ABSTRACTS OF THE JOINT INTERNATIONAL SYMPOSIA "VITAMIN D IN PREVENTION AND THERAPY" AND "BIOLOGIC EFFECTS OF LIGHT"

8-10 May, 2024

Schlossberg Hotel, Homburg/Saar, Germany

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OP No. 16
VITAMIN D AND CANCER: AN UPDATE

Jörg Bittenbring

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Much has been learnt since the observation in the 1940s that fewer deaths from internal cancers and more skin cancers occur in more rural and southern areas that are more exposed to sunlight. Retrospective analyses have found that mortality rates for colon cancer are lower at sunnier latitudes, and higher vitamin D levels in Women's Health Initiative participants have been shown to have a 50% lower risk of developing breast cancer. Randomized trials of vitamin D supplementation have so far failed to show an overall reduction in cancer incidence. It is discussed that these results were influenced by a too short follow-up period and unknown baseline vitamin D levels in all study participants. Patients with breast, prostate or colorectal cancer consistently have poorer survival rates when vitamin D serum levels are low at the time of diagnosis. General recommendations for vitamin D supplementation apply to cancer patients who are at higher risk of deficiency. There are still questions about vitamin D supplementation and its impact on cancer: Firstly, whether vitamin D can reduce cancer incidence by increasing intake or over a longer duration of supplementation. Secondly, whether vitamin D supplementation can improve cancer survival. Furthermore, if vitamin D supplementation proves beneficial, does it then affect the tumor cells directly or does it improve the immune system's ability to combat cancer. For example, chemotherapy for Hodgkins' disease is more effective when sufficient vitamin D levels are present. A recent meta-analysis suggests that although the overall effect is small, there is a trend indicating that daily supplementation for longer periods (>5 years) may be beneficial. A phase II study in colorectal cancer patients showed improved progression-free survival when vitamin D was supplemented. As cancer therapy improves, particularly with immunotherapies, vitamin D is an important player in improving the efficacy of therapeutic antibodies. Higher serum levels of vitamin D have been associated with improved outcomes in rituximab treatment of lymphoma or pembrolizumab treatment of melanoma, as well as seasonal variations in the prognosis of melanoma.

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OP No. 15
RANDOMIZED TRIALS ON THE EFFECTS OF VITAMIN D SUPPLEMENTATION ON MORTALITY AND CARDIOVASCULAR AND CANCER OUTCOMES: META-ANALYSES ACCORDING TO KEY DESIGN FEATURES

Youqing Wang, Tafirenyika Gwenzi, Ben Schöttker and Hermann Brenner

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Background/Aim: In a recent meta-analysis of 80 randomized controlled trials (RCTs) (1), vitamin D supplementation was associated with a significantly reduced risk of all-cause mortality (OR=0.95, 95%CI=0.91-0.99, p=0.013). An association close to statistical significance was also seen for a lower risk of non-cardiovascular mortality; however, supplementation was not statistically significantly associated with a lower risk of any cardiovascular morbidity or mortality outcome. Previous meta-analyses of RCTs have also shown a significantly reduced risk of total cancer mortality with daily use of vitamin D, but not with bolus supplementation (2). *Patients and Methods:* We updated the previous systematic reviews and conducted additional stratified meta-analyses according to key study characteristics, such as type of supplementation (regular versus bolus), initial vitamin D levels, and increase in vitamin D levels by supplementation. *Results:* A particularly strong reduction in all-cause mortality was found in the meta-analysis of 15 studies assessing the impact of daily vitamin D supplementation [relative risk of 0.93 (95%CI=0.87-0.99)], which led to a significant increase in serum vitamin D concentrations (standardized mean difference of serum 25(OH)D >0.8). Meta-analyses of studies employing bolus supplementation did not yield a beneficial effect in any of the assessed subgroups of trials. *Conclusion:* Daily vitamin D supplementation with doses that are sufficient to achieve a relevant increase in serum 25(OH)D levels is a particularly effective approach to reduce all-cause mortality.

1 Ruiz-García A, Pallarés-Carratalá V, Turégano-Yedro M, Torres F, Sapena V, Martin-Gorgojo A, Martin-Moreno JM: Vitamin D supplementation and its impact on mortality and cardiovascular outcomes: systematic review and meta-analysis of 80 randomized clinical trials. Nutrients 15: 1810, 2023. DOI: 10.3390/nu15081810

2 Keum N, Chen QY, Lee DH, Manson JE, Giovannucci E: Vitamin D supplementation and total cancer incidence and mortality by daily *vs*. infrequent large-bolus dosing strategies: a meta-analysis of randomised controlled trials. Br J Cancer 127: 872-878, 2022. DOI: 10.1038/s41416-022-01850-2

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OP No. 32
UV-INDUCED "DARK" CYCLOBUTANE PYRIMIDINE DIMERS: PERSPECTIVES ON FORMATION MECHANISMS AND PHOTOPROTECTION

George J. Delinasios

International Institute of Anticancer Research, Kapandriti, Greece

Cyclobutane pyrimidine dimers (CPDs) are ultraviolet radiation (UV)-induced carcinogenic DNA photoproducts that cause UV-signature mutations in melanoma. In addition to the formation of incident CPDs (iCPDs, formed during irradiation), CPD levels may increase post-UV, with maximal levels observed after 2-3 h. These lesions have been termed "dark CPD" (dCPD) (1). Recent studies have confirmed their presence both *in vitro* and *in vivo*. Although melanin carbonyls have a role in the formation of dCPD, they have also been observed in amelanotic systems, indicating the involvement of certain unknown processes. iCPD and dCPD seem to have different repair kinetics, and it is also unknown whether they have different biological properties. Interestingly, dCPD formation has been found to be prevented by certain antioxidants. This opens the road to a new era of post-solar photoprotection, with specialized skin care additives that are able to block CPD formation and subsequently prevent melanoma.

1 Lawrence KP, Delinasios GJ, Premi S, Young AR, Cooke MS: Perspectives on cyclobutane pyrimidine dimers—rise of the dark dimers. Photochem Photobiol 98: 609-616, 2022. DOI: 10.1111/php.13551

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OP No. 23
PHOTOSENSITIVITY OF ANTI-HYPERTENSION MEDICATION AND SKIN CANCER: HOW STRONG IS THE EVIDENCE?

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Background/Aim: Some anti-hypertensive medications have been associated with increased photosensitivity and even increased risks of non-melanoma skin cancers. However, most of the available evidence is based on observational studies and case reports. *Materials and Methods:* A literature search was performed to evaluate the evidence surrounding antihypertensives and their involvement in photosensitivity and carcinogenesis. *Results:* Preclinical and clinical data are conflicting. There might be an association of long-term hydrochlorothiazide treatment and the development of non-melanoma skin cancers, especially squamous cell carcinoma. The evidence is only based on observational data. Randomized controlled trials do not show an association between antihypertensives and increased risks of cancer. *Conclusion:* Some antihypertensives appear to be associated with increased photosensitivity and increased risks of skin cancer. Nevertheless, the evidence remains conflicting. Patients with increased risks for skin cancer should be informed about the associated risks and cautionary measures should be applied. Antihypertensives, should however, not be discontinued in fear of skin cancer, since hypertension remains the most common cause of death worldwide.

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OP No. 18
EFFECTS OF VITAMIN D SUPPLEMENTATION ON INFLAMMATORY RESPONSE IN PATIENTS WITH CANCER AND PRECANCEROUS LESIONS: SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED TRIALS

Tafirenyika Gwenzi, Anna Zhu, Petra Schrotz-King, Ben Schöttker, Michael Hoffmeister and Hermann Brenner

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Background/Aim: Inflammation is a hallmark of cancer. Vitamin D may suppress tumor progression by modulating the immune-inflammatory processes. This study aimed to assess the impact of vitamin D_3 supplementation (VDS) on serum biomarkers of inflammation in patients with cancer or pre-cancerous lesions, based on evidence from randomized controlled trials (RCTs). *Materials and Methods:* Cochrane, PubMed, and Web of Science databases until November 2022 were searched. We estimated the effects of VDS from pooled standardized mean differences (SMDs) with their 95% confidence intervals (CIs) for inflammatory biomarker levels between VDS and control groups at trial follow-up. *Results:* Meta-analysis of eight RCTs of patients with cancer or pre-cancerous conditions (n=592) showed that VDS significantly reduced serum tumor necrosis factor (TNF)-α (SMD=–1.65; 95%CI=–3.07 to –0.24). VDS also resulted in statistically non-significantly lower interleukin (IL)-6 (SMD=–0.83; 95%CI=–1.78 to 0.13) and C-reactive protein (CRP) (SMD=–0.09; 95%CI=–0.35 to 0.16), whereas IL-10 levels were unchanged (SMD=0.00; 95%CI=–0.50 to 0.49). *Conclusion:* There is evidence of a strong reduction in serum TNF-α levels through VDS in patients with cancer or

precancerous lesions. Meticulously planned future RCTs should validate the potential value of individualized VDS in suppressing tumor-associated inflammation, particularly in patients with hypovitaminosis D. Prospero registration number: CRD42022295694.

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OP No. 1
THE D-LIGHTFUL VITAMIN D: A 100+ YEARS HISTORICAL PERSPECTIVE AND NEW INSIGHTS FOR HOW THE FAT-SOLUBLE VITAMIN INTERACTS WITH BODY FAT

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[2]Area of Preventive Medicine and Public Health, Department of Preventive Medicine and Public Health, Food Sciences, Toxicology and Legal Medicine, School of Pharmacy, University de Valencia, Valencia, Spain;
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[4]Carbogen Amcis BV, Veenendaal, the Netherlands

Throughout evolution, sunlight exposure was essential for the evolutionary development of humans. The lack of sunlight exposure related to rickets was first appreciated by Sniadecki in 1822. 100 years later, it was demonstrated that cod liver oil and exposure to UVB radiation had similar effects in preventing rickets in rats. This led to the discovery of vitamin D and explained why ingesting cod liver oil or being exposed to UVB radiation from a mercury arc lamp or the sun had the same effect in preventing rickets. In the 1970s, it was appreciated that vitamin D requires sequential hydroxylations in the liver and kidneys before it could become active to regulate calcium and bone metabolism. One of the last frontiers in vitamin D research is to understand mechanisms involved in the storage and release of vitamin D from fat cells (adipocytes). To investigate how vitamin D interacts with lipid droplets in fat cells we conducted the studies evaluating how a fluorescent labeled vitamin D interacts with cultured primary adipocytes and lipid droplets.

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OP No. 14
WHAT IS THE OPTIMAL VITAMIN D STATUS FOR SKELETAL AND NONSKELETAL HEALTH OUTCOMES?

Michael F. Holick

Section of Endocrinology, Diabetes, Nutrition, Department of Medicine, Boston University Chobanian & Avedisian School of Medicine, Boston, MA, U.S.A.

It is well recognized that most tissues and cells in the body possess a vitamin D receptor (VDR) but also have the capacity to produce 1,25-dihydroxyvitamin D. The primary function of vitamin D is to maintain serum calcium and phosphorus concentrations in the normal range not only for a normal bone mineralization, but also for a wide variety of metabolic activities. The primary function of vitamin D is to increase intestinal calcium and phosphate absorption. Furthermore, there is an inverse relationship between serum 25-hydroxyvitamin D [25(OH)D] and parathyroid hormone (PTH). This inverse relationship plateaus when the serum 25(OH)D approaches 30 ng/ml. Osteomalacia, that was observed in deceased adults until the serum 25(OH)D reached at least 30 ng/ml, provides convincing evidence, along with the plateauing of PTH, that for maximum bone health, serum 25(OH)D levels should be at least 30 ng/ml. Numerous clinical studies have suggested that to benefit from the non-skeletal functions of vitamin D, the 25(OH)D levels should be at least 40 ng/ml. An evaluation of the dose-dependent effect of vitamin D on the immune system revealed that after taking either 600, 4,000, or 10,000 IUs daily for 6 months, gene expression was significantly influenced in a dose-dependent manner. Various clinical trials has revealed that maintaining a 25(OH)D level of at least 40 ng/ml reduces the risk of infection with COVID 19, decreases the morbidity and mortality associated with COVID 19, autoimmune disorders, and the progression from prediabetes to type 2 diabetes. Therefore, it is reasonable to maintain a circulating serum concentration of 25(OH)D of at least 40 ng/ml and up to 100 ng/ml (considered safe) to take advantage of all the skeletal and nonskeletal health benefits of vitamin D.

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OP No. 35
STANDARD OF CARE AND NOVEL APPROACHES FOR TREATING VITAMIN D DEFICIENCY: SUNLIGHT, SUPPLEMENTS AND A METABOLITE

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Section of Endocrinology, Department of Medicine, Boston University Chobanian & Avedisian School of Medicine, Boston, MA, U.S.A.

One hundred years ago, vitamin D was added to milk at a concentration of 100 IU per 8 ounces. In the 1940s, studies

suggested that to prevent overt rickets, infants/childs require 200 IU daily. As a result, for safety considerations, the recommended daily allowance for everyone was 400 IUs daily. This changed in 2010 When the Institute of Medicine recommended daily vitamin D intake for maximum bone health: 400 IU for infants and children, and 600 IU for adults. The Endocrine Society in 2011 recommended that infants up to 1 year of age, children, and adults require 400-1,000, 600-1,000, 1,500-2,000 IU, respectively, for maximum bone health. The Society also recognized that obese adults require between 2-3 times more. Furthermore, to treat vitamin D deficiency, infants required 50,000 IU weekly or 2000 IU daily for 6 weeks, while children and adults required 50,000 IU weekly for 8 weeks to correct vitamin D deficiency. To maintain vitamin D sufficiency in adults, it was recommended they take 50,000 IU every two weeks, which is equivalent of 3,300 IU daily. This maintained a 25(OH)D level of at least 30 ng/ml, which is necessary for maximum bone health. Both vitamin D_2 and vitamin D_3 are equally effective in maintaining total circulating 25(OH)D as well as 1,25-dihydroxyvitamin D levels. Patients with fat malabsorption syndromes and obese patients require larger doses of vitamin D, yet in many cases, these dosed are still ineffective. 25-hydroxyvitamin D_3 is more water-soluble than vitamin D_3. Clinical studies have shown that 25-hydroxyvitamin D_3 is absorbed directly into the portal system and therefore is much more bioavailable in normal, obese, and malabsorption patients. Sensible sun exposure and lamps that emit UVB radiation can also be effective in maintaining serum 25(OH)D concentrations.

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OP No. 5
SYNTHESIS OF DEUTERIUM-LABELLED VITAMIN D_3 AND D_2 FOR THEIR USE IN LC-MS/MS APPLICATIONS

Lars Kattner

Endotherm Life Science Molecules, Science Park 2, Saarbruecken, Germany

Background/Aim: Simultaneous assaying of various vitamin D metabolites in human tissue and biofluids by liquid chromatography-tandem mass spectrometry (LC-MS/MS) represents a new promising tool for the differentiated diagnosis of vitamin D-related diseases. Particularly, the concentration of vitamin D_3 and D_2 is of significant importance to be measured, since these hormones are stored in fat tissue and released into the serum for subsequent metabolization. For their use as calibration and reference standards, vitamin D_3 and D_2 have to be labelled with multiple deuterium atoms. Therefore, *de novo* synthesis of deuterium-labelled vitamin D_3 and D_2 has to be developed in a convergent synthetic approach. *Materials and Methods:* A new chemical synthesis of 6-fold labeled vitamin D_3 and D_2 for their use in LC-MS/MS applications was developed. *Results:* The products were obtained in good yield and high purity. *Conclusion:* The use of 6-fold deuterium labeled vitamin D_3 (Figure 1A) and D_2 (Figure 1B) enables advancements in LC-MS/MS applications towards the differentiated diagnosis of vitamin D-related diseases.

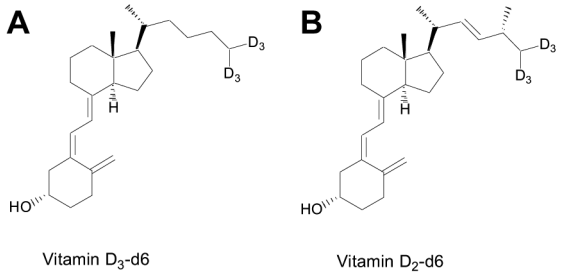

Figure 1. *Chemical structure of deuterium-labeled vitamin D_3-d6 (A) and vitamin D_2 -d6 (B).*

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OP No. 28
QUANTIFYING ULTRAVIOLET RADIATION EXPOSURE IN DANISH CHILDREN ATTENDING KINDERGARTEN

Catharina Margrethe Lerche, Rami Nabil Al-Chaer, Jakob Heydenreich, Peter Alshede Philipsen and Hans Christian Wulf

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Background/Aim: Discussion about the necessity of sunscreen usage in kindergartens often arise, yet there is a notable gap in knowledge regarding the extent of ultraviolet radiation (UVR) exposure in children, particularly those aged 3-6 years. This study aimed to quantify the UVR exposure in Danish children aged 3-6 years on a typical summer day, differentiating between clear-sky and lightly overcast conditions, utilizing personal UVR dosimeters. *Patients and Methods:* Participants included children from two distinct types of kindergartens – a traditional Danish kindergarten with a playground (n=20) and an outdoor kindergarten where children spend the entire day in a forest setting (n=17). Personal wristborne dosimeters were worn by the children, and their clothing coverage was recorded between 9-11 am, 11 am-1 pm, and 1-3 pm. *Results:* On a clear summer day, children from the outdoor kindergarten received 2.3 standard

erythema dose (SED) (range=0.8-3.6), constituting 7.3% of ambient UVR. This was significantly higher than the 1.0 SED (0.4-1.8) received by children from the traditional kindergarten (3.4% of ambient), p=0.0000016. Also, on lightly overcast days, the outdoor kindergarten children received significantly more UVR (1.4 SED, 0.6-2.1, 5.7% of ambient) compared to traditional kindergarten children (0.9 SED, 0.2-1.6, 3.9% of ambient), p=0.0065. Notably, the outdoor kindergarten children wore significantly more clothing than the children in the traditional kindergarten. *Conclusion:* Children in both types of kindergartens receive relatively high doses of UVR in localized areas. This highlights the importance of sunscreen application during kindergarten hours.

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OP No. 32
UV-INDUCED SKIN CANCER: NEW INSIGHTS FROM ANIMAL MODELS

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[2]Department of Dermatology, Private Hospital Molholm, Vejle, Denmark;
[3]Department of Dermatology, Aalborg University Hospital, Aalborg, Denmark

Background/Aim: Ultraviolet radiation (UVR) poses a significant risk for keratinocyte carcinoma, necessitating innovative photoprotective approaches. *Materials and Methods:* This study investigated oral supplementation with various compounds, including hesperidin methyl chalcone, phloroglucinol, syringic acid, quercetin, fisetin, rutin, bucillamine, carvedilol, metformin, and phenformin, to evaluate their efficacy in mitigating UVR-induced photocarcinogenesis in hairless mice. *Results:* Notably, phloroglucinol and syringic acid, along with nicotinamide, demonstrated delayed tumor onset, while quercetin and fisetin exacerbated photocarcinogenesis. Additionally, drug repurposing with bucillamine, carvedilol, metformin, and phenformin did not significantly affect tumor development. Further exploration involved combining nicotinamide with metformin or phloroglucinol, and revealed that nicotinamide combined with phloroglucinol exhibited comparable photoprotective effects to nicotinamide alone, emphasizing potential synergies. *Conclusion:* This study underscores the complex interplay of different compounds in influencing UVR-induced carcinogenesis and highlights avenues for enhancing photoprotection through strategic combinations.

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OP No. 20
VITAMIN D AND STILLBIRTH

Pelle G. Lindqvist

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Background/Aim: Two retrospective studies of prospective cohorts showed doubled odds of birth asphyxia among women with low plasma vitamin D levels and one reported a 4-fold increase in the odds of stillbirth. It was not known if this was caused by low sun exposure or by vitamin D per se. *Patients and Methods:* The stillbirth rate, including all pregnancies in Finland and Sweden between 1994 to 2021 (n>4 million), was analysed. Due to 50% of the population having low plasma vitamin D, Finland implemented an extensive National Vitamin D fortification program in 2003, which was doubled in 2009 due to an insufficient effect. After 2009, only 10% had low vitamin D levels. Stillbirth rates were compared using cross-tabulation with 95% confidence intervals. *Results:* Stillbirth rate decreased from 4.1‰ before 2003 to 3.2‰ to 2.8‰ after 2009. Meanwhile, the Swedish stillbirth rate remained constant at 3.9‰ untill 2018 when the Finish fortification was implemented in Sweden. Thereafter, it decreased to 3.2‰. All results had p<0.001. *Conclusion:* In our large study of National vitamin D fortification, improved vitamin D status was associated with a lower stillbirth rate in a dose-dependent manner.

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OP No. 27
SUN EXPOSURE AND TYPE 2 DIABETES, AN ENLIGHTED PATH TOWARDS CAUSALITY

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Background/Aim: An inverse association between type 2 diabetes mellitus (T2DM) and vitamin D levels exist. Since there is scarcity of large population-based human data, we conducted a reanalysis of our data from the large Melanoma in Southern Sweden (MISS) cohort. Additionally, we reviewed the major steps from observational findings towards causality regarding the above relationship. *Patients and Methods:* The MISS cohort comprises one thousand women from each age group between 25 and 64 without cancer drawn from the Southern Swedish population registry in 1990. At the inception of the study, 74% answered a written inquiry (n=29,518) and provided detailed information on their

sun exposure habits and other variables. At the 11-year follow-up, there were answers from 23,962 participants. We analysed the data with logistic regression analysis with T2DM as the dependent variable and sun exposure, age, BMI, education, parity, smoking, and exercise as independent variables. *Results:* There was a dose-dependent inverse relationship between sun exposure and incidental T2DM. Compared to those with the greatest sun exposure habits, those with moderate and low sun exposure were at 40% and 140% higher odds of T2DM during the follow up (OR=1.4, 95%CI=1.2-1.8, and OR=2.4, 95%CI=1.8-3.3, respectively). In addition, lean women had the greatest reduction in T2DM with increasing sun exposure with ORs of 1.9 and 3.7. Compared to those with strenuous exercise, women with moderate and low exercise habits had ORs of 1.6 and 2.1, respectively. *Conclusion:* We show a dose-dependent inverse association between sun exposure and T2DM. In addition, we identify four important steps towards causality.

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OP No. 8
VITAMIN D AND RESPIRATORY TRACT INFECTIONS

Jakob Linseisen

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Background/Aim: There is accumulating evidence that vitamin D may beneficially affect several extra-skeletal diseases, including respiratory tract infections. The present work aimed to update the findings of an umbrella review published in 2019. *Materials and Methods:* We identified published systematic reviews (SRs) and meta-analyses (MAs) of cohort studies and randomized controlled trials (RCTs) on the impact of vitamin D on acute respiratory tract infections (ARI). Also, the available evidence on vitamin D status or supplementation of vitamin D and the risk of SARS-CoV-2 infections and the severity of COVID-19 was summarized. New SRs and MAs published between 2019 and 2023 were searched in PubMed and Cochrane reviews library. *Results:* Observational data on primary prevention suggest an inverse association between vitamin D status and the risk of ARI in adults. SRs of RCTs support the observational findings in the case of ARI in adults but did not clearly show an effect on the course of the infection. In children, studies do not clearly support a beneficial effect of vitamin D supplementation on ARI susceptibility. Concerning the susceptibility of SARS-CoV-2 infection, there is hardly any influence of the vitamin D status. However, a better vitamin D status or supplementation with vitamin D seems to be inversely associated with the severity of COVID-19. These effects were largely restricted to patients with deficient or insufficient vitamin D status. *Conclusion:* At least in adults, beneficial effects of a sufficient vitamin D status on the risk and severity of ARI and COVID-19 underpin the public health relevance of combatting insufficient vitamin D status. Best effects were seen with regular low-dose oral vitamin D supplements.

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OP No. 6
VITAMIN D ANALOGS: LESSONS LEARNED FROM A CENTURY OF CHEMICAL RESEARCH AND STRUCTURAL INSIGHTS

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One century ago, vitamin D_3 (colecalciferol) was discovered. Since then, more than 1,778 vitamin D receptor (VDR)-ligands have been published (1). Among them, 60 structures were selected according to their outstanding biological properties. In recent decades, structure-function relationships have been determined to support the chemical modifications of the secosteroid structure of vitamin D hormone, specifically 1α,25-dihydroxyvitamina D_3 or calcitriol. VDR-ligand interactions can be agonistic or antagonistic. We will discuss their interaction with VDR by molecular docking, and demonstrating how these calculations are useful for understanding the biological properties of the compounds. Unfortunately, calcemic activities cannot be evaluated, but based on the synthetic efforts made, there are some structural hints that may yield compounds with a low calcemic index.

1 Maestro MA, Seoane S: The centennial collection of VDR ligands: metabolites, analogs, hybrids and non-secosteroidal ligands. Nutrients 14: 4927, 2022. DOI: 10.3390/nu14224927

16
OP No. 10
VITAMIN D AND CARDIO-VASCULAR HEALTH

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The potential impact of vitamin D on the risk of cardiovascular disease (CVD) has been extensively examined for two decades. Observational data indicate a strong non-linear association between vitamin D and CVD, with the highest CVD risk observed at severe vitamin D deficiency. Preclinical data and randomized controlled trials (RCTs) show beneficial effects of vitamin D on surrogate parameters of vascular and cardiac function. However, Mendelian randomization studies and large RCTs in the general population and in patients with chronic kidney disease generally report no significant effect of vitamin D supplementation on the risk of CVD. An emerging approach to assess individual vitamin D status includes consideration of the metabolite $24,25(OH)_2D$, which is low in "functional" vitamin D deficiency. In the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, $24,25(OH)_2$ vitamin D was associated with high parathyroid hormone levels, accelerated bone metabolism, and high all-cause mortality, irrespective of 25(OH) vitamin D concentrations. In conclusion, there is currently no strong evidence for beneficial vitamin D effects on CVD risk, neither in the general population nor in high-risk groups. Whether subgroups such as individuals with severe vitamin D deficiency, functional vitamin D deficiency or a combination of low vitamin D with specific gene variants and/or certain nutrition/lifestyle factors would benefit from vitamin D (metabolite) administration remains to be studied.

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OP No. 30
MANAGEMENT OF PHOTODERMATOSES

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Background/Aim: Photodermatoses are a group of skin diseases that result from an abnormal response to sunlight, especially its ultraviolet component. They are divided into phototoxic and photoallergic reactions triggered by known photosensitizers and idiopathic photodermatoses, where the exact pathomechanism remains unclear. Their diagnosis can be challenging due to overlapping symptoms and confusing terminology. While some types are extremely rare, such as hydroa vacciniforme (prevalence 0.34 per 100,000), others, such as polymorphic light eruption (prevalence 10% to 20%), are very common. *Materials and Methods:* Management of photodermatoses begins with clinical recognition of characteristic lesions localized predominantly to light-exposed areas of the skin. Detailed history-taking, phototesting and photopatch testing are required to establish a correct diagnosis, especially if patients present during disease-free intervals. *Results/Conclusion:* Although photodermatoses are not life-threatening, they can significantly diminish quality of life. Therefore, preventative care holds as much significance as treatment.

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OP No. 24
NEW ACTION SPECTRA FOR VITAMIN D FORMATION AND DNA DAMAGE IN HUMAN SKIN FOR RISK-BENEFIT ESTIMATION

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Background/Aim: Ultraviolet (UV) radiation on human skin causes DNA damage, most commonly cyclobutane pyrimidine dimers (CPDs), while also facilitating the beneficial effect of vitamin D_3 synthesis. The biological effects after UV exposure depend on wavelength and can be described by weighting functions known as action spectra. So far, these action spectra are derived from separate studies and exposure regimes. This study aimed to accurately quantify the CPD and vitamin D_3 action spectra obtained under identical exposure regimes. *Materials and Methods:* We obtained excess waistband skin after surgical removal from two individuals. From each person's skin tissue, 82 biopsies were prepared: Two non-irradiated controls and 80 irradiated with one of 10 UV-LEDs with wavelengths from 280 to 335 nm. For each wavelength, four doses with linear increments were given. Quantification of CPDs in the skin was conducted using HPLC-MS/MS. Quantification of vitamin D_3 was performed by UHPLC-MS/MS. For each wavelength, a linear dose response was calculated, and the regression slopes are presented as action spectra. *Results:* Both action spectra exhibited maximal peaks at 290 nm with a decrease towards higher wavelengths. From 295 to 310 nm, the normalized action spectra of vitamin D_3 were 1.4 to 1.7 times higher than the CPD action spectra. Below 290 nm and above 310 nm the CPD action spectra were 1.3-10 times higher. *Conclusion:* There is a window from 295 to 310 nm where vitamin D_3 production is relatively higher than CPD production.

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OP No. 34
DETECTION OF CUTANEOUS MALIGNANT MELANOMA USING TAPE STRIP-DERIVED RNA

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Background/Aim: Distinguishing cutaneous malignant melanoma (CMM) from nevi can be challenging. Therefore, suspicious lesions are often excised, leading to the removal of many benign lesions in order to identify a single CMM. The use of tape strip-derived ribonucleic acid (RNA) to separate CMM from nevi has been proposed (1) and we have published a study protocol to test the method in a real-life hospital setting (2). This study aimed to validate whether RNA profiles can be used to distinguish CMM in clinically suspicious lesions. *Materials and Methods:* Lesions clinically assessed as CMM were tape stripped just before surgical excision (n=200). Subsequently, RNA on the tape strips was analyzed using quantitative realtime polymerase chain reaction with TaqMan technology for the expression levels of 11 genes. RNA levels were normalized to the housekeeping gene RPL18. Based on these measurements, we developed a rule-out test for CMM. *Results:* Histopathology revealed 73 CMMs and 127 non-CMMs. A high proportion of CMM could resulted from inclusion during the COVID-19 shutdown. Based on the RNA levels of two oncogenes, PRAME and KIT, our test correctly identified all CMMs with 100% sensitivity. The test also included patient age and sample storage time. Our test demonstrated 32% specificity and correctly excluded 41 non-CMM lesions (3). *Conclusion:* The tape stripped derived RNA can detect CMM and reduce the removal of benign lesions by 32% without overlooking any CMMs.

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OP No. 21
GUIDELINES FOR PREVENTING AND TREATING VITAMIN D DEFICIENCY: AN UPDATE

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Background/Aim: Health authority guidelines for vitamin D intake are mainly focused on its role in skeletal health. The general framework of these guidelines is to first establish target serum 25-Hydroxyvitamin D (25(OH)D) concentrations that meet the vitamin D requirements, and then to calculate the vitamin D doses that are needed to achieve these 25(OH)D ranges, particularly during periods of minimal to no sunlight-induced vitamin D synthesis (*i.e.*, during winter), assuming other nutrient intakes are adequate. *Materials and Methods:* This is a narrative review on vitamin D guidelines and their recent updates as well as clinical studies that may have an impact on future clinical practices related to vitamin D. *Results:* Vitamin D guidelines are heterogeneous and frequently suffer from significant limitations and low quality. Recent findings that may have an impact on future vitamin D guidelines include: (a) significant safety data on vitamin D, (b) observations revealing substantial interindividual variability in the dose response curve of vitamin D intake and serum 25(OH)D, particularly high vitamin D requirements in certain populations depending on ethnicity and/or region, and (c) promising data on some extra-skeletal health benefits of vitamin D. *Conclusion:* Vitamin D guidelines remain inconsistent regarding dosing recommendations. However, in view of recently published guidelines and accumulating data on the safety and efficacy of vitamin D, recommendations for vitamin D treatment with doses ranging from 800 to 2,000 international units (20 to 50 μg) seem to be reasonable.

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OP No. 9
EVIDENCE BASED MEDICINE: HOW IS IT APPLIED IN THE FIELD OF VITAMIN D *VERSUS* COVID-19

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Background/Aim: The coronavirus disease 2019 (COVID-19) pandemic was a global challenge for health-care systems and science as it required rapid public health

actions to minimize the disease burden. Numerous measures against COVID-19 have been applied with an enormous impact on our society, thus requiring a critical appraisal of their justification with regard to the principles of evidence-based medicine. As a comparator, we evaluated the evidence levels and the measures against vitamin D deficiency in order to investigate whether the principles of evidence-based medicine are consistently followed regardless of the underlying disease or treatment. *Materials and Methods:* This is a narrative review adhering to the scale for the quality assessment of narrative review articles (SANRA) recommendations. Evidence on main measures against COVID-19 and against vitamin D deficiency were reviewed and compared in terms of the respective evidence levels that were used to justify or deny public health actions concerning these two pandemics. *Results:* For several measures against COVID-19, in particular masking mandates, certain drugs against COVID-19, and repeated vaccine boosters, we observed a low or even contradicting evidence level for their implementation in clinical practice. Despite partially higher evidence levels for certain measures against vitamin D deficiency, the respective public health actions and implementations were significantly less as compared to COVID-19. *Conclusion:* Certain measures against COVID-19 were not sufficiently justified when following evidence-based medicine, as applied for vitamin D. This requires a critical review and public discussion in order to improve decision-making processes for future global health challenges.

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OP No. 7
DEVELOPMENT OF SELECTIVE VDR MODULATORS

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The activities of 1,25-dihydroxyvitamin D ($1,25D_3$), and its analogues are mediated through the nuclear vitamin D receptor (VDR), a ligand-regulated transcription factor. VDR ligands have been extensively investigated as anticancer agents. Based on the exploitation of the structural knowledge about VDR-ligand interactions, we have developed novel safer and disease-tailored selective analogs. In addition, we have recently identified a family of molecules that normalize VDR activity and are selective drug candidates for the treatment of hypercalcemia or hypercalciuria associated with high vitamin D levels, characteristic of several rare and refractory disorders. Novel VDR antagonists and small molecules that inhibit receptor-coactivator interactions will be discussed.

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OP No. 17
UMBRELLA REVIEW ON BREAST, COLORECTAL, PANCREATIC, PROSTATE, AND LUNG CANCER INCIDENCE AND MORTALITY AND VITAMIN D

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Background/Aim: Cancer is a major public health problem in western societies, with several mechanisms linking cancer to vitamin D. The beneficial influence of vitamin D on cancer has been discussed; however, recent reviews on the extra-skeletal effects of vitamin D have not extensively explored its connection to cancer. *Materials and Methods:* An umbrella review (PROSPERO: CRD42021244758) was conducted to provide an overview of systematic reviews examining the relationship between vitamin D and the incidence and mortality of five of the most important cancers. Forty-one systematic reviews were included (breast n=14, colorectal n=15, pancreatic n=3, prostate n=11, lung n=10), comprising 280 individual studies. *Results:* With the exception of the incidence of prostate cancer, no harmful associations were found between higher 25(OH)D levels or vitamin D intake and cancer. For the other cancers, there were mostly inverse associations with 25(OH)D levels and risk. The associations between vitamin D intake and incidence of the five cancers were less conclusive. Mostly inverse associations between 25(OH)D levels and mortality were observed. Associations between mortality and vitamin D intake were again less conclusive (no data available for pancreatic and lung cancer). *Conclusion:* There is an inverse correlation between circulating vitamin D and cancer risk and stronger evidence for an inverse correlation between mortality and vitamin D levels for most of the studied cancers. Data for vitamin D intake are less conclusive. As most reviews analysed observational studies, conclusions on causality can not be made; however, sufficient 25(OH)D levels might have a protective effect against cancer. Therefore, it seems important to conduct further studies on the topic of vitamin D and cancer to elucidate its role more definitively.

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OP No. 13
ASSOCIATION OF 25-HYDROXYVITAMIN D STATUS AND VITAMIN D SUPPLEMENTATION USE WITH MORTALITY DUE TO 18 FREQUENT CANCER TYPES

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Background/Aim: While there is accumulative evidence to support the association of serum 25-hydroxyvitamin D (25(OH)D) levels and vitamin D supplement use with total cancer mortality, the available evidence on the association of 25(OH)D with mortality from distinct cancer sites mainly focuses on the most common cancers. Moreover, real-world evidence on vitamin D supplement use is still constrained by limitations in sample size and the comprehensive adjustment of pertinent confounding variables. *Patients and Methods:* This study used cause-specific Cox regression models, adjusted for 48 covariates, to investigate the association of vitamin D deficiency, insufficiency, and vitamin D supplement use with total cancer mortality and 18 cancer site-specific mortality using the UK Biobank cohort. *Results:* Of the included 411,436 participants, 4.1% and 20.3% regularly took vitamin D or multivitamin supplements, respectively. The majority of participants were either vitamin D deficient (21.1%) or insufficient (34.4%). Over a median follow-up of 12.7 years, a substantial difference in the strength of the association of 25(OH)D levels and vitamin D supplement use with mortality across 18 specific cancer sites was observed. Vitamin D deficiency was significantly associated with increased mortality from total cancer and four specific cancers, *i.e.*, stomach, colorectal, lung, and prostate cancers. Vitamin D insufficiency was associated with increased colorectal and lung cancer mortality. In comparison to non-users, vitamin D supplement intake was observed to be associated with decreased total cancer and lung cancer mortality. *Conclusion:* Vitamin D deficiency and insufficiency were associated with multiple cancer site-specific cause of death. The potential of vitamin D supplement use for sustaining a sufficient 25(OH)D status was suggested as a viable measure to reduce lung cancer mortality. Clinical trials involving individuals with deficient 25(OH)D levels are required to assess this hypothesis.

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OP No. 11

ASSOCIATIONS OF VITAMIN D DEFICIENCY AND BIOMARKERS OF SYSTEMIC INFLAMMATORY RESPONSE WITH ALL-CAUSE AND CAUSE-SPECIFIC MORTALITY

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Background/Aim: The association between vitamin D deficiency and mortality is well-known; however, it remains unclear whether this association could be explained by the immune-modulating effects of vitamin D, which might provide protection against a systemic inflammatory response (SIR) leading to adverse health outcomes. Therefore, this study aimed to explore the associations of vitamin D deficiency and biomarkers of SIR with mortality. *Materials and Methods:* This study used logistic regression with adjustments for 51 covariates to examine the association between vitamin D deficiency and nine SIR biomarkers in 397,737 participants, aged 37-73 years, from the UK Biobank cohort. Cox regression and mediation analysis were further employed to assess the associations of biomarkers of SIR and vitamin D deficiency with mortality. *Results:* Vitamin D deficiency was associated with unfavorable levels of all the six blood cell count-based biomarkers. After adjusting for weight data, the associations with the three C-reactive protein (CRP)-based biomarkers were not statistically significant. Both vitamin D deficiency and SIR biomarkers were significantly associated with all-cause mortality and cause-specific mortality. The strength of the associations remained unchanged when vitamin D deficiency and SIR biomarkers were simultaneously tested together in the same model. Mediation analysis further supported the findings. *Conclusion:* Vitamin D deficiency is associated with unfavorable levels of blood cell count-based SIR biomarkers, but not CRP-based biomarkers. Both vitamin D deficiency and systemic inflammation were independently and strongly associated with the mortality outcomes and there is a lack of evidence supporting the hypothesis that systemic inflammation mediates the associations between vitamin D deficiency and mortality. Exploring clinical interventions targeting both vitamin D deficiency and the underlying causes of systemic inflammation holds potential significance.

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OP No. 4

GENOMIC EFFECTS OF NEW BIOLOGICALLY ACTIVE VITAMIN D AND LUMISTEROL METABOLITES: PRESENT CONCEPTS AND FUTURE OUTLOOK

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Recent findings have challenged the current dogma that vitamin D_3 is solely activated through sequential hydroxylation at C25 and C1α to produce 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$], which predominantly

acts by activating vitamin D receptor (VDR)-mediated pathways. We have discovered alternative pathways of vitamin D_3 activation initiated by CYP11A1, which in combination with other CYPs, generate at least 16 novel biologically active hydroxyderivatives. Also, lumisterol can be activated by CYP11A1 and CYP27A1 to biologically active hydroxyderivatives. These metabolites can exert their phenotypic effects locally or at the systemic level through interactions with different nuclear receptors. Vitamin D_3 hydroxyderivatives with an hydroxyl at C1α show increased selectivity toward the VDR. The derivatives without C1α(OH) act predominantly on alternative nuclear receptors, functioning as inverse agonists on the retinoid-related orphan receptors (ROR)α and γ or as agonists on the aryl hydrocarbon receptor (AhR), liver X receptors (LXR)α and β, and peroxisome proliferator-activated receptor gamma (PPARγ). They show lower selectivity for the VDR. The activation of the alternative nuclear receptors is defined by the number and position of the hydroxyl groups in the secosteroidal side chain. In addition, tachysterol and lumisterol derivatives can act on RORα and γ, AhR, LXRα and β or PPARγ. While tachysterol compunds can act on the genomic site of VDR, lumisterol hydroxyderivatives lack such capability. However, they can interact with the non-genomic binding site of the VDR, as per molecular modeling. Since these compounds are biologically active, their local interaction with specific receptors determines their final phenotypic effects. The challenging question is defining the ligand-dependent interactions between these diverse receptors.

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OP No. 22
NEW PERSPECTIVES ON THE ROLE OF NOVEL SECOSTEROIDS IN UV RADIATION-INDUCED SKIN CANCERS

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Exposure of the skin to ultraviolet radiation (UVR) generates genetic mutations and oxidative stress leading to cancer formation, including squamous and basal cell carcinomas (SCC and BCC), the most common malignancies in humans, and melanoma, the most deadly skin tumor. UVB also induces production of vitamin D_3 in the skin, which can be locally activated to classical 1,25$(OH)_2D_3$). In addition, at least 16 hydroxyderivatives of vitamin D_3 can be produced in the skin through alternative pathways initiated by CYP11A1. These hydroxyderivatives of vitamin D_3 can induce photoprotective pathways against DNA damage and oxidative stress. These actions can inhibit UVR-induced carcinogenesis. Furthermore, vitamin D_3 hydroxyderivatives can induce the keratinocyte differentiation program, inhibit proliferation of malignant keratinocytes and melanocytes, and exert anti-inflammatory activities. These properties indicate that while UVB can induce skin cancer, it also leads to local production of secosteroidal compounds that can inhibit tumor initiation, promotion, and progression. Vitamin D_3 hydroxyderivatives exert their phenotypic effects through interaction with the vitamin D receptor (VDR), considered as a tumor suppressor gene, and a number of other nuclear receptors. The selectivity to such receptors is defined by the chemical structure of each secosteroid. Furthermore, vitamin D_3 hydroxyderivatives without C1α(OH) are non-calcemic and act predominantly on alternative nuclear receptors to the VDR. Recently discovered hydroxyderivatives of lumisterol have shown radioprotective, anti-oxidative, antiproliferative, and anticancer effects. Thus, a variety of steroidal molecules produced in the skin secondary to UVB exposure can induce photoprotective mechanisms against UVR and show anticancerogenic activities. These molecules can have chemopreventive utilities against skin cancer.

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OP No. 29
REGULATION OF THE CENTRAL NEUROENDOCRINE AND IMMUNE SYSTEM BY ULTRAVIOLET RADIATION: IMPLICATIONS FOR THE REGULATION OF HOMEOSTASIS

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The ultraviolet spectrum of solar radiation reaching the surface of Earth (UVR: γ=290-400 nm) is widely recognised for its damaging effects on the skin, eye, and other exposed anatomical structures. However, there are also positive effects of UVR, examplified by UVB (γ=290-315 nm) induced transformation of 7-dehydrocholesterol to vitamin D through enzymatic activation, leading to further phenotypic consequences. This includes the production of not only classical 1,25$(OH)_2D_3$, but also of at least 16 novel biologically active hydroxyderivatives of D_3 and of several hydroxyderivatives of lumisterol and tachysterol with full or shorthened side chains. These derivatives can exert their

phenotypic effects locally or at systemic levels through interactions with different nuclear receptors. Aside from initiation of the above diverse secosteroidal signaling cascades affecting body functions, UVR can also stimulate cutaneous production of classical neurohormones, including CRH and CRH-related peptides, POMC derived ACTH, β-endorphin and MSH peptides, enkephalins, hormonally active cytokines, glucocorticoids, precursors to biogenic amines, and other bioactive molecules including ci-UCA, PAF, tryptophan derivatives, indolic or kynuric melatonin metabolites and finally NO and NO^- as examples. These molecules, either alone or in coordination, can regulate local homoeostasis and skin functions or have systemic affects after entry into the circulation or local activation of sensory nerves, which are then transmitted to the brain and other coordinating centers. Based on the existing experimental and epidemiologic data, a Yin-Yan role for UVR is proposed, which in a wavelength-dependent fashion, activates precise cutaneous neuroimmunoendocrine responses processed to the brain, endocrine, and immune system to regulate functions of internal organs and consequently body homeostasis with beneficial health effects. These effects occur in addition to UVR-induced skin pathology.

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OP No. 3
VITAMIN D AND INFLAMMATION

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Changes in vitamin D levels have been associated with inflammatory diseases, such as rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, asthma or multiple sclerosis (MS). It has become clear that vitamin D, *via* its active metabolite 1,25(OH)2D3 and its vitamin D receptor, stimulates the innate immune system and alleviates the responses of the adaptive immune system. Due to its regulatory functions within the immune system, vitamin D also affects inflammatory processes associated with immune reactions. Transcriptome- and genome-wide analyses have indicated that vitamin D signaling modulates many inflammatory responses on various levels. This includes (i) the modulation of the expression of genes that code for pro-inflammatory mediators, such as cyclooxygenases or 5-lipoxygenase, (ii) the regulation of the expression of antimicrobial peptides as part of the innate immune system, (iii) the interplay with other transcription factors such as NF-κB, which is involved in the regulation of inflammatory gene expression, and (iv) the activation of signaling cascades that are responsible for inflammatory reactions, *e.g.*, MAP kinases. Vitamin D targets immune cells, such as dendritic cells (DCs), monocytes/macrophages, and B-and T cells, as well as various other tissues and cell types, leading to vitamin D receptor-mediated individual responses of each cell type. One hallmark of these vitamin D effects is the cell-type dependent regulation of genes that trigger inflammatory processes, such as the 5-lipoxygenase pathway, as well as the interaction between vitamin D signaling and other pro- and anti-inflammatory signaling cascades.

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OP No. 37
CURRENT STATUS OF UV-BASED PHOTOTHERAPIES IN THE MANAGEMENT OF SKIN DISEASES - THE TIMES THEY ARE A-CHANGIN'

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Currently employed UV-based phototherapies in dermatology mainly comprise narrowband UVB (NB UVB) phototherapy, UVA1 phototherapy, and photochemotherapy (psoralen + UVA, PUVA). NB UVB is the most frequently used type of phototherapy and involves a relatively narrow waveband in the UVB range between 310-315 nm. NB UVB is effective for a wide range of dermatological disorders, such as psoriasis, eczema, vitiligo, lichen planus, chronic urticaria or cutaneous T-cell lymphoma. UVA1 phototherapy (340-400 nm) was promoted in the 1990s as a promising therapeutic concept for the management of patients with atopic dermatitis. Whereas it has not met the expectations in atopic dermatitis, UVA1 has subsequently been shown to be highly effective in the treatment of sclerosing skin disorders for which it has become one of the therapeutic mainstays. Finally, photochemotherapy was a therapeutic breakthrough in the early 1970s when studies demonstrated its high efficacy in psoriasis. However, since photochemotherapy involves the administration of a photosensitizer in combination with UVA irradiation, it is a more complex procedure with more short-term and long-term side effects and has therefore become a second-line treatment. With the upcoming of new systemic drugs since the early 2000s, therapeutic approaches have steadily changed. Biologic therapies were developed and licensed for psoriasis and other UV-responsive diseases and dermatology is recently flooded with an increasing number of Janus kinase inhibitors and other novel treatments that are likewise used for dermatological conditions, which traditionally had been candidates for UV treatment. Against the background of a rapidly transforming therapeutic landscape, the role of phototherapies in dermatology is profoundly challenged and likely to lose some of its former importance in the future.

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OP No. 12
HOW TO CONCLUDE THAT HYPERCALCEMIA IS CAUSED BY VITAMIN D TOXICITY

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Background/Aim: Hypercalcemia is the hallmark of vitamin D toxicity, but by definition, hypercalcemia exists in 2.5% of any healthy population. The challenge is to know whether a high vitamin D is causal or coincidental with hypercalcemia. This study aimed to determine the threshold above which serum 25-hydroxyvitamin D [25(OH)D] increases the risk of hypercalcemia. *Patients and Methods:* In this cross-sectional, observational study, 4,701 adults were grouped according to 50 nmol/l increments in serum 25(OH)D and compared for risk of hypercalcemia and serum calcium. Subjects had either consumed vitamin D_3 on their own, or were provided with vitamin D_3 in amounts higher than 4,000 IU/d. The occurrence of hypercalcemia [*i.e.*, albumin-corrected serum calcium >2.55 mmol/l (>10.20 mg/dl)], and mean serum calcium were compared across seven progressively higher groupings of serum 25(OH)D. The reference group comprised individuals with 25(OH)D levels between 50-100 nmol/l, as targeted by the recommended dietary allowance for vitamin D. *Results:* Risk of hypercalcemia differed among the groups (Chi-Square p=0.0001). Compared to the reference group (n=2,094), of whom 3.4% had hypercalcemia as per laboratory reference range, the risk of hypercalcemia was significantly higher only in the group with serum 25(OH)D >300 nmol/l (>120 ng/ml) (n=29), where 17.2% had hypercalcemia (multiple-comparison-adjusted p=0.001 *versus* reference). Serum calcium differed among the 25(OH)D groupings (ANOVA p=0.001): compared to the reference group with a mean calcium level of 2.37 (SD 0.11) mmol/l, those with 25(OH)D <50 nmol/l (n=941) had lower calcium levels at 2.35 (SD 0.12) mmol/l (multiple comparison-adjusted p=0.00016), whereas those with 25(OH)D >300 nmol/l (n=29) had higher calcium levels at 2.45 (SD 0.17) mmol/l (p=0.001*). Conclusion:* Most cases of hypercalcemia are not attributable to vitamin D. However, if the serum 25(OH)D exceeds 300 nmol/l – a threshold much lower than that inferred by the Institute of Medicine (IOM) – then vitamin D toxicity is the probable cause. Incrementally lower serum calcium coinciding with 25(OH)D <50.1 nmol/l may impair bone mineralization.

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OP No. 26
HOW TO GIVE THE GENERAL PUBLIC SIMPLE, USEFUL ADVICE ABOUT SUN EXPOSURE, TO MAXIMIZE THE BENEFITS AND MINIMIZE THE RISKS

Reinhold Vieth and Participation of all conference attendees

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Background: In 1992, Holloway proposed the risk-focused "shadow rule" *i.e.*, Avoid sun if your shadow is shorter than your height. Many people want their serum 25(OH)D levels to be higher than 75 nmol/l. Is there a safe way to deliver that level through sunshine? The following online tool may help answer the question: https://fastrt.nilu.no/VitD_quartMED.html
For discussion:
1. Should sun exposure be advised at all?
2. If the solar elevation angle is less than 45 degrees (long shadow), should the public be advised that there is no harm from cancer, but only benefit due to vitamin D and endorphins?
3. Is the shadow rule reliable enough to serve as the basis for any advice at all?
4. Is a daily vitamin D intake of 25 mcg truly enough to replace sun exposure?
5. What advice should be given to people who want their serum 25(OH)D higher than 75 nmol/l?" (for context, to ensure >75 nmol/l for everyone, a daily vitamin D intake of 100 mcg or 4,000 IU is needed for all).
Conclusion: Until now, health-policy makers advised the public to avoid sunshine and to consume "recommended" daily intakes of vitamin D. Surely, this advice is irresponsible when epidemiological evidence consistently relates sun exposure to better overall health and lower mortality.

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OP No. 25
SUN EXPOSURE AND SUN PROTECTION

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Background/Aim: Sun exposure is the main reason for skin cancer development, calling for knowledge of sun exposure habits and a need for proper sun protection. This study aimed to investigate sun exposure habits of the (Danish) population and provide understanding of protecting measures to avoid sunburn. *Patients and Methods:* The Standard Erythema

Dose (SED) is the ultraviolet radiation (UVR) dose required to provoke erythema in an individual highly sensitive to UVR. The average Caucasian can tolerate 3-4 SED before developing a sunburn. Measurements by SunSavers are used to determine UVR exposure of the population, and studies on sunscreen use and its effectiveness have been performed. *Results:* The average Dane receives a total of about 200 SED a year (range is very wide, between 20-1000 SED). The cumulative daily dose in summer in Northern Europe is up to 36 SED, whereas at the Equator, it can be about 65 SED. The effectiveness of sunscreen highly depends on layer thickness and experiments have been performed to establish this relationship. A person tolerating 4 SED would need a sun protection factor of 36/4=9 to avoid sunburn if outdoors all day during the summer in Denmark. Thus, a sunscreen of SPF 9 is necessary, provided it is used correctly. This means applying 2 mg/cm^2 of sunscreen (approximately 35-40 g in total) to the skin. As only a third to a fourth of this amount of sunscreen is typically applied in real life, we recommend two subsequent applications of sunscreen in the morning before going outdoors, with a 15-minute interval between applications, to enhance layer thickness. Under these circumstances, a sunscreen labeled SPF 50 will provide a SPF 9 in real life, and even with the double-application method, 10% of the skin surface may remain without any sunscreen coverage at all. *Conclusion:* Better sunscreen practices and a reduction in UVR exposure are needed to avoid sunburn and reduce the long-term risk of skin cancer.

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OP No. 31
SIMPLIFYING TECHNOLOGIES FOR PHOTOTESTING

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Background/Aim: Some people react abnormally to ultraviolet radiation (UVR). To determine the dose eliciting just perceptible erythema, a minimal erythema dose (MED) test is performed. The test results are compared to those of normally sensitive individuals with the same complexion. The MED test is followed by a photoprovocation test performed over 3-5 days to diagnose abnormal skin reactions such as polymorphic light eruption, solar urticaria, or chronic actinic dermatitis). This study aimed to develop equipment that simplifies the testing procedure. *Materials and Methods:* The MED test is typically performed by manually covering of test spots at various time intervals, which is quite time-consuming for the staff. Therefore, new technologies are being developed. *Results:* We have developed a MED Test Patch folio with six density filters giving about 20% decremental doses in one session. Light sources to fit directly to the size of a MED Test Patch have been developed, consisting of a Solar Simulator and LED light sources with maximum emission at 309 nm, 370 nm, and 415 nm. Using the light sources without the Test Patch will expose a skin area of 4×6 cm, used in the photoprovocation test. As the light sources fit directly to the Test Patch, the surrounding skin does not need to be covered. All systems are now used daily as part of routine practice. *Conclusion:* New technologies for easier MED and photoprovocation testing have been developed (1).

1 Wulf HC, Heydenreich J, Philipsen PA: Equipment developed for simplifying routine phototesting in dermatology. Photochem Photobiol Sci 22(12): 2907-2917, 2023. DOI: 10.1007/s43630-023-00494-2

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OP No. 35
PHOTODYNAMIC THERAPY WITHOUT SIDE EFFECTS

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Background/Aim: Photodynamic therapy (PDT) is used in the treatment of sun-induced actinic keratoses (AK). The original treatment modality consists of superficial curettage, application of 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL), and occlusion for 3 hours, followed by illumination with red LED 37 J/cm^2. This treatment is associated with unpleasant and painful pretreatment (curettage), severe pain during illumination, and a long wait in the clinic. This study aimed to counteract the unpleasant side effects and simplify the procedure. *Materials and Methods:* To address the side effects and simplify the treatment we proposed to: (i) reduce pre-treatment pain, bleeding, and oozing by omitting curettage (of particular concern in patients treated with anticoagulants); (ii): shorten the MAL incubation time from 3 h to 30 min (pulse PDT) to minimize pain and risk of post-treatment inflammation; (iii): use topical corticosteroids combined with different PDT modalities to further reduce inflammation without loss of effect. Long illumination time, as in daylight PDT, should be used. *Results:* The effect of these steps has totally removed pretreatment oozing/bleeding and pain, reduced pain during illumination from a 7 to <2 (scale 0-10), and reduced inflammation by two thirds. The treatment efficacy was not changed. *Conclusion:* PDT is now a convenient and agreeable treatment modality for patients with AK.

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OP No. 19
FUNCTIONAL ASSESSMENT OF VITAMIN D STATUS BY A NOVEL METABOLIC APPROACH: THE LOW VITAMIN D PROFILE CONCEPT

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Background/Aim: Determining 25-hydroxyvitamin D [25(OH)D], 24,25-dihydroxyvitamin D [24,25$(OH)_2$D] and the vitamin D metabolite ratio (VMR) allows the characterization of a functional vitamin D deficiency that is based on the concept of relatively low 24,25$(OH)_2$D concentrations. We evaluated whether such an approach provides additional diagnostic information compared to serum 25(OH)D alone, when relating the respective vitamin D status classifications to bone metabolism and mortality. *Patients and Methods:* We investigated 4,466 individuals derived from two independent cohort studies, DESIRE (n=2010) and LURIC (n=2456). Vitamin D deficiency based on serum 25(OH)D below 50 nmol/l was further stratified by the presence or absence of functional vitamin D deficiency that was classified when 24,25$(OH)_2$D was below 3 nmol/l and the VMR was below 4%. Parathyroid hormone (PTH) bone turnover markers were measured in both cohorts, whereas mortality was exclusively recorded in LURIC patients over a median follow-up of 9.9 years. *Results:* Serum 25(OH)D deficiency with <50 nmol/l was present in 483 (24.0%) and 1,701 (69.3%) participants of DESIRE and LURIC. However, only 77 (3.8%) and 521 (21.2%) participants were identified as having functional vitamin D deficiency with the combined measurement of 25(OH) and 24,25$(OH)_2$D. Affected patients were characterized by significantly accelerated bone metabolism and markedly higher all-cause mortality, regardless of the serum 25(OH)D concentration. In contrast, bone turnover and mortality were equally low in individuals with serum 25(OH)D concentrations ≥50 nmol/l and those with functional vitamin D sufficiency. *Conclusion:* The simultaneous measurement of 25(OH) and 24,25$(OH)_2$D allows a personalized assessment of the patients' vitamin D status that is based on metabolic principles. This approach substantially improves the identification of individuals with vitamin D deficiency that is metabolically relevant and harbours an increased risk of mortality.

Poster presentations (PP)

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PP No. 1
ASSOCIATION BETWEEN VITAMIN D STATUS AND MELANOMA RISK AND PROGNOSIS: META-ANALYSES AND SYSTEMATIC REVIEW

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Background/Aim: Solar UV radiation represents the most important environmental risk factor for skin cancer. On the other hand, UV-B-induced cutaneous vitamin D synthesis exerts anti-carcinogenic (anti-proliferative, anti-angiogenic and pro-apoptotic) effects on melanocytes and keratinocytes *in vitro*. This anti-tumor effect has been reported to be mediated not only by the vitamin D receptor (VDR), which has been described as a tumor suppressor in the skin, but also by other nuclear receptors. As melanoma is the deadliest skin cancer and its incidence is on the rise, identifying potential risk and prognostic factors is of high importance. This study aimed to assess the relevance of the vitamin D status for melanoma risk and prognosis. *Materials and Methods:* A systematic review and meta-analyses were conducted according to PRISMA guidelines, using Databases Medline (*via* PubMed) and ISI (Web of Science), until December 31st, 2022. Study quality and risk of bias were evaluated by applying the "Newcastle Ottawa scale" and level of evidence was assessed based on the recommendations of the "Oxford Center for Evidence-based Medicine". Standardized mean differences (SMD) and odds ratios (OR) with 95% confidence intervals (95%CI) were derived from random-effects meta-analyses to account for possible heterogeneity across studies. Moderator analyses to investigate systematic differences in the effect sizes and subgroup analyses were performed. Nine different meta-analyses were carried out, assessing association

(OR and SMD) of vitamin D status [25(OH)D serum concentration] with melanoma risk and various prognostic factors (Breslow thickness, mitotic rate, tumor stage, and ulceration status). *Results:* A total of 26 studies were eligible for inclusion. Significantly lower mean serum 25(OH)D levels were found when comparing melanoma patients with healthy controls [SMD=–0.40 (–0.74; –0.06)]. There was a non-significant trend for an increased melanoma risk in patients with vitamin D deficiency [OR=1.79 (0.95; 3.37)], comparing study participants with ≤20 *vs*. >20 ng/ml 25(OH)D serum levels. Due to significant heterogeneity across studies and no indicative funnel plot and Egger's test, subgroup analyses were carried out. Interestingly, restricting the geographic region to southern European studies resulted in significant results [SMD=–1.02 (*p*-value <0.0001); OR=1.62 (*p*-value=0.002)] comparing melanoma risk in study participants with ≤20 *vs*. >20 ng/ml 25(OH)D serum levels. Funnel plots and Egger's tests were all negative. In terms of prognosis, low serum 25(OH)D serum levels were associated in melanoma patients with higher Breslow thickness [SMD=–0.14 (–0.22; –0.07, comparing >1 mm *vs*. ≤1 mm)]. Low mean 25(OH)D serum levels were significantly associated with the presence of mitoses [SMD=–0.30 (–0.57; –0.02, comparing mitoses present *vs*. absent)] and with ulcerated primary tumors [SMD=–0.20 (–0.30; –0.11, comparing ulceration present *vs*. absent)], and were not significantly associated with higher tumor stage [SMD=–0.33 (–0.69; 0.03, comparing highest *vs*. lowest tumor stage)]. We observed significantly increased risks for thicker tumors [OR=1.85 (1.23; 2.8)], for mitotic tumors [OR=2.02 (1.21; 3.36)], and for higher tumor stage [OR=1.54 (1.01; 2.38)], in vitamin D deficient patients [comparing patients with ≤20 *vs*. >20 ng/ml 25(OH)D serum levels]. Among the studies analyzing melanoma prognosis, the heterogeneity tests and tests for Funnel Plot Asymmetry were negative, except for heterogeneity tests for the analyses on tumor stage and mitotic status and mean serum levels. *Conclusion:* Our meta-analyses show an association of vitamin D status with melanoma risk and prognosis, adding to the constantly growing body of evidence supporting a tumor-protective role of vitamin D. These findings need to be considered when developing recommendations for skin cancer prevention.

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PP No. 2
IMPACT OF ORAL VITAMIN D SUPPLEMENTATION ON SERUM 25-HYDROXYVITAMIN D LEVELS IN EUROPE IN HEALTHY ADULTS: META-ANALYSIS AND SYSTEMATIC REVIEW

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Background/Aim: To generate reliable data that enable health authorities to re-evaluate recommendations for oral vitamin-D uptake, we performed a meta-analysis to determine the impact of supplementation on vitamin D status [25-hydroxyvitamin-D (25(OH)D) serum levels] in healthy adults in Europe. *Materials and Methods:* From publications detected (n=4,005) in our literature search (PUBMED, through January 02,2022), 49 primary clinical studies [7,320 subjects, 73 study arms, median duration of intervention 136.78 days (range=7-1,088 days); mean weighted baseline 25(OH)D-concentration and mean age were 33.01 *vs*. 33.84 nmol/l and 46.8 *vs*. 44.8 years in vitamin-D and placebo groups, respectively] fulfilled the criteria for inclusion in our meta-analysis. *Results:* Applying random-effects models, 25(OH)D-serum levels were increased by 36.28 nmol/l (95%CI=31.97-40.59) in the vitamin-D supplement group compared to the placebo group, with a relative serum increment of 1.77 nmol/l per 2.5 μg vitamin-D daily. The relative 25(OH)D-serum increment was dependent on various factors, including dosage and baseline 25(OH)D-serum concentration, decreasing with increasing dosage of vitamin D and with increasing baseline serum levels. We estimate that supplementation of all healthy adults in Europe with appr. 25 μg vitamin D (1,000 IU) daily would raise 25(OH)D-serum levels in 95% of the population to the target of ≥50 nmol/l. *Conclusion:* Our work provides health authorities in Europe with reliable data that help to re-define recommendations for oral vitamin-D uptake.

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PP No. 3
DIFFERENTIAL REGULATION OF CIRCADIAN CLOCK GENES (CCGS) BY UV-B RADIATION AND 1,25-DIHYDROXYVITAMIN D IN HUMAN EPIDERMAL KERATINOCYTES: A PILOT STUDY DURING DIFFERENT STAGES OF SKIN PHOTOCARCINOGENESIS

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Background/Aim: Accumulating evidence indicates that our body`s time-keeping system, known as the circadian clock (CC), exerts many new and important physiological and pathophysiological functions. It has been shown that the CC not only controls our sleep-awake rhythm, but also modulates many other cellular processes in peripheral tissues, including carcinogenesis. Interestingly, it has been reported that ultraviolet B radiation (UV-B), representing the most important environmental risk factor for photocarcinogenesis of skin cancer, regulates in many cell types the expression of genes that control the CC (CCGs). Moreover, it has been demonstrated that these CCGs, in turn, modulate susceptibility for UV-B-induced cellular damage. It was the aim of this laboratory investigation to gain further insights into the CCs' putative role for UV-B-induced photocarcinogenesis of skin cancer. *Materials and Methods:* Using real-time PCR, we analyzed the expression of two core CCGs [brain and muscle ARNT-like 1 (Bmal1) and Period-2 (Per2)] at several time points (0-60 h) in HaCaT cells that were treated with and without 1,25-dihydroxyvitamin D (D_3) and/or UV-B. Then, we conducted a cosinor analysis to evaluate the effect of these conditions on the expression of these CCGs and an extended mixed-effects linear modeling to account for both fixed effects of experimental conditions and random inter-individual variability. Next, we investigated the expression of these two CCGs in keratinocytes representing different stages of skin photocarcinogenesis, comparing normal (normal human epidermal keratinocytes – NHEK; p53 wild type), pre-cancerous (HaCaT keratinocytes; mutated p53 status) and malignant (Squamous Cell Carcinoma cells, SCL-1; p53 null status) keratinocytes that were cultured for 12 h under the same conditions. *Results:* We demonstrate that in HaCaT cells, expression of Bmal1 reveals a robust circadian rhythm, whereas the evidence for such a circadian rhythm of Per2 expression was limited. Overall expression of both genes, but markedly for Bmal1, was increased following UV-B-treatment, whereas overall expression of Per2 was suppressed following treatment with D_3. Both UVB and $1,25(OH)_2D_3$ induced a significant phase-shift for expression of Bmal1 ($p<0.05$ for Acrophase), while no specific effect on amplitude of Bmal1 expression was detected. When we compared different treatment modalities (UV-B and/or D_3) or cell types (NHEK, HaCaT and SCL-1 cells), differential effects on expression of BMAL1 and Per2 were found. *Conclusion:* Comparing epidermal keratinocytes representing different stages of skin photocarcinogenesis, we provide evidence for a time-keeping system in human skin, which is regulated by UV-B and disturbed during skin photocarcinogenesis. Our finding, that this pattern of circadian rhythm was differentially altered by treatment with UV-B, as compared to treatment with D_3, does not support the hypothesis that the expression of these CCGs may be regulated *via* UV-B-induced synthesis of vitamin D. However, it remains to be investigated whether photoprotective properties of vitamin D are at least in part modulated *via* regulation of the CC.

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PP No. 4

A CRITICAL REVIEW OF KEY DESIGN FEATURES OF RANDOMIZED CONTROLLED TRIALS ASSESSING THE IMPACT OF VITAMIN D SUPPLEMENTATION ON MORTALITY

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Background/Aim: Observational epidemiological studies have rather consistently found a strong inverse curvilinear relationship between vitamin D status and mortality, with strongly increased mortality among pople with vitamin deficiency and essentially a null association among people with normal range vitamin D levels. Randomized controlled trials (RCTs) on the effects of vitamin D supplementation on mortality have yielded inconsistent results, with many trials reporting null results. *Materials and Methods:* In a systematic literature review, we critically reviewed design features of RCTs on the effects of vitamin D supplementation on mortality, such as sample size, baseline and follow-up vitamin D levels, vitamin D doses and mode of supplementation, and length of implementation and follow-up. *Results:* There was great heterogeneity in key design features. The vast majority of trials had other primary endpoints and were clearly underpowered for detecting a potential impact on mortality. Only a fraction of studies measured and reported baseline and follow-up vitamin D levels. In many of the studies reporting such levels, only a minority of participants had vitamin D deficiency at baseline, and increases in vitamin D levels by supplementation were generally modest. A large proportion of studies applied single or intermittent bolus supplementation rather than regular supplementation of physiological doses. *Conclusion:* There is a large heterogeneity in RCTs reporting on the effects of vitamin D supplementation on mortality, with the majority of studies having design features that appear inappropriate for evaluating supplementation effects on mortality that could plausibly be expected from epidemiological evidence.

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