Clinical Letter

Efficacy of topical caffeine in male androgenetic alopecia

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Dear Editors,

Caffeine-containing shampoos are currently widely advertised for the treatment of androgenetic alopecia (AGA). To date, however, systematic reviews of the available evidence regarding efficacy and tolerability are still lacking.

Medline (OvidSP) and the Cochrane Library (Wiley) were searched for randomized controlled (RCT) and nonrandomized trials investigating the topical application of caffeine-containing products on hairs or follicles. Inclusion criteria were: male participants, clinically diagnosed AGA of any severity. There were no restrictions regarding language. In vitro studies were excluded. Using the following search strategy, the databases were searched on October 19, 2015: (hair [MeSH] OR hair [ti, ab.]) AND (caffeine [MeSH] OR caffeine [ti, ab.]). Based on title and abstract, the studies retrieved were reviewed for their relevance (inclusion and exclusion criteria). Suitable studies (full text) were included or excluded according to inclusion and exclusion criteria. The data of included studies were extracted using a standardized table. Screening and data extraction were carried out twice by two independent reviewers (AB, CD/AA; Golpur et al. was reviewed once). The results were subsequently compared, and differences in the assessment were resolved by a third reviewer (AN).

In order to assess potential publication bias, the experts (n = 19) of the European S3 guideline were contacted once by e-mail in February 2016, and asked for information about any studies they knew of that had been conducted but not published. All included studies were evaluated using the Cochrane Risk of Bias Assessment Tool [1] or adapted criteria based on the Scottish Intercollegiate Guidelines Network (SIGN) Methodology Checklist [2].

The systematic literature search conducted on October 19, 2015, initially yielded 81 hits. Two other studies [3, 4] were known to the authors. Following the exclusion of duplicate hits (2) and off-topic articles, five studies were included after title/abstract, and full-text screening (Figure 1). With respect to our question about potential publication bias, we received an answer from 13 experts (response rate 68.4 %). Two experts reported knowing about an unpublished study on the efficacy of caffeine but could not provide any further details.

Three RCTs [5–7] and two before-after studies [3, 4] on the efficacy of topical caffeine in male androgenetic alopecia were included (Table 1). Only one RCT directly compared caffeine-containing shampoo with placebo, whereas the other studies investigated potential additive effects of caffeine shampoo in combination with minoxidil and azelaic acid.

Sisto et al. (2013) compared caffeine shampoo with a placebo shampoo in patients with grade II–IV AGA (according to Hamilton and Norwood) [5]. After randomization, there was a greater percentage of grade IV AGA patients in the placebo than in the active treatment group. The primary study endpoint was patient satisfaction after six months of treatment; for this outcome 84.8 % of individuals in the active treatment group and 36.4 % in the placebo group reported to be satisfied. Three other, patient-assessed outcomes were included. With regard to (A) intensity of hair loss, (B) speed of progression of hair loss, and (C) number of hairs shed while combing, a statistically significantly greater improvement was reported in the active treatment group compared to those receiving placebo. Although the study endpoints as assessed by patients themselves were similar to the physicians' assessment, the risk of bias was "high", given that uncontrolled before-after comparisons and multiple tests were conducted (Table 2).

Golpur et al. (2013) evaluated the additional effects of a topical solution containing caffeine and minoxidil 2.5 % compared to topical minoxidil alone (2.5 % solution) on the number of hairs in 30 patients (per study arm) [7]. Included were men ≥ 23 years of age with above grade 5 AGA (Hamilton and Norwood). Hair density was measured in

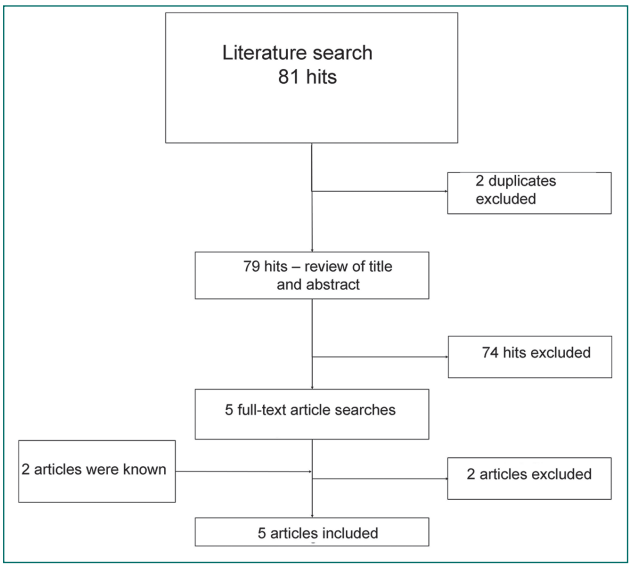

Figure 1 Study selection flow chart.

Table 1 Study characteristics.

Author, year	Intervention	Study duration	n	AGA grade (Hamilton-Norwood) (BL)	Age (BL)	Time of assessment	Definition of primary study endpoint	Result (primary study endpoint)	Definition of other study endpoints	Results of other study endpoints	Study dropouts	Comment
Caffeine monotherapy versus placebo (1 RCT)												
Sisto 2013	Shampoo (placebo) 7 ml QD for 6 months; exposure time: 2 min, followed by rinsing	6 months	33	II: 39.4 % III: 42.4 % IV: 18.2 %	37.5 ± 8.3	3/6 months	Number of satisfied participants after 6 months	n = 12 (36.4 %)	1) Patient assessment after 6 months regarding a) intensity of hair loss, b) speed of progression of hair loss, c) amount of hairs shed while combing 2) Physician assessment after 6 months regarding a) hair thickness, b) speed of progression of hair loss, c) amount of hairs shed while combing 3) Physician assessment after 6 months a) efficacy and b) preference active substance vs. placebo	1 a–c)[1] statistically significant improvement in the active treatment group compared to placebo and BL/month 3 2 a–c) statistically significant improvement in the active treatment group compared to placebo and BL/month 3 3 a) active treatment 72.7 % 3 b) active treatment 72.7 %	0	–
	Caffeine shampoo 7 ml QD for 6 months; exposure time: 2 min, followed by rinsing		33	II: 36.3 % III: 54.5 % IV: 9.1 %	35.5 ± 7.1			n = 28 (84.8 %)				

Table 1 Continued.

Author, year	Intervention	Study duration	n	AGA grade (Hamilton-Norwood) (BL)	Age (BL)	Time of assessment	Definition of primary study endpoint	Result (primary study endpoint)	Definition of other study endpoints	Results of other study endpoints	Study dropouts	Comment
Caffeine in combination with minoxidil / azelaic acid versus placebo (2 RCT)												
Golpur 2013	Caffeine + minoxidil 2.5 % topical solution 1 ml BID	150 d	30	≥ grade V for at least 5 years	20–30: 66.3 % (n = 41) 30–40: 20 % (n = 12) 40–50: 11.6 % (n = 7)	Day 0, 7, 30, 60, 90, 120, 150	Number of hairs (± SD) in 3 defined areas (1 cm²) analyzed using a template and a lens	0: 4.93 hairs (± 0.18) 7: 4.93 (± 0.24) 30: 4.90 (± 0.24) 60: 4.93 (± 0.25) 90: 4.96 (± 0.26) 120: 5.17 (± 0.31) 150: 5.39 (± 0.29) (difference between table/text)	Patient satisfaction after 150 days	1. 14 individuals (58.33 %) very satisfied 2. 7 individuals (29.17 %) moderately satisfied 3. 3 individuals (12.5 %) hardly satisfied	n = 6, due to burning sensation and erythema of the scalp	*Corrections/differences between table and text
	Minoxidil 2.5 % topical solution 1 ml BID		30					0: 4.33 hairs (± 0.17) 7: 4.30 (± 0.16) 30: 4.30 (± 0.18) 60: 4.33 (± 0.21) 90: 4.35 (± 0.24) 120: 4.35 (± 0.25) 150: 4.59 (± 0.29) (Table/text difference)		1. 12 individuals (41.38 %) very satisfied 2. 8 individuals (27.59 %) moderately satisfied 3. 9 individuals (31.03 %) hardly satisfied	n = 1 due to burning sensation and erythema of the scalp	
Pazoki-Toroudi 2013	Caffeine 1 % + minoxidil 5 % + azelaic acid 1.5 % topical solution	32 weeks	40	n.i.	23	12/32 weeks	Wash test (number of lost hairs) after 12 weeks	Decrease in hair loss using caffeine/minoxidil/azelaic acid and minoxidil solution compared to placebo (week 12) Caffeine/minoxidil/azelaic acid after 12 weeks showed similar results as minoxidil solution after 36 weeks	Patient satisfaction and physician assessment of caffeine/minoxidil/azelaic acid vs. minoxidil solution / placebo (point in time not specified)	Caffeine/minoxidil/azelaic acid statistically significantly better than minoxidil 5 % and placebo	n.i.	Data only available in the form of an abstract
	Minoxidil 5 % topical solution		20									
	Placebo topical solution		11									

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Table 1 Continued.

Author, year	Intervention	Study duration	n	AGA grade (Hamilton-Norwood) (BL)	Age (BL)	Time of assessment	Definition of primary study endpoint	Result (primary study endpoint)	Definition of other study endpoints	Results of other study endpoints	Study dropouts	Comment
Caffeine monotherapy (2 interventional studies [before-after studies])												
Bussoletti 2010	Caffeine shampoo 1 % 7 ml QD for 6 months; exposure time: 2 min, followed by rinsing	6 months	30	II–IV	18–55 (mean: 37)	0/3/6 months	Hair pull test: i) Decrease in the number of lost hairs (BL: 20.07 ± 2.73) ii) Number of subjects showing a decrease in the number of lost hairs in the hair pull test	i) 18.63 ± 3.19 (–7.17 % after 3 months) 17.43 ± 2.98 (–13.15 % after 6 months) ii) 60 % (3 months), 70 % (6 months.)	1. Physician assessment after 6 months (4-point scale [very slight – strong]) regarding a) hair thickness, b) speed of progression of hair loss, c) number of hairs lost 2. Patient assessment after 6 months (4-point scale [very slight – strong]) regarding a) intensity of hair loss, b) number of hairs lost while combing 3. Patient satisfaction	1. a), b), c): statistically significant improvement (after 6 months) 2. a), b): statistically significant reduction 3. satisfied patients: 67 %	0	–
Bussoletti 2011	Caffeine lotion QD for 4 months; exposure time: 2 min, without rinsing	4 months	40	II–IV	19–55 (mean: 37)	0, 2, 4 months	Hair pull test: i) Decrease in lost hairs (BL 19.90) ii) Number of subjects showing a decrease in the number of lost hairs in the hair pull test	i) 18.28 (–8.14 % after 2 months), 16.85 (–15.33 % after 4 months) ii) 75 % (2 months), 83 % (4 months)	1. Physician assessment after 4 months regarding number (n/%) of participants with improvement a) hair thickness b) progression of hair loss c) number of hairs lost d) Positive clinical assessment in terms of efficacy 2. Number (n/%) of patients after 4 months with subjective assessment regarding improvement a) intensity of hair loss b) improvement or normalization of hair loss c) fewer hairs lost while combing d) hairs becoming thicker e) satisfaction f) desire to continue treatment / recommendation of treatment to others	1a) 21 / 53 % 1b) 17 / 43 % 1c) 34 / 85 % 1d) 21 / 53 % 2a) 32 / 80 % 2b) 32 / 80 % 2c) 32 / 80 % 2d) 20 / 50 % 2e) 32 / 80 % 2f) 32 / 80 % and 32 / 80 %	0	–

[1]Before-after results per arm were not individually extracted as they are uncontrolled.
*Differences between tables and text.
Statistically significant – statistical significance was reported and/or a P value was given; values/test results were missing
Abbr.: AGA, androgenetic alopecia; BID, twice daily; BL, baseline; n.i., no information; QD, once daily.

Table 2 Assessment of bias risk (Cochrane Risk of Bias Tool [first part]/ criteria adapted from the SIGN tool [second part]).

Author, year	Summary, RoB	RoB: sequence generation	RoB: allocation concealment	RoB: blinding of patients, personal, outcome assessors	RoB: incomplete outcome data	RoB: selective reporting	RoB: other sources of bias
Caffeine monotherapy versus placebo (1 RCT)							
Sisto 2013	High	Unclear risk: no information regarding generation of the randomization sequence	Low risk: predefined randomization list unknown to investigational center	Unclear risk: identical packaging; labelled by sponsor, differences between the shampoos (color, odor, other characteristics not reported)	Unclear risk: no loss to follow-up	High risk: in some cases, only the statistical significance is stated without stating the absolute values; limited assessability of clinical relevance; multiple testing including before-after per study arm (no control) (outcomes/ no adjustment)	High risk: recruitment unclear; potential bias due to other different characteristics of the shampoos, no even randomization with regard to AGA grade; secondary endpoints are not independent
Caffeine in combination with minoxidil / azelaic acid versus placebo (2 RCTs)							
Golpur 2013	High	Unclear risk: no information regarding generation of the randomization sequence	Low risk: predefined randomization list unknown to investigational center	Low/unclear risk: double blind, packaging of the medications in both groups identical, not distinguishable for patient or investigator	High risk: no information about what happened to study dropouts	High risk: only P values were reported as results.	Recruitment unclear, no information about the comparability of the shampoos; potential bias due to other different characteristics of the shampoos; no information about successful/ even randomization with regard to AGA grade
Pazoki-Toroudi 2013	High	Unclear risk: no information regarding generation of the randomization sequence	Unclear risk: no information about allocation concealment	Unclear risk: "double blind" without further description of the blinding method	Unclear risk: no information about study dropouts/ missing data	High risk: data for week 32 is only partially reported and data for week 6 not at all	Recruitment unclear, no information about the comparability of the placebo shampoo, potential bias due to other different characteristics of the shampoos, no information about AGA grade or successful/even randomization with regard to AGA grade; only abstract available

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Table 2 Continued.

Author, year	Summary, RoB	RoB: sequence generation	RoB: allocation concealment	RoB: blinding of patients, personal, outcome assessors	RoB: incomplete outcome data	RoB: selective reporting	RoB: other sources of bias
Caffeine monotherapy (2 interventional studies [before-after studies])							
Bussoletti 2010	High	Regression toward the mean; large number of statistical tests with small number of participants, no adjustment for confounders	n.i.	No photographic assessment/defined target area, no blinding	Treatment adherence not controlled/adjusted	Multiple analyses of the intervention-outcome relationship; tolerability recorded by means of a diary; no further information	Questionable clinical relevance of the improvement in the hair pull test; missing definition of the clinical relevance of the decrease in the number of hairs lost in the hair pull test; endpoints are not independent
Bussoletti 2011	High	Regression toward the mean; large number of statistical tests with small number of participants, no adjustment for confounders	n.i.	No photographic assessment/defined target area, no blinding; double-barreled questions	Treatment adherence not controlled/adjusted	Multiple analyses of the intervention-outcome relationship – described as explorative; tolerability analyzed	Questionable clinical relevance of the improvement in the hair pull test; missing definition of the clinical relevance of the decrease in the number of hairs lost in the hair pull test; secondary endpoints are not independent

Abbr.: RoB, risk of bias; SIGN, Scottish Intercollegiate Guidelines Network, n.i., no information.

three alopecia areas (1 cm^2 each) on days 0, 7, 30, 60, 90, 120, and 150. From day 120 onward, combined treatment showed statistically significantly better results. Prior to that point in time, there was no statistically significant difference. On caffeine plus minoxidil 2.5 %, 58.33 % (21/24) of patients were satisfied with the treatment; on minoxidil alone, 41.37 % (20/29). In the minoxidil group, there were six dropouts due to a burning sensation and erythema of the scalp; in the combination treatment group, there was one dropout. The risk of bias was assessed as being "high".

Pazoki-Toroudi et al. (2013) studied the combination of caffeine 1 %, minoxidil 5 %, and azelaic acid 1.5 % versus minoxidil 5 % monotherapy or placebo [6]. Study endpoints included a reduction in the number of hairs lost in the hair wash test, self-assessment by patients, and assessment by a dermatologist. The scales or measuring instruments used in these assessments were not specified. The solution consisting of caffeine 1 % plus minoxidil 5 % plus azelaic acid 1.5 % was shown to be superior to minoxidil 5 % alone as well as to placebo (12 weeks). Information needed to assess the study's methodological quality was insufficient as only a published abstract was available.

In an uncontrolled trial, Bussoletti et al. (2010) investigated the efficacy of caffeine shampoo after three and six months [4]. After six months, there was a statistically significant decrease in the number of hairs lost in the hair pull test. In addition, there were significant improvements in all other endpoints subjectively assessed by patients and physicians. In another uncontrolled study aimed at evaluating a caffeine-containing lotion after four months of application, Bussoletti et al. (2011) likewise showed an improvement in the hair pull test as well as in the subjective assessments by physicians and patients [3]. In both studies, the risk of bias was determined to be "high". There is no information available on patient recruitment or study design. Neither is there any comprehensible information regarding adjustment for potential confounder variables or control of the frequency of application or additional use of other products/drugs (Table 2).

Compared to placebo, caffeine shampoo as monotherapy was shown to be superior in the included study, both in terms of the participants' satisfaction and with regard to a decrease in hair loss; however, there was only one RCT, which did have methodological limitations [5].

In two clinically controlled studies, the combination of caffeine and minoxidil (additionally in combination with azelaic acid in one study) likewise showed positive effects compared to minoxidil alone as well as placebo. Here, too, considerable limitations in terms of methodological study quality and reporting of results were present. The survey among experts revealed a potential risk of publication bias.

Uncontrolled studies are generally markedly limited in their validity. The results of the hair pull test in particular shows great variability due to periodic flares with an increased number of telogen hairs. Thus, there should be a sufficiently large number of patients and a control group to compare to?.

The European S3 guideline on the treatment of AGA mentions caffeine as a therapeutic option but – given the lack of evidence – does not issue a recommendation for or against AGA treatment with caffeine. Regarding the assessment of results in the context of clinical studies, the guideline primarily recommends the use of global photographic assessments in order to achieve a standardized evaluation of the entire scalp or, alternatively, measurement of hair density, anagen/telogen ratio, or terminal/vellus hair ratio in clearly defined target regions. With respect to assessing the efficacy of caffeine as monotherapy, no such studies exist. Assessments by patients themselves or by investigators are of limited value.

In vitro and penetration studies on the effects of caffeine on hair follicles have confirmed the penetration and accumulation of topical caffeine [8–12]. However, it must be borne in mind that penetration and accumulation cannot be equated with stimulation of the hair root. To date, data on the effects of topical caffeine on the hair root is insufficient [13, 14].

There is currently limited data on the efficacy of caffeine in androgenetic alopecia. Given that an assessment of the efficacy of available shampoos or solutions as monotherapy – based on criteria recommended in the European guideline – continues to be unfeasible, studies with high methodological standards are desirable.

Conflict of interest

AB is co-author of the European S3 guideline "Treatment of androgenetic alopecia in men and women". AA, AN, CD and SR do not report any conflict of interest.

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