Current Best Evidence

Current best evidence from dermatology literature

Roh MR, Kim T-K, Chung KY. Treatment of infraorbital dark circles by autologous fat transplantation: A pilot study. Br J Dermatol 2009;160:1022-1025.

Infraorbital dark circles are a cosmetic concern for a large number of individuals. However, the exact definition and precise cause has not been elucidated clearly. In their experience infraorbital dark circles due to thin and translucent lower eyelid skin overlying the orbicularis oculi muscle can be treated successfully with autologous fat transplantation. They conducted this study to clarify the nature of dark circles under the eyes and determine the efficacy of autologous fat transplantation. Ten patients with dark circles due to increased vascularity and translucency of the skin were included. They received at least one autologous fat transplantation and follow-up evaluations were conducted at least 3 months after the last treatment. An average of 1·6 autologous fat transplantations were done in both infraorbital areas. Patients showed an average of 78% improvement (average grading scale: 2·6 out of 4). Most of the patients showed improvement in the infraorbital darkening and contour of the lower eyelids. Authors conclude that autologous fat transplantation is an effective method for the treatment of infraorbital dark circles due to thin and translucent lower eyelid skin overlying the orbicularis oculi muscle.

Comment: Infraorbital dark circles are thought to have a multifactorial aetiology. One of the primary causes is excessive pigmentation, which is seen in conditions such as dermal melanocytosis and postinflammatory hyperpigmentation. Infraorbital dark circles are observed in dermal melanocytosis such as naevus of Ota and acquired bilateral naevus of Ota-like macules (Hori's naevus). Postinflammatory hyperpigmentation under the eyelids is usually caused by allergic or atopic dermatitis. This condition usually appears as a slightly curved band of brownish skin approximating the shape of the underlying inferior orbital rim. The pigmentation looks darker when it is present below the bulging of the lower eyelids induced by the pseudoherniation of orbital fat. The bulging lower eyelids add a shadow effect and worsen the appearance. When the lower eyelid skin is manually stretched, the area of pigmentation spreads out without any blanching or significant lightening of the pigmentation.

Another common cause of infraorbital darkening is due to thin and translucent lower eyelid skin overlying the orbicularis oculi muscle. The orbicularis oculi muscle lies right beneath the skin with little or no subcutaneous fat and the darkness may be due to the visible prominence of the subcutaneous vascular plexus or vasculature contained within the muscle. This condition usually involves the medial half of the lower eyelids with violaceous appearance, which is consistent with prominent blood vessels covered by a thin layer of skin. The violaceous appearance is usually accentuated during menstruation. This hypervascular appearance was suggested to be due to the combination of exceptional transparency of the overlying skin and excessive subcutaneous vascularity.

In some of these patients, the darkening is aggravated by the association with a tear trough, which is a depression centred over the medial inferior orbital rim. The condition aggravates with ageing due to the loss of subcutaneous fat with thinning of the skin over the orbital rim ligaments, which confers a hollowness aspect to the orbital rim area. Tear troughs were present in patients older than 45 years in their cases. The combination of the hollowness and the overlying pseudoherniation of the infraorbital fat accentuates the shadow in the tear trough depending on the lighting conditions.

Another cause of infraorbital dark circles is shadowing due to skin laxity. Dermatochalasia and periocular rhytides are a common manifestation of ageing. Over time, collagen and elastin in the thin tissue of the eyelids and periorbital skin undergo both ultraviolet-induced and age-related degeneration. In addition, the damaged epidermis releases collagenases, which further contributes to collagen degeneration. Skin

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laxity due to photoageing imparts a shadowing appearance on the lower eyelids, which results in infraoribital dark circles. In the majority of patients, infraorbital dark circles are due to a combination of the previous causes.

Treatments for these conditions vary with the cause. For infraorbital hyperpigmentation, treatment such as bleaching creams, topical retinoic acids, chemical peels and pigment-specific laser therapy have been used. Lowe et al. reported that Q-switched ruby (694 nm) laser was effective in lightening the hyperpigmentation after two treatments. High-energy, pulsed CO_2 laser, which is a nonpigment specific laser system, also showed successful results for the treatment of infraorbital dark circles. In these cases, dark circles were due to skin laxity and the beneficial effects were due to the ability to tighten dermal tissue and improve surface texture by vaporizing intracellular water.

Although treatments aimed at hyperpigmentation and skin laxity have been tried, there are no reports of treating dark circles due to thin and translucent lower eyelid skin overlying the orbicularis oculi muscle. This study showed excellent improvement of infraorbital dark circles mainly due to these factors with autologous fat transplantation. In some of their patients with accompanying tear trough, the condition was also successfully corrected with autologous fat transplantation.

Ten patients were treated with autologous fat transplantation for infraorbital dark circles due to thin skin overlying the orbicularis oculi muscle. Donor sites of the fat, usually at the buttocks or lower abdomen, were tumesced using Klein's technique. After a 20-min period for vasoconstriction, fat was aspirated using a 10-mL Luer lock syringe and a blunt 14-gauge cannula. Aspirated fat was drained of the fluid component including the oil layer and blood on a lint-free autoclaved filter paper and the fatty tissue that includes the stromal cells was transferred to 1-mL syringes for injection with an 18-gauge cannula. Nerve or field blocks were done using 1% lidocaine with 1 : 100 000 adrenaline before the injection. The adit for the cannula was made with an 18G needle in the junction of the nasal ala with the cheek and small droplets of fat were injected under both eyes between the skin and the muscle layer. If the tear trough was prominent, some fat was injected above the infraorbital bony margin. A mean volume of 1–2 cm^3 of fat, depending on the amount of depression, was placed in each infraorbital area. Remaining fat was stored at 4 °C for 2 h, then slowly cooled down to −20 °C for 2 h followed by long-term storage at −70 °C. Patients were examined 1 week postoperatively and further injections were done at 3-month intervals using the frozen fat. At least one fat injection was done and the patients were evaluated at least 3 months from the last treatment.

Prey S, Paul C. Effect of folic or folinic acid supplementation on methotrexate-associated safety and efficacy in inflammatory disease: A systematic review. Br J Dermatol 2009;160:622-628.

Methotrexate is a folic acid antagonist widely used for the treatment of inflammatory disorders for more than 50 years. Methotrexate is a standard systemic therapy for severe psoriasis and rheumatoid arthritis. Folic acid supplementation has been advocated to limit the toxicity of methotrexate on blood cells, gastrointestinal tract and liver. However, there is still controversy regarding the usefulness of folic acid supplementation. The authors sought to assess the evidence for the efficacy of folic acid supplementation in patients treated with methotrexate for inflammatory diseases. They also investigated whether folic acid supplementation may decrease the efficacy of methotrexate. Cochrane and MEDLINE databases were systematically searched. Randomized controlled trials in patients treated with methotrexate for rheumatoid arthritis or psoriasis with or without arthritis were included. Study selection, assessment of methodological quality, data extraction and analysis were carried out by two independent researchers. They selected double-blind randomized placebo-controlled trials. Analysis was performed for each subgroup of side-effects: gastrointestinal, mucocutaneous, haematological and hepatic. Six randomized controlled trials met the inclusion criteria, with a total sample of 648 patients. There were 257 patients in the placebo group, 198 patients treated with folic acid, and 193 patients treated with folinic acid. The statistical analysis showed a significant reduction of 35·8% of hepatic side-effects induced by methotrexate for patients with supplementation with folic or folinic acid (95% confidence interval −0·467 to −0·248). There was no statistical difference for mucocutaneous and gastrointestinal side-effects although there was a trend in favour of supplementation. The effect of supplementation on haematological side-effects could not be assessed accurately due to a low incidence of these events in the population studied. They were

unable to analyse the effect of supplementation on the effectiveness of methotrexate, as markers of activity used in each study were not comparable. Finally concluded that supplementation with folic acid is an effective measure to reduce hepatic adverse effects associated with methotrexate treatment. There is no difference between folinic acid and folic acid, but the lower cost of the latter promotes its use.

Comment: This systematic review shows that folic or folinic acid supplementation significantly reduces the incidence of hepatic side-effects of methotrexate. There was no statistical difference for mucocutaneous and gastrointestinal side-effects. The effect on haematological side-effects could not be assessed accurately due to low incidence of these events in the population studied.

It is unclear whether folic or folinic acid supplementation is associated with a reduction of the efficacy of methotrexate. Some data suggest that patients receiving supplementation may need higher doses of methotrexate. Previous studies have shown that the anti-inflammatory effect of methotrexate, especially in psoriasis or rheumatoid arthritis, is not exclusively related to folate metabolism. Other mechanisms may be involved, such as the inhibition of aminoimidazole carboxamide ribonucleotide transformylase, which induces the accumulation of adenosine, a potent anti-inflammatory agent. The effect of supplementation on the risk of methotrexate long-term side-effects (i.e. liver fibrosis) has not been assessed. As liver fibrosis is associated with high cumulative exposure to methotrexate, the role of folic or folinic acid supplementation to prevent liver fibrosis deserves further study. This may be especially relevant for patients with psoriasis, who have a high risk of developing liver fibrosis in the presence of comorbidities such as diabetes, obesity and alcohol consumption.

There is a high level of uncertainty regarding the nature of supplementation and the dose. There is no evidence that folinic acid is more effective than folic acid although definite evidence is still lacking. The dose of folic/folinic acid supplementation to be used has not been prospectively defined. There was a high level of heterogeneity between trials, the dose varying from 5 to 27·5 mg of folic acid per week, and 1 to 5 mg of folinic acid per week. The trial of van Ede *et al*., which compared the efficacy of supplementation with folic acid 1 mg daily vs. folinic acid 2·5 mg weekly vs. placebo, did not show any significant difference between the two modalities of supplementation. Only one trial compared two doses of folic acid, and showed that a high dose of folic acid (27·5 mg weekly) was not more effective than a low dose of 5 mg weekly.

So authors conclude that low-dose folic supplementation is associated with a reduction of hepatic side-effects of methotrexate and therefore can be recommended in clinical practice. Under folic supplementation a higher dose of methotrexate may be required to obtain clinical efficacy in some patients.

Josefson A, Färm G, Magnuson A, Meding B. Nickel allergy as risk factor for hand eczema: A population-based study. Br J Dermatol 2009;160:828-834.

In population-based studies using self-reported nickel allergy, a hand eczema prevalence of 30–43% has been reported in individuals with nickel allergy. In a previous Swedish study, 958 schoolgirls were patch tested for nickel. In a questionnaire follow up 20 years later no association was found between nickel allergy and hand eczema. Here authors investigated further the relation between nickel allergy and hand eczema. Three hundred and sixty-nine women, still living in the same geographical area, now aged 30–40 years, were patch tested and clinically investigated regarding hand eczema. Patch testing showed 30·1% nickel-positive individuals. The adjusted prevalence proportion ratio (PPR) for hand eczema after age 15 years in relation to nickel patch test results was 1·03 (95% confidence interval, CI 0·71–1·50). A history of childhood eczema was reported by 35·9%, and the PPR for hand eczema in relation to childhood eczema was 3·68 (95% CI 2·45–5·54). When analysing the relation separately in women with and without a history of childhood eczema a statistical interaction was found. The hand eczema risk was doubled in nickel-positive women without a history of childhood eczema, with a PPR of 2·23 (95% CI 1·10–4·49) for hand eczema after age 15 years. Authors conclude that a doubled risk for hand eczema was found in nickel-positive women without a history of childhood eczema. When analysing all participants, there was no statistically significant difference between nickel-positive and nickel-negative women regarding occurrence of hand eczema. The most important risk factor for hand eczema was childhood eczema. The risk for hand eczema in nickel-positive women may previously have been overestimated.

Comment: A possible relation between nickel allergy

and hand eczema was investigated in the present study. In their previous questionnaire study, contact allergy to nickel in childhood did not seem to influence the occurrence of hand eczema later in life. In the present study the established cohort of women from the general population was re-tested for nickel allergy and clinically investigated for hand eczema. When analysing the total of 369 women, there was no statistically significant difference regarding hand eczema between nickel-positive and nickel-negative individuals. However, when analysing the results with regard to history of childhood eczema there was a doubled risk for hand eczema in nickel-positive individuals without a history of childhood eczema, while there was no increased risk for women with a history of childhood eczema. The same trend was found for all three hand eczema outcomes – hand eczema after 15 years of age, hand eczema in the past 12 months and 'current hand eczema'.

The most important risk factor for hand eczema seems to be a history of childhood eczema. In this study the PPR was 3·0–4·3. Also in the questionnaire study there was a tripled risk for hand eczema in women with a history of childhood eczema. This is in concordance with previous studies.

Authors found that a positive nickel test was associated with an increased risk for hand eczema only among women without a history of childhood eczema. Among women with a history of childhood eczema there was no such association. The fact that the PPRs for hand eczema are considerably higher for history of childhood eczema than for nickel allergy may have contributed to this observation.

Sunderkötter C, Herrgott I, Brückner C, Moinzadeh P, Pfeiffer C, Gerß§ J, *et al*. Comparison of patients with and without digital ulcers in systemic sclerosis: detection of possible risk factors. Br J Dermatol 2009; 160:835-843.

Digital ulcers (DU) are a major complication in the course of systemic sclerosis (SSc). In recent years, efficacious, but expensive therapies (e.g. iloprost, sildenafil, bosentan) have been shown to improve healing or to reduce the recurrence of DU. For optimal management it would be useful to identify the risk factors for DU. Such statistical analyses have been rare because they require a high number of patients. Authors aim was to identify potential risk factors for DU in patients with SSc. They used the registry of the German Network for Systemic Scleroderma and evaluated the data of 1881 patients included by August 2007. They assessed potential risk factors for DU by comparing patients with (24.1%) and without active DU at time of entry (75.9%). Multivariate analysis revealed that male sex, presence of pulmonary arterial hypertension (PAH), involvement of the oesophagus, diffuse skin sclerosis (only when PAH was present), anti-Scl70 antibodies, young age at onset of Raynaud's phenomenon (RP), and elevated erythrocyte sedimentation rate (ESR) significantly impacted on the appearance of DU. Certain combinations increased the patients' probability of presenting with DU, with the highest probability (88%) for male patients with early onset of RP, ESR > 30 mm h^{-1}, anti-Scl70 antibodies and PAH. Patients with DU developed RP, skin sclerosis and organ involvement approximately 2–3 years earlier than patients without DU. The results reveal possible risk factors for the occurrence of DU in SSc. As DU are prone to local complications, prophylactic vasoactive treatment for patients presenting with these factors may be justified.

Comment: Multivariate analysis of datasets from 1881 patients with SSc revealed that male sex, presence of PAH, involvement of the oesophagus, the extent of skin sclerosis as assessed by the modified Rodnan skin score (mRSS), anti-Scl70 antibodies (but not ACA), young age at onset of RP, and an elevated ESR represent significant risk factors for the occurrence of DU in SSc.

In the univariate analysis these factors and the presence of the diffuse form of SSc, lung fibrosis and involvement of the heart or upper gastrointestinal tract were significantly more frequent among patients with DU and resulted in an elevated relative risk for DU with an OR of 1·46 (involvement of upper gastrointestinal tract) or 1·85 (male sex) and 2·23 (presence of anti-Scl70 antibodies). A high total mRSS and mRSS of the hands, and young age at the onset of RP, skin sclerosis or organ involvement were also associated with DU.

The highest probability for DU in the course of the disease (probability of 88%) is given by the combination of male sex, an early onset of RP, an elevated ESR > 30 mm h^{-1}, anti-Scl70 antibodies and involvement of the pulmonary artery system or the oesophagus.

Their findings that patients with a limited form of

disease suffer less frequently from ulcers (22%) than patients with diffuse sclerosis (34%) is in contrast to most previous studies which reported a higher prevalence of DU in patients with the limited form of the disease. One recent study, however, also showed by univariate analysis (n = 3656) a higher frequency of severe digital vasculopathy among patients with diffuse SSc than among patients with limited SSc. Authors suggest that the higher occurrence of DU in diffuse SSc compared with limited SSc indicates that ulceration results not only from local impairment of blood flow (reflected by RP), but also from other pathological processes which in diffuse SSc, but not in limited SSc, contribute to more organ complications.

Cook-Norris RH, Zic JA, Boyd AS. Meyerson's naevus: A clinical and histopathological study of 11 cases. Australas J Dermatol 2008;49:191-195.

Authors undertook a clinical and histopathological analysis of patients presenting with Meyerson's naevi. Eleven patients with the characteristic histological features of a Meyerson's naevus were identified over a 5-year period. Diagnostic criteria included epidermal spongiosis and a dermal inflammatory infiltrate associated with a banal junctional or compound naevus. Cases were excluded if naevus cells showed moderate to severe atypia or regression. Patients were contacted by phone and interviewed regarding their lesions. The most common clinical appearance was a solitary, pruritic, erythematous eruption encircling a pre-existing pigmented naevus. The trunk and proximal upper extremities were preferentially affected. Only one clinician listed Meyerson's naevus in the clinical differential diagnosis. All cases demonstrated a pigmented junctional or compound naevus with epidermal spongiosis, parakeratosis and a perivascular lymphohistiocytic inflammatory infiltrate with scattered eosinophils. The inflammatory infiltrate consisted almost exclusively of CD3+ lymphocytes, the majority of which were CD4+. However, a substantial number were CD8+. In all patients, the lesions cleared with excision or spontaneously, without recurrence or progression to melanoma. The aetiology of this entity remains unclear and most clinicians are unlikely to be familiar with it.

Comment: Meyerson's naevus was first described in 1971 in two patients with pruritic, 'papulosquamous' eruptions around pre-existing pigmented naevi on the trunk and proximal extremities. Subsequent cases have been reported. These lesions present as an erythematous, scaly eruption encircling a pre-existing pigmented naevus. Depigmentation and involution of naevi are not associated features and progression to melanoma has not been reported. Meyerson's phenomenon consists of a similar reaction surrounding cutaneous neoplasms including keloids, arthropod assaults, seborrhoeic keratoses, basal cell and squamous cell carcinomas, and dermatofibromas.

Meyerson's naevi appear to be more common in adults, only rarely involving children. Prior reports have shown a male predominance, with a predilection for the summer months. Lesions typically arise on the trunk, the proximal extremities, and less commonly, the distal extremities. These naevi have been reported in association with atopy, coexistence with halo naevi after severe sunburn, progression to halo naevi and subsequent development of vitiligo.

Histopathology demonstrates a pigmented junctional or compound naevus without atypia or regression. The epidermis is variably spongiotic with occasional parakeratosis. The dermis contains a perivascular inflammatory infiltrate predominantly composed of $CD4^+$ lymphocytes with occasional eosinophils.

Meyerson's naevi are clinically and histologically distinct from the common halo naevus (Sutton's naevi, depigmented naevi). The eczematous halo does not show depigmentation, and is typically erythematous, scaly, and often pruritic. Meyerson's naevi reportedly lack the atypical melanocytes or significant numbers of CD8+ cells typically found in halo naevi, findings that are at odds with their results. However, this study was limited, as immunohistochemical staining was performed on a single specimen. The eczematous changes often resolve after several weeks or months without naevus involution. Topical corticosteroids speed resolution in most cases and are considered the treatment of choice. The dermatitis has also been reported to clear after excision of the central naevus. Recurrence has been commonly reported but was not seen in their patients.

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