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# Hormones and skin: A never ending love story!

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The human skin is a fascinating organ, representing both the site of production of a multitude of different hormones and an important target tissue for their pleiotropic biologic effects. Correlatives for many of the classical endocrine pathways, including parathyroid hormone related peptide-, thyroid hormone-, and vitamin D pathways have now also been found in the skin. The close but fragile relationship between skin and hormones reminds one sometimes on love stories, that in most cases start and may stay happy but that also may have unhappy periods of time. Similarly, the relationship of skin and hormones is perfect in a healthy person but may exert in many diseases deleterious effects on the skin. Some examples of important interactions in this never ending love story are presented by the papers published in this special issue. While several articles are focused on the relevance of the vitamin D endocrine system for skin physiology and human health, others deal with the close but damageable relationship of the skin with thyroid, pancreas, and other hormone-producing organs.

In the first paper, Dima A. Youssef et al.[1] discuss important antimicrobial implications of vitamin D. They explain that convincing evidence exists that vitamin D has a potential antimicrobial activity and its deficiency has deleterious effects on general well-being and longevity. The authors state that vitamin D may reduce the risk of infection through multiple mechanisms and that it boosts innate immunity by modulating production of anti-microbial peptides (AMPs) and cytokine response. Moreover, vitamin D and its analogues via these mechanisms are playing an increasing role in the management of atopic dermatitis, psoriasis, vitiligo, acne and rosacea. The authors explain that vitamin D may reduce susceptibility to infection in patients with atopic dermatitis and the ability to regulate local immune and inflammatory responses offers exciting potential for understanding and treating chronic inflammatory skin diseases. Moreover, B and T cell activation as well as boosting the activity of monocytes and macrophages also contribute to a potent systemic anti-microbial effect. The authors explain that the direct invasion by pathogenic organisms may be minimized at sites such as the respiratory tract by enhancing clearance of invading organisms. A vitamin D replete state appears to benefit most infections, with the possible noteworthy exception of Leishmaniasis. Antibiotics remain an expensive option, and misuse of these agents results in significant antibiotic resistance and contributes to escalating health care costs. The authors conclude that vitamin D constitutes an inexpensive prophylactic option and possibly therapeutic product either by itself or as a synergistic agent to traditional antimicrobial agents. In their review, the authors discuss the possible mechanisms by which vitamin D may have a therapeutic role in managing a variety of infections.

In the second article Pisit Pitukcheewanont et al.[2] take a look at the interaction of skin and pancreas. They report an interesting case with Scleroderma-like skin changes (early morphea-type skin changes of the trunk and extremities) not involving the hand in a prepubertal male with type I diabetes mellitus. The authors explain that, to their knowledge there have been no reports of scleroderma-like skin changes, not affecting the hand in prepubertal patients with type I diabetes mellitus.

In the following paper, Shwetha Thukuntla and Pratima Kumar[3] report on the effects of androgens on the skin. They present an interesting case with improvement of venous leg ulcers with androgen replacement therapy in a patient with undiagnosed Klinefelter syndrome.

In the fourth article, Fatme Al Anouti et al.[4] demonstrate and discuss their surprising findings on vitamin D deficiency and sun avoidance among university students at Abu Dhabi, United Arab Emirates. They convincingly show that vitamin D deficiency could be a major public health burden among young Emirati adults, mostly because of sun deprivation in a sun-blessed country. Their study included a random sample of 138 females and 70 males tested for serum 25-hydroxyvitamin D [25(OH)D] status. To further evaluate the predictors of vitamin D status in this population, the authors examined diet, obesity and sun exposure. In summer, the mean serum 25(OH)D concentration for females was 20.9 ± 14.9 nmol/L, whereas that for males was 27.3 ± 15.7 nmol/L. Females scored significantly higher than males on the sun avoidance inventory (SAI), indicating that females avoid sun exposure to a greater extent than males, possibly explaining the lower vitamin D status. Moreover, the authors reported that a significant negative correlation also existed between SAI and vitamin D status (Pearson's $r = -0.33$; $p < 0.01$), but no significant association was evident between vitamin D status and body mass index (Pearson's $r = 0.03$; $p = 0.33$) or low dietary intake of vitamin D-fortified foods (Pearson's $r = 0.08$; $p = 0.13$). The mean serum 25(OH)D concentration for females tested in winter was 31.3 ± 12.3 nmol/L while in the summer, it was 20.9 ± 14.9 nmol/L. This difference was statistically significant, suggesting that seasonal variation plays an important role in vitamin D status in the United Arab Emirates. The authors concluded that fortification of foods and drinks with vitamin D, supplementation and sensible sun exposure are important steps toward minimizing vitamin D deficiency.

In the following article, Jörg Dötsch[5] analyzes the association of low birth weight, bone metabolism and fracture risk. He

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explains that, as for other diseases of higher age, low birth weight was expected to be a risk factor for an altered bone metabolism and osteoporosis. However, he concludes that there is no consistent long term effect of low birth weight on bone mineral density or hip fracture risk later in life. He points out that, whether methodological weaknesses in the studies performed so far are causal or whether postnatal factors such as physical activity and nutrition are of higher importance can only be speculated upon at present.

In the next paper, Dianne E. Godar et al.[6] present their very interesting investigation of "Solar UV Doses of Adult Americans and Vitamin $D_3$ Production." They explain that sunlight contains UV radiation that affects human health in both detrimental (skin cancers) and beneficial (vitamin $D_3$) ways. An evaluation of the vitamin D status of adult Americans (22–40, 41–59, 60+ yrs) show many have deficient or insufficient serum levels of 25-hydroxyvitamin D, indicating they are not getting enough from sunlight or dietary sources. The authors point out that those findings are in conflict with calculated values that insist people make "ample" vitamin $D_3$ (≥1,000 IU/day) from their "casual" or everyday outdoor exposures. The authors investigated this situation using the outdoor UV doses of indoor-working adult Americans (~7,000) in the north (45°N) and south (35°N) to calculate how much vitamin $D_3$ they produce each season of the year with and without vacationing. To do vitamin $D_3$ calculations properly, the authors used action spectrum and geometric conversion factors, not previously incorporated into other calculations. They found that few indoor-working adults over 21 yrs meet their daily vitamin D needs from everyday outdoor exposures anytime during the year, including summer. Only a few "outdoorsy" Caucasians (22–60 yrs) can meet their vitamin $D_3$ needs (~2,000 IU/day) during the summer, but only if they do not wear sunscreens except on beach vacations. The authors conclude that most indoor-working adult Americans do not go outside enough to meet their vitamin $D_3$ needs all year. The authors further conclude that only some outdoor-working adults can make enough vitamin $D_3$ without using sunscreen but other adults cannot, even with a vacation during the summer. Indoor-working African Americans can never make enough vitamin $D_3$ during the year even with a three-week vacation.

The following two articles (refs. 7 and 8) deal with the relationship of skin and thyroid (hormones). Kristen Lo Sicco, Sean McGuire and Joseph C. English[7] present their interesting retrospective study of thyroid structural abnormalities in alopecia patients. They explain that thyroid dysfunction is classically associated with alopecia, however, studies focusing on manual thyroid examinations, with ultrasonography of palpable abnormalities, in alopecia patients are lacking. The authors now found that 20.2% (74/367) of manual thyroid exams performed were deemed abnormal and 78.8% (41/52) of patients who had an ultrasound had an abnormal finding. Twenty-two of the 74 patients did not obtain the requested ultrasound. Non-scarring alopecia was associated with 36 of 41 patients with abnormal ultrasounds (Telogen effluvium 29.3%, Androgenetic alopecia 27.8%, Alopecia areata 24.4%, and Traction alopecia 9.8%). The authors explain that no one specific structural abnormality was associated with a specific hair loss type and that, of note, 78% (32/41) of patients with an abnormal ultrasound exam had normal thyroid function tests and only 9/41 (22%) patients had both. The authors conclude that the manual examination of the thyroid in alopecia patients may identify additional thyroid abnormalities not detected with serologic evaluation alone. They further conclude that prospective studies are required to evaluate the necessity and significance of manual thyroid palpation and subsequent ultrasound studies in this patient population.

In the next article, Vicenzo Nuzzo et al.[8] report their single center experience on idiopathic chronic urticaria and thyroid autoimmunity. They explain that urticaria is one of the most frequent dermatosis, being its prevalence in general population estimated about 20%. Their prospective case-control study was aimed at determining the prevalence of thyroid autoimmune disorders in a cohort of patients with chronic urticaria (CU), all living within an area with mild-to-moderate iodine deficiency. Fifty-four consecutive patients affected by CU were recruited and compared to 108 healthy controls. Assessment of the thyroid function included measurement of serum concentrations of TSH, FT3, FT4, anti-thyreoglobulin (anti-TG) and anti-peroxidase (anti-TPO) antibodies. Ultrasound scan of the thyroid gland was performed in all subjects using a 7.5 MHz linear transducer. All subjects were followed up for 6 months. The authors explain that the prevalence of thyroid antibodies was significantly higher in our cohort of patients with CU than in controls (22% vs. 6.5%) and that Hashimoto's thyroiditis was also more frequent in patients than controls (18.5% vs. 1.8%). These frequencies do not differ from those previously reported by some other authors and confirm the association between CU and thyroid autoimmunity also in the area of iodine deficiency. However, the authors concluded that presence of antibodies or thyroiditis does not seem to influence clinical course of CU and that their results suggest that screening for thyroid function may be useful in all the patients with CU.

In the following article, Hedwig Stanisz et al.[9] report their very interesting in vitro investigation demonstrating reciprocal responses of fibroblasts and melanocytes to α-MSH depending on MC1R polymorphisms. They explain that the melanocortin 1-receptor (MC1R) exhibits several variants in form of single nucleotide polymorphisms (SNPs) which are known to differentially regulate melanocyte function. However, whether and how MC1R polymorphisms also affect fibroblast function, has not been investigated so far. The authors now measured intracellular cyclic adenosine monophosphate (cAMP) concentrations (cAMP-EIA) and cellular proliferation (CellTiter-Blue) upon stimulation with alpha-melanocyte stimulating hormone (α-MSH) in eight different human fibroblast and melanocyte cell lines with wild type and different MC1R SNPs. They found that fibroblasts, as well as melanocytes, show differences in MC1R function depending on the MC1R genotype. MC1R stimulation with α-MSH in wild type (MC1Rwt) melanocytes results in an increase of intracellular cAMP and cellular proliferation. In contrast, MC1Rwt fibroblasts react with a decrease of intracellular cAMP and proliferation. In MC1R polymorphic fibroblasts (R163Q, R151C and V60L) both effects are significantly alleviated. Similar, but inverse effects could be found in MC1R polymorphic melanocytes (R142H and V92M) with a significantly lower cAMP increase and proliferation rate

compared to MC1Rwt melanocytes. The authors concluded that the MC1R displays reciprocal growth responses in melanocytes and fibroblasts, depending on the MC1R genotype, and that thus, the MC1R seems to be not solely important for the skin pigmentary system, but also for the fibroblast function, and might influence different processes of the dermal compartment like wound healing, fibrosis and keloid formation.

Finally in the tenth paper, Ayuko Kikuzawa et al.[10] report the very interesting case of an Eccrine angiomatous hamartoma with sudden enlargement and pain in an adolescent girl after menarche.

In summary, the articles published in this issue demonstrate the close relationship of skin and hormones. They underline the fact, that the interaction of skin and hormones is perfect in a healthy person but may exert in many diseases deleterious effects on the skin. Some examples of this important interaction are presented by the papers published in this special issue. In summary, the articles published in this issue demonstrate impressively, again, the importance of dermato-endocrinology, not only for skin physiology and for a broad variety of common or rare skin diseases, but also for internal medicine and other medical disciplines.

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