profile, glucose tolerance, fertility, and BMI in the MTF group, and improvement in the clinical manifestations of PCOS, such as hyperandrogenic status and menstrual-cycle regulation, in the OC group.

The last clinical trial, by Bahadur et al.,[19] was conducted in 72 women with PCOS, who were divided into 2 groups receiving MTF 1000 mg with or without the addition of myo-inositol plus D-chiro-inositol to evaluate changes in clinical, metabolic, and hormonal parameters, including acne. Acne was assessed using the Global Acne Score (GAS). Significant improvement was observed in the group treated with both drugs in acne score and menstrual-cycle regulation ($P = .04$). Significant differences were also observed in LH ($P = .002$), the LH/FSH ratio ($P = .007$), total cholesterol ($P = .040$), LDL ($P = .0001$), and postprandial insulin ($P = .005$), whose levels were lower in the group treated with both drugs, and in HDL ($P = .049$), which was higher in this same group. Another study conducted in women with PCOS21 evaluated improvement in physical and quality-of-life aspects of treatment with MTF, including acne, using a questionnaire adapted from the WHO, and showed improvement in acne and hirsutism, mood changes, daily energy levels, and menstrual irregularities. No significant differences were observed in the ability to conceive or in body weight.

Two additional studies [20,22] evaluated the efficacy profile of treatment with metformin 1000 mg and showed improvements in the GAGS scale after treatment ($P < .001$). According to Albalat et al.,[20] IGF-1 levels decreased with treatment, which appears to support the idea of a relationship between IGF-1 levels, insulin levels and resistance, and acne. However, the study by Kamboj et al.[22] showed an increase in IGF-1 levels in the treated group, contrary to this hypothesis. This study also showed a decrease in the free androgen index after an increase in sex hormone-binding globulin (SHBG), with a decrease in testosterone, and a decrease in mRNA-level expression of several lipogenic genes, such as FOXO1, without a reduction at the protein level.

Bicalutamide

After the bibliographic search, no study or clinical trial was found evaluating the safety or efficacy profil eof bicalutamide for the treatment of adult female acne. However, after reviewing the bibliography included in other studies, a pilot study[23] conducted in women diagnosed with female-pattern alopecia was identified, which showed improvement in other hyperandrogenic symptoms, such as acne, seborrhea, and hirsutism. A retrospective study conducted in 23 transgender patients[24] who received bicalutamide 50 mg as an androgen hormone inhibitor for male-to-female transition was also found; in this study, patients reported subjective improvement in acne. Among patients treated only with bicalutamide, 84.6% experienced gynecomastia, which in this case was perceived as a positive effect. Similarly, Reolid et al. conducted a study including 7 cases of women aged ≥ 25 years diagnosed with acne (mean age, 32 ± 6.9 years SD) who received a mean bicalutamide dose of 36 ± 10.2 mg/day. Mean treatment duration was 21.6 months (range, 3–42), with a good safety profile. After 3 months of treatment, acne improvement was observed in 85.7% of patients (6/7), with somewhat more time being required for hirsutism (6 months).[25]

What adverse effects do these antiandrogenic drugs cause?

Spironolactone

Treatment with spironolactone was generally well tolerated.[10–13] Adverse effects were mild in most cases, and few patients discontinued treatment because of them. The most frequently reported adverse effect was menstrual irregularities. Among nonmenstrual adverse effects,

dizziness, orthostatic hypotension, and fatigue were noteworthy. Only one of the studies showed a slight increase in blood potassium levels.[11]

In the study by Patiyasikunt et al.,[10] higher rates of menstrual irregularities and dizziness were observed in the SPL 50 group than in the other 2 groups ($P = .013$, $P = .039$). No changes were observed among groups in breast tenderness or enlargement, fatigue, weight gain, or potassium and creatinine levels. In the study by Garg et al.,[13,21] women (23% of those who remained in follow-up) discontinued treatment because of adverse effects, 15 of them nonmenstrual—dizziness, headache, polyuria, fatigue, dry skin, anxiety, and abdominal pain—and 6 menstrual. In the study by Charny et al.,[12] 51 (46.4%) women had adverse effects, of them menstrual and 26 nonmenstrual. Only 6 (5.5%) patients discontinued treatment because they could not tolerate these effects: excessive drowsiness, polyuria, tachycardia, pruritus, and anxiety. In the study by Sabbadin et al.,[11] the most frequent adverse effect was menstrual irregularities, occurring in 68.2% of patients, especially in women with classic-phenotype PCOS (81.4% vs 40% in those with the ovulatory phenotype). A total of 6% of patients reported orthostatic hypotension and mild hyperkalemia (K+, 4.5–5 mmol/L).

Metformin

Of the 9 studies included in the review on this drug, 6 reported the adverse effects caused by metformin or by other drugs evaluated in the studies. The adverse effects reported with metformin use were GI discomfort[14–17,20] and hypoglycemia in 3 patients[20] among the total number of patients in all studies. No other serious adverse effects were observed in any study.

In the study by Robinson et al.,[14] among the 41 patients treated with MTF, none experienced hypoglycemia, whereas 13 (31.7%) experienced GI symptoms—nausea, vomiting, discomfort, and abdominal bloating—which did not last longer than 2 weeks. In the study by Sadati et al.,[15] only 3 (7.5%) patients treated with MTF experienced mild-to-moderate GI discomfort, and 1 patient treated with doxycycline reported mild photosensitivity during treatment. In the study by Li et al.,[16] GI symptoms caused by MTF were mild at a dose of 500 mg, moderate at 1000 mg, and severe at 1500 mg, although patients adapted to treatment within 1–5 weeks and only 1 patient required dose reduction. No adverse effects related to rosiglitazone were observed. The study by Kumar et al.[17] reported that 2 (2.2%) patients had transient, mild gastrointestinal intolerance with metformin and 1 (1.1%) developed a self-limited rash with the OC. The study by Albalat et al.[20] showed mild and infrequent adverse effects— GI in 6 patients (12%) and hypoglycemia in 3 (6%)—and Kamboj et al.22 reported that no patient experienced adverse effects with MTF use.

Discussion

Acne is one of the most common skin diseases.[26] In the case of adult female acne, therapeutic management is particularly complex because of the lack of effectiveness of treatments in many cases, the tendency toward chronicity and/or recurrence, and resistance to some of the available treatments.[2] In patients who do not respond to topical treatments or, in more severe cases, to antibiotic or isotretinoin treatment, other orally administered drugs are available to attempt to control the disease, such as antiandrogenic drugs.

As shown in this systematic review, spironolactone and metformin are treatments that have demonstrated efficacy and good tolerability for the management of adult female acne in different types of studies.

Spironolactone is a potassium-sparing diuretic approved by the FDA for the management of heart failure, arterial hypertension, edema associated with liver cirrhosis or nephrotic syndrome, and hyperaldosteronism.[7] However, several studies have demonstrated its effectiveness for off-label use in the treatment of various dermatological diseases caused by alterations related to androgen hormones, such as female-pattern alopecia, hirsutism, and acne. This drug blocks androgen hormone receptors in the sebaceous glands and has been shown to reduce acne even when there is no increase in these hormones in the blood.[27]

A clinical trial[10] compared the use of low-dose spironolactone (25–50 mg) with placebo and observed a 75% decrease in acne in the treated group compared with 30% in the placebo group. Two other studies[12,13] evaluated lesion improvement independently on the face, chest, and back, also showing reductions in acne scores > 70% in all areas. Currently, spironolactone is included in the American clinical guidelines for the management of acne with level II–III evidence and a grade B recommendation.[5] It is therefore an option to consider in the management of this condition, especially in patients who do not respond to other first-line treatments such as isotretinoin or antibiotics. In addition, greater use of this drug would also be of interest to reduce the frequency of antibiotic administration, given the growing global problem of antibiotic resistance today.[28] A retrospective study[29] indicated that the use of antiandrogenic drugs is associated with a shorter duration of antibiotic treatments, and that early administration may reduce the use of systemic antibiotics in acne treatment.

Metformin is a drug approved by the FDA for use in type 2 diabetes mellitus, as it is a hypoglycemic agent that reduces insulin resistance by decreasing hepatic glucose production and stimulating glucose uptake by muscle cells. However, it has also been observed to reduce inflammation and hyperandrogenism to some extent, and it is believed to exert an effect on steroid hormone production by modulating androgen production at the ovarian and adrenal levels.[8] For all these reasons, several studies have been conducted to evaluate the effect of off-label metformin use in diseases associated with a hyperandrogenic state. This drug has been compared in clinical trials with other therapeutic options such as tetracyclines, oral contraceptives, and other types of antidiabetic drugs. However, the lack of studies comparing it with a placebo group makes interpretation of improvements in acne difficult.

Several studies[14,16–19,21] have demonstrated significant improvements in metabolic parameters such as the lipid profile—HDL, LDL, total cholesterol, and triglycerides—BMI, body weight, and hip circumference, as well as improvements in acne, although in the latter case no significant differences were observed between the compared groups in most studies. Two studies comparing metformin with oral contraceptives[17,18] demonstrated superior results with the latter in improving hyperandrogenic symptoms, suggesting that metformin may be a good second-line therapeutic option in patients who do not tolerate or reject these drugs, or in patients with metabolic alterations such as dyslipidemia, diabetes, overweight, and so forth, either alone or in combination with OCs. Two other studies compared metformin with oral antibiotics, tetracyclines, either alone or in combination. One of them[14] showed better results with combination therapy, although without a control group, whereas the other[15] showed superior results with the antibiotic for skin lesions. Two further studies, whose objective was to evaluate the relationship between IGF-1 and acne severity, also obtained contradictory results: one[20] showed a reduction in the levels of this hormone after treatment, suggesting a relationship between its levels, insulin resistance, and acne, whereas the other[22] showed an increase in IGF-1 levels in the treated group, contrary to that idea. All this suggests that metformin should be considered for use in acne in combination with other drugs that have shown more evident results, or as another option when these other treatments are not indicated, are not well tolerated, are not effective, or are rejected by the patients themselves.

Regarding the tolerability and safety profile of antiandrogenic drugs, as has been observed, these drugs are generally well tolerated, with mostly mild adverse effects that very rarely require dose reduction or treatment discontinuation. In the case of spironolactone, the most frequently observed adverse effect was menstrual irregularities. Nonmenstrual adverse effects were also observed, such as dizziness, orthostatic hypotension, fatigue, and increased urinary frequency; these were also mild and well tolerated in most cases.

Numerous studies suggested the need to monitor serum potassium levels in patients taking spironolactone because of the risk of hyperkalemia. However, other studies have indicated that this monitoring is not necessary in young, healthy women, since increased potassium is a very infrequent and mild adverse effect. A systematic review based on clinical trials supports this idea.[30] A retrospective study[31] conducted in 133 patients taking spironolactone, excluding women with conditions that could alter potassium levels, such as hypertension or kidney disease, showed that there was no need to monitor these levels in young women. However, monitoring was recommended in patients older than 45 years, since there is a higher age-related risk of hyperkalemia. Thus, potassium monitoring is recommended only in patients aged > 45 years and/or in those with a disease or taking drugs that alter these levels, with measurement at the initial visit and again at follow-up or after dose adjustment.

In the case of metformin, the most frequently observed adverse effects were GI symptoms of varying intensity, although they were mild in most cases. One controlled trial[16] found that the intensity and duration of GI adverse effects increased with the metformin dose, being mild with 500 mg, moderate with 1000 mg, and more intense with 1500 mg. Nevertheless, these symptoms were transient (< 5 weeks), and only one patient required a dose reduction.

Among the studies included in the review, only 1[20] reported other types of adverse effects, in this case hypoglycemia, which was observed in a total of 3 patients. Antiandrogen therapies have been shown in numerous studies to be a very useful option for treating the hyperandrogenic symptoms experienced by women with polycystic ovary syndrome (PCOS). Acne has been reported in 15%–30% of women with PCOS.[3,21] A retrospective study conducted in patients with PCOS[11] showed that spironolactone reduced acne scores by 60% in most patients. In addition, this study showed greater improvement in patients with classic-phenotype PCOS than in those with ovulatory-phenotype PCOS.

Other studies conducted in patients with this syndrome showed good results with metformin, although oral contraceptives produced superior outcomes in these cases,[17,18] either alone or in combination with metformin. Metformin showed better results in the control of insulin resistance, lipid profile, BMI, and glucose tolerance, which are other parameters commonly altered in women with PCOS.

Thus, the use of antiandrogen drugs appears to be useful in patients with acne caused by alterations in androgen hormones or their receptors, in those with hyperandrogenic symptoms, and in patients with contraindications to, intolerance of, or resistance to first-line therapies such as antibiotics and isotretinoin. Furthermore, antiandrogens have shown results comparable to those of oral contraceptives, making them an option for women who do not wish to take these drugs, which may cause adverse effects such as fluid retention, an increased risk of thrombosis, and decreased libido,[6] as well as for women who do not tolerate them or have contraindications to their use. In addition, antiandrogen drugs have a favorable safety profile and exert effects that may facilitate the management of more complex hormonal disorders such as PCOS. In this condition, metformin not only reduces acne and inflammation but also improves the lipid profile and associated insulin resistance.

This systematic review has several limitations. First, the lack of randomized controlled clinical trials evaluating the efficacy of the drugs studied (spironolactone, metformin, and bicalutamide) in representative sample sizes and against placebo control groups reduces both the amount of available information and the quality of the evidence. The studies reviewed do not comprise a large overall sample, and many are observational in design. Furthermore, the variability among the scales available for assessing the primary outcome, in this case acne (AFAST, GAGS, CASS, CADI, IGA, TLC, etc.), makes indirect comparisons between study results difficult. Further research is needed in this field of dermatology, particularly randomized controlled trials comparing antiandrogen drugs with one another and with placebo, as well as studies examining their safety characteristics and patterns of use, to establish new treatment strategies for the management of adult female acne.

In conclusion, antiandrogen drugs are a useful therapeutic alternative for the treatment of adult female acne associated with increased androgen receptor sensitivity or occurring in the context of hyperandrogenism. Spironolactone is a potassium-sparing diuretic that also acts by blocking androgen receptors in the sebaceous glands. Metformin is an antidiabetic drug that reduces insulin resistance and increases cellular glucose uptake and has also been shown to have other properties, including reducing inflammation and modulating androgen hormone synthesis. Accordingly, both drugs are being used off-label for the management of acne as an alternative of considerable interest to currently available first-line treatment when such treatment is ineffective, contraindicated, or poorly tolerated. Their use may also help reduce long-term antibiotic exposure and thereby limit the development of antimicrobial resistance. Both drugs have demonstrated favorable effectiveness, safety, and tolerability profiles in several studies of disorders caused by alterations in androgen hormones or receptors, including adult female acne.

Conflict of interest

The authors declare that they have no conflict of interest.

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