Current best evidence from dermatology literature

Hong HC, Lupin M, O'Shaughnessy KF. Clinical evaluation of a microwave device for treating axillary hyperhidrosis. Dermatol Surg 2012;38:728-35.

In this study, the efficacy of a new third-generation microwave-based device was assessed to treat axillary hyperhidrosis by selectively heating the interface between the skin and underlying fat, where the sweat glands are present.

Thirty-one adults with primary axillary hyperhidrosis were enrolled. All subjects had 1-3 procedure sessions over a 6-month period to treat both axillae. Efficacy was assessed using the Hyperhidrosis Disease Severity Scale (HDSS), gravimetric weight of sweat, and the Dermatologic Life Quality Index (DLQI). Subject safety and adverse effects were assessed at each visit and followed up for 12 months after all procedure sessions were complete.

The results of the study were encouraging and at the 12-month follow-up visit, 90.3% had HDSS scores of 1 or 2, 90.3% had at least a 50% reduction in axillary sweat from baseline, and 85.2% had at least 5 points reduction in DLQI. All subjects experienced transient adverse effects in the treatment area such as swelling, discomfort, and numbness. The most common adverse event (12 subjects) was the presence of altered sensation in the skin of the arm that resolved in all subjects.

Comments: Hyperhidrosis is a condition that affects a large percentage of the population and has a significant impact on their lives. Numerous treatment options are available, but most have significant drawbacks. First-line therapy is topical aluminum chloride with or without salicylic acid, but irritant dermatitis is a common complaint. Second-line options include iontophoresis, which is time-consuming and painful. Botulinum toxin A injections are highly effective, but they must be repeated every 4-6 months and can cause weakness of the underlying muscles. Oral medications include anticholinergic agents and alpha2-adrenergic drugs; however, all of these have side effects which are troublesome and unacceptable to the patients. Third line is surgery to remove/destroy the sweat glands. The device tested is a new noninvasive, microwave-based device for creating thermolysis of sweat glands.

In the microwave treatment procedure, an applicator is placed on the skin surface to deliver focused energy to the dermal-fat interface, to target the sweat glands. Microwaves are preferentially absorbed by tissues with high water content, such as sweat glands and poorly absorbed by fat. A cooling system keeps the heat at the lower skin layer. A heat dome at about 60°C is created along the dermal-fat junction, resulting in sweat gland thermolysis. The results of the study demonstrate that microwave technology is well-suited for targeting sweat glands and provided efficacious and durable treatment for axillary hyperhidrosis. Adverse effects noted in the studies are swelling, bruising, discomfort, and altered sensation in and around the treatment area, but all are short-term. Less common side effects include swelling extending beyond the treatment area, a tight banding sensation in the axilla, and arm and hand numbness lasting less than 24 h. Rarely, brachial nerve palsy may be seen due to variant anatomy.

Microwave ablation may well be the future of hyperhidrosis treatment; however, larger patient numbers and more long-term data are needed before the therapy becomes common in clinical practice.

Trink A, Sorbellini E, Bezzola P, Rodella L, Rezzani R, Ramot Y, *et al*. A randomized, double-blind, placebo and active-controlled, half-head study to evaluate the effects of platelet rich plasma on alopecia areata. Br J Dermatol 2013.

Alopecia areata (AA) is a common auto-immune condition, causing inflammation-induced hair loss. Although a number of treatments have been used; no treatment is either curative or preventive. Platelet-rich plasma (PRP) has emerged as a new treatment modality in dermatology and preliminary evidence has suggested it might have a beneficial role in hair growth.

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This study was done in International Hair Research Foundation, Milan, Italy with the main aim to evaluate the efficacy and safety of PRP for the treatment of AA in a randomized, double-blinded, placebo and active-controlled, half-head, parallel group study. Forty-five AA patients were randomized to receive intralesional injections of PRP, triamcinolone acetonide (TrA) or placebo on one half of their scalp. The other half was not treated. A total of three treatments were given for each patient, with an interval of 1 month from each other. The endpoints were hair regrowth, hair dystrophy as measured by dermoscopy, burning/itching sensation, and cell proliferation as measured by Ki-67 evaluation. Patients were followed up for 1 year.

PRP was found to significantly increase hair regrowth and decrease hair dystrophy and burning/itching sensation when compared with TrA or placebo, and Ki-67 levels, which served as markers for cell proliferation, were significantly higher. No side effects were noted during treatment.

Comments: AA is commonly seen in younger population and the disease burden is substantial, leading to overwhelming effects on the patient's quality of life and self-esteem. So far there are no studies that have evaluated the effect of PRP on hair growth in AA patients. This pilot study is the first to investigate the effects of PRP on AA. However, the authors have included the chronic and relapsing form of AA, and not the more common spontaneously remitting type of AA. Therefore, the results may not be applicable to other age groups or to the spontaneously remitting type. PRP is known to contain more than 20 different growth factors, which are important in promoting cell proliferation and differentiation. These properties are thought to lead to its beneficial effects on acne scarring, hair growth, and wound healing. Although the mechanisms by which PRP exert its effects on hair follicles are still obscure; studies have shown that storing hair grafts in PRP can enhance graft survival, improve hair density, and stimulate growth of transplanted follicular units. Besides this, PRP is also used as mesotherapy in androgenetic alopecia (AGA) or as an adjunct to hair transplant. In addition to its proliferation-inducing effects, PRP is also a potent anti-inflammatory agent, which can suppress cytokine release and thereby limit local tissue inflammation as in AA.

This study has demonstrated that PRP is a new treatment modality for AA, being a safe, and a more efficient alternative for TrA, the current treatment of choice for AA. However, further controlled and randomized studies are needed to validate our findings in a larger cohort of patients.

Su LH, Chen LS, Lin SC, Chen HH. Association of androgenetic alopecia with mortality from diabetes mellitus and heart disease. JAMA Dermatol 2013;149:601-6.

Numerous studies in recent decades have associated male and female AGA with the risk of cardiovascular disease (CVD), metabolic syndrome, insulin resistance, and hypertension. In this study, the authors have tried to investigate the association between AGA and mortality from diabetes mellitus (DM) and heart disease in both males and females.

As part of a community-based integrated screening program, a prospective cohort of 7252 participants aged 30-95 years was enrolled for the study in 2005. Baseline information regarding AGA grading (Norwood and Ludwig classifications) and metabolic syndrome and other risk factors (like family history, diagnoses of chronic diseases (e.g. hypertension, DM, heart disease), drug history, exercise status and smoking status) was collected. Anthropometric measurements (including waist circumference), blood pressure (BP) recordings as well as biochemical analysis of blood glucose and lipids were also carried out. A total of 7126 subjects (2429 men and 4697 women) who provided complete data at baseline were followed up till end of 2010 (57 months) to ascertain the causes of death.

Moderate or severe AGA, defined as Norwood types IV-VII or Ludwig types II and III, was found to be associated with a 2.01-fold higher risk of mortality from DM and heart disease as compared with normal or mild AGA after adjusting for potential confounding factors including metabolic syndrome as well. When the associations with DM and heart disease were evaluated separately, the adjusted odds ratios (2.97 and 2.28, respectively) were also significant. Hence, according to this study, AGA qualifies as an independent predictor of mortality from DM and heart disease in both sexes.

Comments: AGA is a heritable androgen-dependent hair loss, known for its wide prevalence, affecting approximately 30%-40% of adult men and 80% of men by the age of 80 years. It is considered as a dermatological marker for atherosclerosis, as suggested by the presence of common risk factors like age, hypertension, insulin resistance, dyslipidemia, and smoking.

Several studies have found a positive association separately both for early age of onset of AGA as well as severe grade of AGA or vertex baldness, and coronary artery disease (CAD). Various mechanisms have linked these two conditions at the molecular level such as hyperinsulinemia/insulin resistance, chronic inflammation, increased peripheral sensitivity to androgens, and hyperaldosteronism. Hyperinsulinemia, a central factor in metabolic syndrome, has been shown to enhance the influence of dihydrotestosterone on follicular miniaturization. Hence, it forms the basic underlying mechanism linking these two conditions. However in this study, positive association between AGA and mortality with DM and CAD has been shown regardless of the presence of metabolic syndrome, which is unclear at present.

Moreover, the use of same drugs in these two conditions has always signaled toward a common underlying mechanism. Minoxidil, the most common medical therapy in AGA, was originally developed as an antihypertensive agent (vasodilator). Also, spironolactone, which is administered for the treatment of female AGA due to its antiandrogenic effects, is commonly used as an antihypertensive to counteract aldosterone action on BP.

This study also elucidates a two fold higher risk of mortality from DM and heart disease in subjects with moderate to severe grade AGA. Given the importance of primary prevention in these diseases, this study would at least help us to identify susceptible individuals who might benefit from early preventive strategies focused on risk factors such as smoking, cholesterol and blood glucose levels, and elevated BP.

Dowlatshahi EA, Kavousi M, Nijsten T, Ikram MA, Hofman A, Franco OH, *et al*. Psoriasis is not associated with atherosclerosis and incident cardiovascular events: The Rotterdam study. J Invest Dermatol 2013.

Psoriasis has been suggested to be an independent risk factor for CVD; however, available studies have shown inconsistent results. This study builds on data collected by the population-based Rotterdam study, in which the authors have tried to assess the association between psoriasis and CVD morbidity and mortality.

At entry, all participants were evaluated for the presence of cardiovascular risk factors. Next, a cohort of 262 psoriasis and 8,009 reference subjects, aged 45 years and above, were followed up for a mean of 11 years to assess for cardiovascular events.

The hazards of cardiovascular events for psoriasis, as a time-dependent variable, were calculated by using Cox regression. Psoriasis patients were significantly younger, smoked more, and had higher diastolic BP and body mass index (BMI) levels. The adjusted carotid intima-media thickness was 1.02 ± 0.18 mm for psoriasis and 1.02 ± 0.16 mm for reference subjects. Similarly, crude and adjusted ankle-brachial index, pulse-wave velocity, and coronary artery calcium scores did not differ between the two groups. The risk of incident CVD was not increased in psoriasis (adjusted hazard ratio 0.73, 95% confidence interval: 0.50-1.06). The results were similar when coronary heart disease, stroke, and heart failure were analyzed separately. However, detection of carotid plaques in psoriasis patients turned out to be significantly increased than the reference population, only after adjustment. Subgroup analysis showed no difference of results between mild psoriasis or moderate to severe disease, each compared to the reference subject. Even prevalent psoriasis cases at inclusion to the study (with a longer duration of psoriatic disease) were compared to the incident cases and reference subjects and were found to have no increased risk of developing a cardiovascular event.

Comments: Psoriasis is a systemic, inflammatory, immune-mediated disorder affecting skin and joints with a substantial burden of comorbidities. A constellation of lifestyle risk factors prevalent in severe psoriasis like anxiety, depression, sedentary lifestyle, alcohol abuse and smoking together, amounts to a proinflammatory and a prothrombotic state of metabolic syndrome. Epidemiological association has also been observed with inflammatory bowel disease, obesity, dyslipidemia, hypertension, diabetes, and CVD across several studies, more consistently for young patients with severe psoriasis. An independent causal relationship between the proinflammatory state consequent to psoriasis itself and cardiometabolic diseases has also been suggested.

The presence of common genetic traits and a common pathogenic substrate, T-helper type 1 cytokines, has been speculated to be the independent threads linking psoriasis with atherosclerosis. In addition, both diseases share a common pattern of T-cell activation, including chemokines, adhesion molecules, and endothelins and have similar histological features with the involvement of T cells, macrophages, monocytes,

mast cells, connective tissue cells and extracellular matrix.

However, conflicting reports in the recent past have challenged this association. This study found no increased risk of developing atherosclerosis or CVD, among elderly psoriatics with predominantly mild disease, as compared to the general population, after complete matching for CVD risk factors. Earlier studies favoring this association were mostly tertiary center-based case-control studies, often limited by selection bias and information bias. This well-structured long-term cohort study is rather aimed at psoriatic subjects among the population-based Rotterdam study, with mild cases accounting for 76% of the psoriasis cohort, hence being more representative of the overall burden of psoriasis in the community. However at the same time, it was designed to exclude the younger population below 45 years, with type I psoriasis known for a severe disease course, thereby making it the biggest drawback of this study. This limits the generalization of the study findings to younger psoriasis population. Further trials are awaited to refute this long speculated risk of CVD in psoriasis.

Thomas KS, Crook AM, Nunn AJ, Foster KA, Mason JM, Chalmers JR, *et al.* U.K. Dermatology Clinical Trials Network's PATCH I Trial Team. Penicillin to prevent recurrent leg cellulitis. N Engl J Med 2013;368:1695-703.

This UK-based Prophylactic Antibiotics for the Treatment of Cellulitis at Home I (PATCH I) trial was performed to evaluate the efficacy of prophylactic 12-month course of low-dose oral phenoxymethylpenicillin (penicillin) 250 mg administered twice daily, in adult patients (>16 years) with recurrent leg cellulitis.

In this double-blind randomized placebo-controlled trial, 274 patients with recurrent cellulitis of leg (≥2 episodes in last 3 years) were recruited and randomly assigned to receive low-dose oral penicillin (250 mg; n = 136) or placebo (n = 138) twice daily after completing treatment for the index cellulitis episode. Recurrences were assessed both for the prophylaxis phase (0-12 months) and during the follow-up phase (13-36 months). During the prophylaxis phase, 30 of 136 participants (22%) in the penicillin group had a repeat episode as compared with 51 of 138 participants (37%) in the placebo group, thereby leading to almost half the risk of recurrence with the intervention. Also, fewer repeat episodes (76 vs. 122) were encountered in patients while on penicillin prophylaxis. However, the level of protection diminished after the cessation of prophylactic therapy, with equal rates of recurrence in the follow-up period (27% in both groups). Overall, the median time to the first recurrent episode was 626 days in the penicillin group and 532 days in the placebo group. No significant difference in drug-related adverse effects was noted in the two groups. Multivariate analysis identified three factors to be significantly associated with poor response to prophylactic therapy, that is, high BMI (>33), ≥3 previous episodes and preexisting edema (borderline significance).

Comments: This study stems from the earlier published PATCH II trial of a shorter duration (6 months) of penicillin prophylaxis in patients with a single previous episode of cellulitis of the leg. Data from 123 patients showed a 47% reduction in the risk of recurrence with similar dose penicillin as compared to placebo, although the results could not achieve statistical significance (P = 0.08), neither in the treatment phase nor follow-up phase. Inadequate sample size could be responsible for the difference in the results from the two trials. Also, the target population with recurrent cellulitis (at least 2 or more episodes) is more likely to benefit from prophylactic therapy, as evident in PATCH I trial.

Recurrent cellulitis of leg is a troublesome condition both for the patient and the physician in clinical practice, apart from being a burden to health care facilities. Management should target risk factors amenable to treatment, for example, elastic compression stockings for venous insufficiency/leg edema and/or antifungals (topical or oral). Current evidence for the use of prophylactic antibiotics in recurrent leg cellulitis is limited to constitute a recommendation. Oral penicillin offers a cheap and effective option in reducing the morbidity and health care costs associated with repeat episodes. Other regimens like oral amoxicillin and intramuscular benzathine penicillin have been tried with varying results.

This trial was performed in UK where penicillin resistance is not a present issue; however, any evidence of culture sensitivity could have added clarity to this issue. Whether these results can be replicated in developing countries like India is a matter of concern, especially in this era of

emerging methicillin-resistant *Staphylococcus aureus* strains. Long-term administration of antibiotics may also contribute to the increasing prevalence of community-acquired resistance. Hence, prudent selection of an appropriate candidate for prophylaxis is a must and should include recurrent (≥2 episodes) of leg cellulitis, absence of a breach of skin barrier, dose adjustment according to BMI along with effective management of predisposing risk factors.

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