Marine protein extract for androgenic alopecia

Abstract

Background

Oral marine protein extract preparations have been suggested as a possible treatment for hair loss. Hair loss in men can have significant psychosocial consequences and an efficacious and acceptable treatment is highly sought.

Objectives

To assess the results of studies of the use of proprietary preparations containing marine protein extracts in the treatment of hair loss.

Search methods

Studies were as provided.

Selection criteria

Studies involving the use of marine protein extracts for hair loss that report being randomised, controlled, double blind studies applied to adult individuals who report hair loss of at least one year duration

Data collection and analysis

Data were collected from the papers and analysed using a fixed effects model. The main outcome was increase in numbers of hair on the scalp.

Results

Two of three studies which provided sufficient data for the analysis gave a standardised mean difference of 9.12 (95% confidence interval 7.71-10.53; p<0.00001) in favour of the active treatment.

Authors' conclusions

Although the preparations appear to actively promote hair growth and there is significant self reported satisfaction with the preparations, the range of the latter is wide and the quality of the hair growth has not been described. The potential for significant methodological biases remains because of the the poor reporting and the efficacy of these preparations may not be as high was these publications suggest.

Plain language summary

Preparations for baldness

Early hair loss in young men and early in middle age is of significant concern to those who have inherited the hair loss gene, affecting self esteem through to future employment potential and any treatment that can reduce or reverse continuing hair loss is of importance. These preparations containing a marine protein extract appear to significantly increase head hair production when used for six months. The reported study methods are, however only of average quality and do not contain enough detail to exclude a significant bias

Background

Description of the condition

Androgenic alopecia is the most common form of hereditary hair loss that predominantly affects males. A genetic predisposition and the involvement of sex hormones are factors that influence the rate and extent of hair loss which are likely to vary between men and women (1). About 80% of white males suffer hair loss by the age of seventy which begins shortly after puberty, with two peaks of incidence in the third and fifth decades (2). Androgens, in the form of testosterone, are prerequisites for baldness in those genetically susceptible males, binding directly, or as a metabolite, to the dermal papilla. The metabolism of testosterone to its more active dihydrotestosterone is effected through the 5-alpha reductase type 2 enzyme (3). Regional differences in androgen sensitivity and signalling pathways influence the development of baldness that begins with bitemporal recession, followed by vertex baldness which rarely extends to the occipital region of the scalp (4). The development of baldness is associated with an increased turnover of hair cycles accompanied by a marked decease in the anagen (growth) phase and a relative or actual increase in the telogen phase and replacement of anagen hairs with weaker telogen hairs. Areas where baldness predominates show an increased expression of androgen receptors, increased androgen sensitivity and higher levels of 5-alpha reductase.

The complex polygenic nature of hereditary baldness has long been established (5) and associations have been found with mutations (single nucleotide polymorphisms and copy number variants) in several genes, including the androgen receptor gene, although those reported account for less than 50% of the occurrence of hereditary baldness.

Hair offers protection to the skin from sun damage which is lost as a result of baldness, increasing the risk of skin cancer. In addition hair loss can have important psychosocial consequences (6) that can lead to a loss of confidence and low self-esteem. Current treatments for hair loss today involve topical or oral medications, or hair transplantation and proteins from marine fish have been reported to be beneficial in the treatment of hair loss. This review will consider three publications that report intervention studies of marine protein preparations for hair loss (studies A-C).

Description of the intervention

Proprietary forms of marine proteins with or without other vitamins and minerals given as an oral tablet twice daily and compared with either a placebo or fish extract preparation. ViviScal is a marine protein extract accompanied by other vitamins and minerals including L-methionine, L-cysteine, folic acid, vitamin E, selenium and D-biotin in tablet form. Nourkrin appears to be an identical or very similar preparation to ViviScal containing extracts of marine proteins, silica, immunoglobulins and a source of vitamin C in tablet form. Hår Vokse is a preparation from a Norwegegian company containing marine protein extracts. All are described as natural food extracts that provide nutrients important for the growth and nourishment of hair, stimulating dormant hair follicles.

How the intervention might work

The preparations contain various nutrients that might be expected to be available to those on a normal diet combined with extracts of marine proteins and polysaccharides that have been shown to influence androgen metabolism. Possibly this latter component might act to competitively bind dihydrotestosterone, thus reducing its availability to androgen receptors on the skin although none of these publications makes this claim.

Why it is important to do this review

Hair loss leading to baldness is a condition that can result in significant psychosocial consequences in both men and women and medical treatment is limited. These preparations purport to offer hope in treating this condition and gain credibility with a proportion of the population by being preparations of 'natural' ingredients.

Objectives

To assess the effects of preparations containing marine protein extracts for hair loss in adults.

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled studies

Types of participants

Males or females with significant androgenic alopecia (Hamilton Scale III-IV) or hair loss of at least one year duration.

Types of interventions

Experimental preparations took the form of tablets given twice daily, or three times daily in the studies of Hår Vokse and Nourkrin for individuals over 80kg in body weight. Comparative preparations were also in tablet form given twice daily as placebo preparations or as a 'fish extract' preparation. The formulation of the latter 'inactive' preparation is not clear although is said to contain proteins of the same type as used in ViviScal.

Types of outcome measures

Outcomes focus on number of hairs before and after treatment in a bald area of the scalp.

Primary outcomes

Number of hairs in pre-defined areas of the bald scalp, measured before and after treatment of six months duration..

Secondary outcomes

Satisfaction

Data collection and analysis

Selection of studies

Studies described as randomised controlled studies of use of marine protein extract preparations in individuals suffering from inherited alopecia

Data extraction and management

Data was extracted from the publications by the author only. The study authors were not contacted for any secondary information.

Assessment of risk of bias in included studies

Sequence generation: Studies A and C provided no information about how the allocation sequence was generated although the authors used the term 'randomised'. Study A was probably not properly randomised as they divided patients randomly into two groups. No method was stated for study C although it managed to equally divide the treatments between males and females, and between the different types of alopecia. Study B used a method designed to result in equal sized groups (simple block randomisation) but there is a suspicion that some manipulation has also taken place unless some unstated stratification has been employed.

Nevertheless the method used seems to have led to groups of a similar mean age and duration of hair loss and is probably adequate.

Allocation concealment: There is nothing to support adequate allocation concealment in any of the included studies. Studies were allocation concealment is not evident have shown a bias of 18% (95% confidence interval 5-29%) in favour of the active treatment and these reported interventions are very vulnerable to bias.

Blinding of participants, personnel and outcome assessors: It is unclear whether the tablets provided in study A were distinguishable and three people dropped out half way through the study in the inactive treatment group because of lack of efficacy. In studies B and C attempts were made to make the preparations indistinguishable to the participants. There is not mention of whether the personnel were blinded. All three studies were described as being double-blind but only study B mentioned that the outcome assessors were blinded.

Incomplete outcome data: Attrition was reported in studies A and C, the former because of lack of efficacy of non-active treatment and in the latter apparently because the individuals did not want to continue in the study. The loss was not significant.

Selective outcome reporting: There is no evidence of selective outcome reporting in the studies.

Measures of treatment effect

Difference in hair counts from baseline measured at six months. Study B reported only percentage change from baseline. Study C provided only mean counts with no measure of variation and therefore cannot be included in the meta-analysis.

Unit of analysis issues

There are no issues relating to non-standard designs in these studies.

Dealing with missing data

There is no substantial loss of data in studies A and C, but no details are provided in study B. It was, however, stated that all individuals in study B used the active treatment for the prescribed time. There has been no attempt to include missing individuals in any of the studies and it appears that an intention-to-treat analysis has been performed in all cases.

Assessment of heterogeneity

The studies are similar in nature. The age ranges of the participants are different in the three studies with older participants being included in the later studies. An assessment of heterogeneity has been undertaken of the meta-analysis done using study A and B.

Assessment of reporting biases

These reports are all comparisons with a commercial product with an inactive treatment. Two of the publications have the same author who reports no conflict of interest in one of the studies (Hår Vokse™). The funding of study A is not clear but studies B and C were funded by the manufacturers who may have had control over whether these studies were published or not and the results of the publications are used as promotional material fro the manufacturers. It is unclear as to whether other studies have been undertaken that have not demonstrated a treatment effect (publication bias)

Data synthesis

Because data is presented differently in the studies - number of hair measured in different areas, or percentage increase in the number of hairs, the data has been analysed as a standardised mean difference with a fixed effects model. One study provided no assessment of measurement error and so no calculations

were undertaken; ideally the author could be contacted for this information, or for raw data that could facilitate the analysis.

Sensitivity analysis

No sensitivity analyses have been done in any of the studies and were probably not required, although the potential loss of individuals in study B is unclear.

Results

Description of studies

Three studies were included in this analysis. All were described as randomised, controlled and double-blind.

Results of the search

No searches were undertaken.

Included studies

Studies provided were included.

Excluded studies

No studies were excluded

Risk of bias in included studies

The risk of bias is summarised in the table and summarised below.

Allocation (selection bias)

Significant risk of bias

Blinding (performance bias and detection bias)

Unclear risk of bias

Incomplete outcome data (attrition bias)

Low risk of bias

Selective reporting (reporting bias)

Low risk of bias

Other potential sources of bias

It is not clear whether or not these studies have been undertaken on behalf of the particular manufacturers. While data is provided attesting to the efficacy of each individual preparation, these preparations have not been assessed against each other, or against any other form of treatment for hair loss.

Effects of interventions

All three studies demonstrated an increase in number of hairs at six months over the baseline. The increase was between 32% and 38% in the intervention group, in comparison with an increase of between 0.9% and 2.1% in the control group. A meta-analysis of studies A and B showed a standardised mean difference of 9.12 (95% confidence interval 7.71-10.53, $p<0.00001$). Heterogeneity was not significant ($Chi^2 = 3.27$, $p=0.07$).

No adverse effects were reported and participants in studies B and C reported a self-evaluation of satisfaction with the active treatment of, on average 5.8 (range 0-10) on a visual analogue scale of 0-10, which in study C

was reported to achieve high statistical significance in comparison with placebo (p<0.001).

Discussion

Summary of main results

All three interventions produced an increase in the number of recorded hairs of about 35% over six months. A meta-analysis of two studies involving ViviScal and Hår Vokse showed that these preparations were significant in increasing the numbers of hair (p<0.00001). Paricipants in the study found the preparations acceptable and no side effects were reported.

Overall completeness and applicability of evidence

These studies have been done in a predominantly or exclusively northern European males in ages ranging from young adult to middle age with a one year history of baldness

Quality of the evidence

The three studies have on average a Jadad quality score (12) of 2 (with a range of 0 - very poor, to 5 - rigorous), The Jadad score does not consider allocation concealment which has not been addressed in any of these studies.

Potential biases in the review process

No searches have been undertaken for other studies of marine protein extracts in the treatment of baldness that may have been unpublished.

Agreements and disagreements with other studies or reviews

These three randomised controlled double blind studies reported a benefit of percentage hair growth of between about 30% and 40% over six months. This contrasts with several other uncontrolled non-blinded studies (7-11) that indicated a much high benefit of marine protein treatment for hair loss in the order of 70% to 85%.

Authors' conclusions

Implications for practice

These preparations all appear to be efficacious although the quality and appearance of the increased hair production is unclear. Nevertheless individuals reported a significant degree of satisfaction after six months in comparison with the placebo preparations, although there was a wide range in these self-evaluations. The poor reporting of the methodology in each of the studies means that significant biases cannot be excluded.

The effects of long-term use of these preparations has not been considered, nor has the time to return to pretreatment levels been explored if treatment is stopped.

Implications for research

These preparations should be the subject of a properly documented randomised controlled double-blind trial undertaken by an independent organisation.

Characteristics of studies

Characteristics of included studies

A

Methods	Randomised controlled double-blind study
Participants	Males with androgenic alopecia (Hamilton scale III or IV) - n=40
Interventions	Viviscal tablets or fish extract tables given twice daily for six months
Outcomes	Non-vellus hair counts within a 2.5cm diameter area of the balding posterior vertex reported at baseline and at six months
Notes	Counting was done with the aid of illumination and magnification with a template. A 5mm punch biopsy was taken from the centre of the bald scalp at the beginning and end of the study, reportedly to locate the target area for hair counts

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation is not stated (divided randomly in to two groups) although the methods section indicates that the division was undertaken so that the number in each group was identical. Table 1 indicates that the two treatment groups were similar in their baseline characteristics
Allocation concealment (selection bias)	High risk	No information was provided about allocation concealment
Blinding of participants and personnel (performance bias)	Unclear risk	The study was described as double blind in the abstract only but no details were given. Probably the participants were blinded to treatment. Whether or not the person giving the treatment to the individual was blinded is not clear.
Blinding of outcome assessment (detection bias)	Unclear risk	The study does not indicate whether the assessor of the clinical outcome was blind or not.
Incomplete outcome data (attrition bias)	Low risk	3/20 (15%) were not able to be evaluated in the non active treatment group. This difference, although unbalanced, is probably not significant
Selective reporting (reporting bias)	Low risk	No evidence of reporting bias in text
Other bias	Unclear risk	This is a Finnish study although it is not clear what the participants' origin was. Finland is a relatively isolated population group that has significant genetic differences compared with other populations, even within Europe. There is no detail about the selection of individuals for the study, other than the relative degree of baldness and an unsupported comment that they were 'in good health'. The majority of participants were in their twenties.

B

Methods	Randomised, placebo-controlled, double blind study
Participants	Males or females aged 18 and over with hair loss of at least one year duration - n=60
Interventions	Hår Vokse or placebo capsules taken twice daily (three times if participants over 80kg)
Outcomes	Hair counts of four areas of the scalp: percentage increase from baseline at 2, 4 and 6 months
Notes	Four pre-defined standardised photographs of scalp enlarged x80 for counting. The same areas were assessed on each occasion. Method for this was standardised and details provided in a separate publication.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Simple block randomisation (blocks of six). Table 1 indicated that the individuals were similar at baseline and evenly distributed between the two groups but without stratification the even distribution of the female participants and those with alopecia areata is fortuitous at best...
Allocation concealment (selection bias)	High risk	No information provided
Blinding of participants and personnel (performance bias)	Unclear risk	Capsules of active and placebo treatment had identical appearance and placed in similar bottles. Unclear as to whether personnel were blind
Blinding of outcome assessment (detection bias)	Low risk	Photographs were assessed blind for hair counting by a trained individual
Incomplete outcome data (attrition bias)	Unclear risk	Nothing reported but this is completely unclear as only percentages or means are presented.
Selective reporting (reporting bias)	Low risk	No evidence of reporting bias in text
Other bias	Unclear risk	This is a Norweigain study and individuals were recruited through a local newspaper advert and so it is likely that most, if not all, individuals were from northern Europe. Most of the participants were male aged between from about 30 to the mid 40s and suffering from androgenic alopecia.

C

Methods	Randomised, double-blind, placebo controlled trial
Participants	Males or females, aged 18 or above, suffering hair loss over a one year period at the time of recruitment - n=60

Interventions	Nourkrin or placebo tablets taken twice daily (three times daily for those over 80kg body weight)
Outcomes	Mean hair count over four 6.25 cm^2 areas at baseline and after six months
Notes	Four pre-defined areas were selected: vertex, forehead and above each ear. Hairs were counted with illumination and magnification. No attempt made to ensure that exactly the same area of the scalp was used in the two assessments but areas are relatively large.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of randomisation is not provided but has been engineered so as to produce an exactly even allocation to the two groups. Table 1 reports only sex, age and duration of hair loss..
Allocation concealment (selection bias)	High risk	No information provided.
Blinding of participants and personnel (performance bias)	Unclear risk	Capsules of active and placebo treatment had identical appearance and placed in similar bottles. Unclear as to whether personnel were blind
Blinding of outcome assessment (detection bias)	High risk	No report provided of assessors being blinded
Incomplete outcome data (attrition bias)	Low risk	5/60 (16.3%) were not able to be evaluated but the loss was balanced between the two treatment groups.
Selective reporting (reporting bias)	Unclear risk	No evidence of reporting bias in text
Other bias	Unclear risk	This is a Norwegian study and individuals were recruited through a local newspaper advert and so it is likely that most, if not all, individuals were from northern Europe. Most of the participants were male aged between about 30 and early 50s and mainly suffering from androgenic alopecia.

Footnotes

References to studies

Included studies

A

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Other references

Additional references

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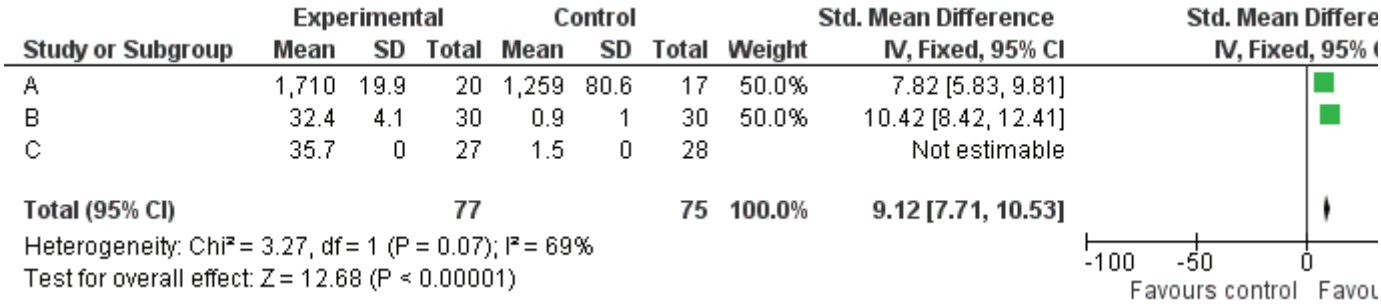
Data and analyses

1 Marine protein extract compared with placebo or inactive treatment

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Hair growth at six months	3	152	Std. Mean Difference (IV, Fixed, 95% CI)	9.12 [7.71, 10.53]

Figures

Figure 1 (Analysis 1.1)



Forest plot of comparison: 1 Marine protein extract compared with placebo or inactive treatment, outcome: 1.1 Hair growth at six months.