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REVIEW ARTICLE

Impact of ultraviolet radiation on cardiovascular and metabolic disorders: The role of nitric oxide and vitamin D

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Abstract

Background/Purpose: Ultraviolet (UV) radiation has both harmful and beneficial effects on human skin and health. It causes skin damage, aging, and cancer; however, it is also a primary source of vitamin D. Additionally, UV radiation can impact energy metabolism and has protective effects on several cardiovascular and metabolic disorders in mice and humans. However, the mechanisms of UV protection against these diseases have not been clearly identified.

Methods: This review summarizes the systemic effects of UV radiation on hypertension and several metabolic diseases such as obesity, diabetes, and nonalcoholic fatty liver disease (NAFLD) in mice, and we also consider the mechanisms of action of the related regulators nitric oxide (NO) and vitamin D.

Results: UV exposure can lower blood pressure and prevent the development of cardiovascular diseases and metabolic disorders, such as metabolic syndrome, obesity, and type 2 diabetes, primarily through mechanisms that depend on UV-induced NO. UV radiation may also effectively delay the onset of type 1 diabetes through mechanisms that rely on UV-induced vitamin D. UV-induced NO and vitamin D play roles in preventing and slowing the progression of NAFLD.

Conclusion: UV exposure is a promising nonpharmacological intervention for cardiovascular and metabolic disorders. NO and vitamin D may play a crucial role in mediating these effects. However, further investigations are required to elucidate the exact mechanisms and determine the optimal dosage and exposure duration of UV radiation.

KEYWORDS
hypertension, metabolic disorders, nitric oxide, ultraviolet, vitamin D

1 | INTRODUCTION

Sunshine is an essential environmental variable that is inextricably linked to daily life. Depending on the wavelength, sunlight reaching the Earth's surface can be separated into three types of radiation: visible, ultraviolet, and infrared. Although Ultraviolet (UV) light can be divided into UVA (315–400 nm), UVB (280–315 nm), and UVC (100–280 nm), all UVC and the majority of UVB are absorbed by the stratospheric ozone layer, resulting in more than 95% UVA.[1] Furthermore, the UVB/UVA ratio is not constant because the UVB intensity varies with latitude, season, and time of day. Because longer wavelengths penetrate deeper than shorter ones, UVA radiation

reaches the dermis, whereas UVB radiation primarily penetrates the epidermis and rarely enters the dermis.[2] Given that radiation energy and wavelength are inversely proportional, UVB radiation has more energy than UVA radiation. The distinctions between UVA and UVB lead to different types of skin damage. UVA induces oxidative damage to DNA and accelerates skin aging with a loss of collagen fibers in the dermis, whereas UVB increases the risk of skin carcinogenesis in the epidermis.[3] Furthermore, based on the duration, the impact of UV radiation on the skin can be classified as acute or chronic. Tanning (increased melanogenesis), immunosuppression, and sunburn (erythema) are acute UV radiation reactions, whereas photoaging, immunosuppression, and skin cancer are chronic effects.[1] In addition to the aforementioned harmful consequences, sun exposure could induce the production of NO and vitamin D from the skin, which seem to be helpful for preventing various chronic diseases.[4–6] Notably, sun exposure protects against high blood pressure, cardiovascular diseases, and metabolic disorders, and insufficient sun exposure increases the risk of these diseases.

Nitric oxide (NO), an endogenous vasodilator, is produced by the vascular endothelium[7] when one of the three nitric oxide synthase (NOS) enzymes in the NOS family reacts with L-arginine.[8] NO-related compounds, such as nitrate, nitrite, and S-nitrosothiols (RSNOs) are major forms of NO storage,[9,10] and large quantities of nitrogen oxides, primarily nitrates, are stored in the skin.[11] Significant amounts of NO derivatives are released when the skin is exposed to UVA radiation, making NO available for promoting biological activities, including vasodilation.[12] Conversely, UVB has been reported to mediate NO production via inflammatory mediators that upregulate iNOS activity in human skin endothelial cells, through a molecular mechanism distinct from UVA-mediated induction.[13] Physiological NO levels regulate mammalian energy metabolism.[14] The modulation of NO-mediated pathways with L-arginine supplementation has been shown to prevent metabolic disorders.[15–17]

Vitamin D synthesis is widely recognized to be associated with UV exposure. The skin produces over 80% of vitamin D with UVR of a specific low wavelength, 290–315 nm (UVB), while the remaining 20% is obtained through food.[18] 7-Dehydrocholesterol (7-DHC) stored in the epidermis is converted by UVB into provitamin D, which, with heat, is transformed into vitamin D. Vitamin D synthesized in the skin is then transported to the liver, where it is converted to the first hydroxylated form, 25-hydroxyvitamin D (25(OH)D), along with vitamin D absorbed from food through the small intestine.[19] Serum 25(OH)D is subsequently hydroxylated into the bioactive form 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D_3$), which binds to the vitamin D receptor (VDR) to perform its function.[19] VDR is present in almost all cell types,[20] suggesting that each tissue in the body may be influenced by vitamin D. The most recognized function of vitamin D is maintaining calcium-phosphorus homeostasis and bone metabolism.[21] Numerous studies have found links between vitamin D deficiency and various chronic diseases.[22–24]

This mini review highlights how UV radiation affects energy metabolism with cardiovascular and metabolic diseases and the underlying mechanisms associated with skin-derived vitamin D and NO.

2 | HYPERTENSION AND CARDIOVASCULAR DISEASES

Hypertension is a significant risk factor for cardiovascular and cerebrovascular disorders (CVDs). The prevalence of hypertension and CVD increases with latitude[25] and is higher in winter than in summer.[26] However, UV radiation intensity diminishes during winter and with increasing latitude. An increasing body of research indicates that exposure to sunlight protects against high blood pressure and cardiovascular diseases.[27] Insufficient sun exposure also increases the risk of heart diseases.[5] Oplander et al. found that UVA irradiation of healthy human skin led to a considerable reduction in blood pressure.[28] A randomized controlled trial revealed a reduction in blood pressure accompanied by an elevation in circulating nitrite levels and a decrease in plasma nitrate levels in normotensive young adult males following UVA exposure to the skin.[29] Following UV exposure, there is an increase in the expression of inducible nitric oxide synthase (iNOS), an enzyme that catalyzes the conversion of L-arginine into NO in the human skin after 8–10 h[30]; however, Paunel et al.[31] demonstrated that the highest production of NO resulting from the decomposition of nitrite and RSNOs occurred 20 min after ex vivo human skin exposure to UVA exposure. These findings indicate that the effects of UVA radiation are mediated by the release of NO stores from skin via the alternative nitrate-nitrite NO pathway, independent of NOS.[29] The photoactivity of RSNOs, N-nitrosamines (RNNOs), and nitrite in rat vascular tissues in vitro have been demonstrated previously.[32] Rodriguez et al.[32] determined the NO release spectra of RSNOs (310–340 nm) and nitrite (310–350 nm), which were in the UVA wavelength range. Ferguson et al. showed that chronic UV exposure (8% UVB and 92% UVA) decreased atheromata in atherosclerosis-prone mice fed a diet high in fat and sugar.[33]

The NO signaling pathway is crucial for regulating blood pressure and cardiovascular function[34] as it acts as a potent vasodilator, relaxing smooth muscle cells around blood vessels, improving blood flow, and reducing blood pressure.[35] Dysregulation of this pathway can lead to CVDs such as hypertension.[36] It also inhibits platelet activation, leukocyte adhesion, and vascular smooth muscle cell proliferation, reducing the risk of atherosclerosis and thrombosis.[37] In hypertension, there is evidence of decreased NO production and increased NO degradation due to oxidative stress and inflammation.[38] This leads to vasoconstriction, reduced blood flow, and elevated blood pressure, all of which contribute to the development of cardiovascular diseases.[34] Several drugs target the NO pathway for treating hypertension CVDs,[39] including ACE inhibitors, angiotensin receptor blockers, and organic nitrate drugs. These drugs either increase or enhance NO production, leading to vasodilation, reduced blood pressure, and improved cardiovascular function.[40] UVA exposure might release NO from the skin into the bloodstream, subsequently reducing blood pressure and cardiovascular mortality.[4]

An observational study on ambient UV and blood pressure found a more pronounced reduction in blood pressure with UVB than UVA.[41] A recent study determined that UVB can enhance skin NO production, with its peak at 280–285 nm.[42] Additionally,

a substantial quantity of RSNO was produced in irradiated human skin, peaking at 320 nm (within the UVA region).[42] Although a lower 25-hydroxyvitamin D (25(OH)D) concentration is linked to increased hypertension and the incidence of cardiovascular diseases,[22] vitamin D supplementation does not reduce blood pressure or the risk of CVD.[43] A recent randomized controlled trial also revealed that UV light (comprising 54.6% UVB) had a short-term but not a long-term impact on blood pressure reduction compared to oral vitamin D supplementation in nursing home residents with dementia,[44] indicating that UVB-induced vitamin D might not be the primary mediator of the beneficial effects of sun exposure. Long-term narrowband UVB phototherapy reduced both cardiovascular and cerebrovascular risk in patients with vitiligo.[45]

UVB exposure was reported to decrease the formation of angiotensin II-induced abdominal aortic aneurysms in apolipoprotein E-deficient (ApoE−/−) mice, driven by UVB-dependent expansion of regulatory T cells.[46] Similar results have shown that UVB prevents atherosclerosis in mice by activating regulatory T cells[47] and stimulating the polarization of M2 macrophages.[48] UVB exposure induces interleukin-33 expression in keratinocytes and dermal fibroblasts,[49] which has been shown to have a protective effect against atherosclerosis,[50] suggesting another potential avenue for preventing atherosclerosis. In summary, the impacts of UVB on hypertension and CVD might be attributed to UVB-induced NO and immunomodulation, rather than to vitamin D.

3 | METABOLIC SYNDROME AND OBESITY

Metabolic syndrome is a collection of metabolic dysfunctions, such as dyslipidemia, hypertension, hyperglycemia, abdominal/central obesity, and insulin resistance. In a Dutch study (1993–1997), both body mass index (BMI) and waist circumference levels were higher in winter than in summer.[51] An increase in body fat and BMI was observed in a cross-sectional study of individuals who avoided sun exposure and had lower vitamin D levels, compared to those whose skin was exposed to more sunlight.[52] Another recent human study showed that lower serum 25(OH)D levels were associated with an increased risk of metabolic syndrome.[23] Although vitamin D supplementation may reduce all-cause and cancer-related mortality among middle-aged and older individuals, there is no evidence that it affects cardiovascular disease, obesity, or glucose metabolism.[53] A recent mouse experiment showed chronic UVR (spectrum with 65% UVB) suppressed obesity and type 2 diabetes in high-fat diet-fed mice, characterized by weight gain, impaired glucose and insulin tolerance, fatty liver, and gonadal fat deposition.[54] However, vitamin D supplementation had no effect, suggesting that benefits from UV light for metabolic syndrome are independent of vitamin D.

Geldenhuys et al. reported that the topical application of NO donors to the dorsal skin replicated the effects of UV (spectrum with 65% UVB) in mice, whereas NO scavengers prevented the positive impact of UV.[54] Another mouse experiment demonstrated that both broadband UV (spectrum with 65% UVB) and solar UV (spectrum with 4% UVB and 96% UVA) reduced fasting insulin levels and the extent of hepatic steatosis with the same amount of UVB exposure (1 kJ/m^2 UVB twice a week for 6 weeks).[55] Moreover, broadband UV significantly reduced mouse weight gain and NO scavenging and prevented hepatic lipid accumulation,[55] suggesting that the prevention of metabolic syndrome by UVA and UVB is associated with increased NO levels. Dhamrait et al. showed NO released from UV-irradiated skin was necessary for the inhibitory effects of UVR (spectrum with 65% UVB) on hepatic fat formation, iBAT whitening, and interscapular skin temperatures.[56] These findings suggest that sunlight exposure may effectively prevent the development of metabolic syndrome and obesity through mechanisms dependent on UVR-induced NO rather than vitamin D.

NO may promote the degradation of proinflammatory cytokines, thereby reducing inflammation.[57] NO derived from endothelial nitric oxide synthase (eNOS) promotes mitochondrial biogenesis, as evidenced by the observation that mice lacking eNOS have reduced numbers of mitochondria in skeletal muscle and adipose tissue.[58,59] In contrast to wild-type mice, Kanuri et al.[60] discovered that iNOS knockout mice had significantly increased body weight and fat content but reduced respiratory exchange ratio (RER), volume of carbon dioxide (VCO2), and heat generation. NO activates NOS, which increases the levels of the cyclic guanosine monophosphate (cGMP)/vasodilatory-stimulated phosphoprotein (VASP) signaling pathway. This, in turn, triggers a cascade of reactions that increases glucose uptake, stimulates insulin secretion, modulates inflammation, and exhibits anti-obesity effects.[61]

4 | DIABETES MELLITUS

4.1 | Type 2 diabetes mellitus (T2DM)

Diabetes is one of the most common endocrine diseases and is characterized by elevated blood glucose levels. The two most prevalent symptoms of T2DM are insulin resistance and beta-cell dysfunction.[62] Lindqvist et al. demonstrated a dose-dependent negative correlation between sun exposure and the frequency of T2DM among Swedish women.[63] Supporting this, a systematic review highlighted the potential benefits of recreational sun exposure in decreasing the risk of T2DM incidence.[64] While several studies suggest that vitamin D deficiency might be a risk factor for T2DM,[24,65,66] a recent meta-analysis failed to establish a causal relationship between serum 25(OH)D levels and T2DM.[67] In a study on mice fed a high-fat diet, long-term exposure to suberythemal UV light (spectrum with 65% UVB) resulted in improved glucose tolerance, reduced insulin resistance, dependent on UVR-induced NO rather than vitamin D.[54] Insulin resistance was predisposed in iNOS-knockout mice.[60] Increased endothelial NOS (eNOS) activity protects against the detrimental effects of a high-fat diet on weight gain, without causing systemic insulin resistance, partly through promoting metabolic activity in adipose

tissue in mice overexpressing eNOS mice.[68] NO may regulate insulin sensitivity and blood flow by providing the nutrients required for insulin-sensitive tissues, whereas NO suppression may induce insulin resistance.[69] NO is a crucial signaling molecule involved in multiple physiological processes and is increasingly being recognized as a key contributor to the progression of insulin resistance and T2DM.[70,71] NO participates in many pathways leading to the development of T2DM. One pathway involves decreased NO bioavailability in skeletal muscle and adipose tissue, leading to defective mitochondrial function and insulin resistance.[72] Additionally, NO is involved in insulin signaling, glucose transport, and glucose metabolism, and its dysregulation can cause insulin resistance.[73] Based on these findings, UVR may effectively prevent the development of T2DM via mechanisms that depend on UVR-induced NO production.

4.2 | Type 1 diabetes mellitus (T1DM)

T1DM is a chronic, progressive autoimmune disease characterized by insulin deficiency due to damage to insulin-producing beta cells. A correlation has been found between low UVB irradiation and high incidence rates of T1DM in 51 regions worldwide.[74] 1,25(OH)2D3 has been found to impact the immune system and beta cells in the pancreas, making it a promising candidate for the prevention and intervention of T1DM.[75] In non-obese diabetic (NOD) mice, vitamin D supplementation improves regulatory T cells, reduces insulitis, and delays or prevents the onset of diabetes.[76] Moreover, vitamin D-deficient NOD mice are more susceptible to T1DM.[77] In diabetes-prone mice, 1,25(OH)2D3 increases the proportion of regulatory T cells and causes a Th1/Th2 shift in the islets and pancreatic draining lymph nodes.[78] In accordance with these findings, UVB may effectively delay the onset of T1DM via mechanisms that rely on UVR-induced immunosuppression and an increase in vitamin D.

5 | NAFLD

NAFLD is a chronic liver disorder characterized by the accumulation of excess fat in the liver cells without excessive alcohol consumption. NAFLD is associated with metabolic syndromes,

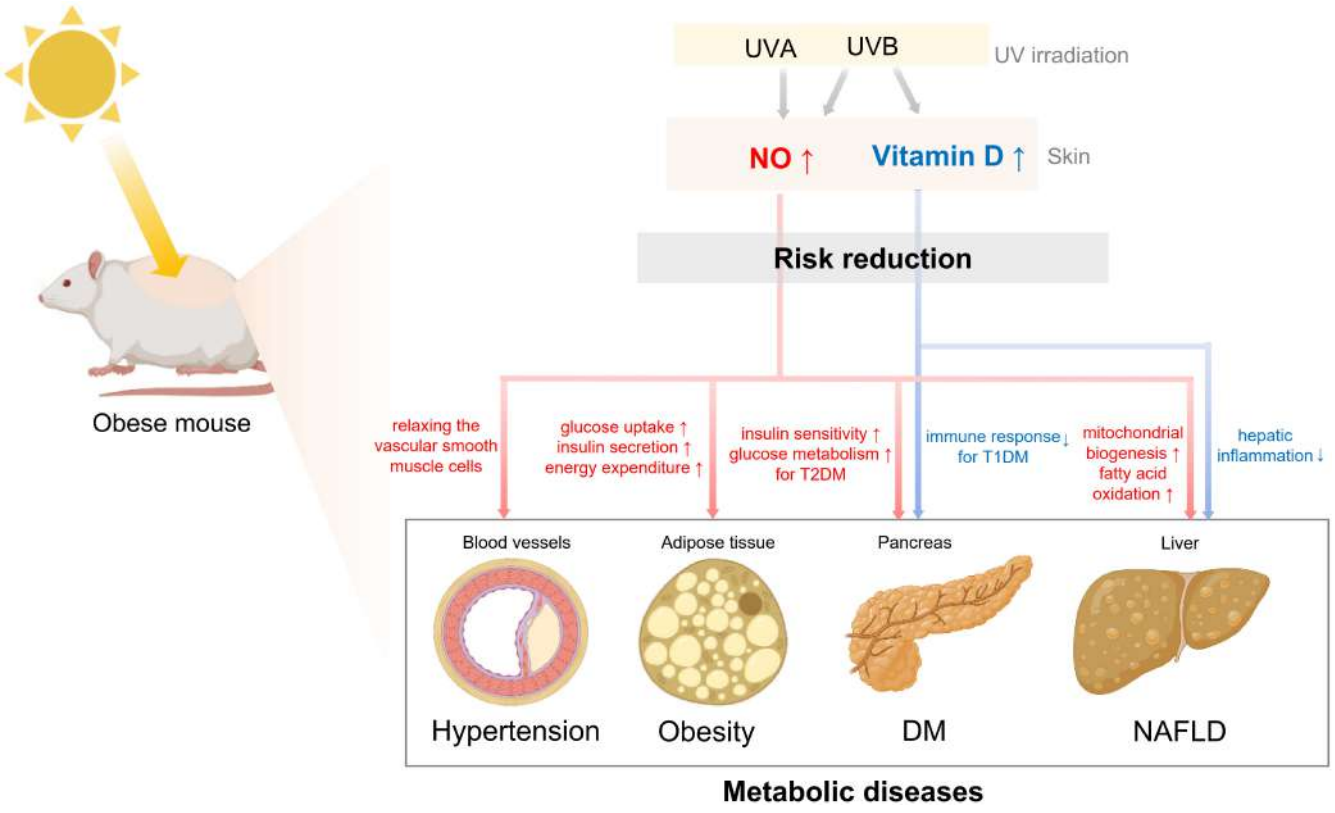

FIGURE 1 Ultraviolet (UV) radiation reduces the risk of cardiovascular and metabolic diseases in obese mice. Sunlight contains UVA and UVB. Both UVA and UVB exposure induces the production of nitric oxide (NO) through the skin. Vitamin D, however, is only stimulated by UVB. UV-induced NO reduces the risk of hypertension with vascular smooth muscle cell relaxation. NO also enhances glucose uptake, insulin secretion, and energy expenditure in adipose tissue, thereby preventing obesity. Type 2 DM can be prevented by UV-induced NO which improves insulin sensitivity and glucose metabolism. Both NO and vitamin D can lower the risk of NAFLD. NO increases oxidative metabolism in liver tissue, while vitamin D reduces hepatic inflammation. Moreover, the risk of type 1 DM can be reduced by a vitamin D-mediated reduction in the immune response. DM, diabetes mellitus; NAFLD, nonalcoholic fatty liver disease.

TABLE 1 Recent rodent studies examining the effects of UV on cardiovascular and metabolic disorders.

Disease models	Rodent strain	Food	UV light type	Radiation exposure	Observation	Reference
Atherosclerosis	Male ApoE−/− mice	A normal diet	Spectrum with 65% UVB	2 or 5 kJ/m^2 UVB once weekly for 14 weeks	UVB inhibited the development and progression of atherosclerosis by regulating regulatory T cells	Sasaki, N., et al. 2017[47]
Atherosclerosis	Male ApoE−/− mice	A high saturated fat and high sugar diet	An output of 8% UVB and 92% UVA	80 kJ/m^2 once a week for 12 weeks	UV reduced atherosclerosis	Ferguson, A. L., et al. 2019[33]
Atherosclerosis	Male ApoE−/− mice	A high-fat diet	100% UVB	25 mJ/cm^2 three times a week for 4 weeks	UVB inhibited atherosclerosis by promoting the polarization of M2 macrophages and limiting the inflammatory response in plaques	Li, X.Y., et al. 2022[48]
Abdominal aortic aneurysm (AAA)	Male ApoE−/− mice	A high-cholesterol diet	Spectrum with 65% UVB	5 kJ/m^2 UVB once weekly for 6 weeks	UVB-dependent expansion of regulatory T cells reduced experimental AAA	Hayashi, T., et al. 2017[46]
Metabolic syndrome	Male C57BL/6 mice	A high saturated fat and high sugar diet	An output of 8% UVB and 92% UVA	80 kJ/m^2 once a week for 18 weeks	UV limited diet-induced obesity but did not affect glucose tolerance	Ferguson, A. L., et al. 2019[33]
Metabolic syndrome	Male C57BL/6 mice	A high-fat diet	Spectrum with 65% UVB	1 kJ/m^2 UVB twice a week or 4 kJ/m^2 UVB once a fortnight for 12 weeks	UVR suppressed weight gain, glucose intolerance, insulin resistance, and nonalcoholic fatty liver disease Vitamin D supplementation could not reproduce the effects of UV, but UVR-induced NO could	Geldenhuys, S., et al. 2014[54]
Metabolic syndrome	Male C57BL/6 mice	A high-fat diet	Spectrum with 65% UVB (FS40)	1 kJ/m^2 UVB twice a week for 6 weeks	Only FS40 UVR reduced mouse weights and weight gain FS40 UVR reduced fasting insulin levels, and the extent of hepatic steatosis and NO scavenging prevented the effects of UV on the liver	Fleury, N., et al. 2017[55]
			Spectrum with 4% UVB and 96% UVA (CLEO)	1 kJ/m^2 UVB twice a week for 6 weeks	Only CLEO UVR reduced circulating LDL cholesterol CLEO UVR reduced fasting insulin levels and the extent of hepatic steatosis	
Metabolic syndrome	Male Ucp1 luciferase transgenic mice	A high-fat diet	Spectrum with 65% UVB	1 kJ/m^2 UVB twice a week for 12 weeks	UVB inhibited glucose intolerance, hepatic fat accumulation, whitening of iBAT, and interscapular skin temperatures	Dhamrait, G.K., et al. 2020[56]
NAFLD	Male Lewis rats	A choline-deficient and iron-supplemented L-amino acid-defined (CDAA) diet	Artificial sunlight	12 h/day for 6 or 12 weeks	Phototherapy ameliorated hepatocyte apoptosis, inflammation, fibrosis, and insulin/leptin resistance Vitamin D3 supplementation ameliorated NASH progression	Nakano, T., et al. 2011[86]
	Male Zucker fa/fa rats	Normal diet	Artificial sunlight	12 h/day for 6 or 12 weeks	Phototherapy ameliorated hepatitis and fibrogenesis but failed to ameliorate the obesity and steatosis	
NAFLD	Male C57BL/6 mice	A high-fat diet	Spectrum with 65% UVB	1 kJ/m^2 UVB twice a week for 12 weeks	UVR reduced hepatic steatosis but did not change body weight	Teng, S., et al. 2019[79]

obesity, and other fat-related diseases. Recent studies have revealed that both solar UV (spectrum with 4% UVB and 96% UVA) and broadband UV (spectrum with 65% UVB) reduce lipid accumulation in the livers of mice fed a high-fat diet.[33,79] The topical application of S-nitroso-N-acetyl-penicillamine (SNAP, a nitric oxide donor) suppresses liver pathology, whereas 2-(4-carboxyphenyl) -4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide (cPTIO) antagonizes the effects of UV radiation,[54] suggesting that UV-induced NO may have a significant impact on the progression of NAFLD. Furthermore, iNOS-knockout mice exhibit disrupted glucose and lipid homeostasis in the liver and adipose tissues.[60] Lack of eNOS reduces liver steatosis by regulating blood flow to the hepatic tissue in eNOS-deficient mice.[80] Sheldon et al. demonstrated that chemical inhibitors of eNOS decreased hepatic mitochondrial respiration and increased hepatic triacylglycerol accumulation in obese rats.[81] The NO signaling pathway is an important regulatory mechanism in NAFLD. Increased NO levels can activate the AMPK pathway, causing decreased lipid synthesis, increased mitochondrial biogenesis, and fatty acid oxidation, thus protecting against further liver damage in NAFLD.[82] NO also activates PPARγ, a nuclear receptor key in regulating inflammation and metabolism. Activation of PPARγ by NO can inhibit the NF-kB and MAPK pathways, reduce TNF-α and IL-6 production, and decrease oxidative stress.[83] Furthermore, PPARγ activation by NO stimulates the expression of genes involved in fatty acid oxidation, preventing further lipid accumulation in hepatocytes and improving NAFLD.[84] Thus, NO plays a central role in NAFLD pathogenesis, and interventions targeting UV-induced NO production may offer promising therapeutic approaches.

Numerous studies have investigated the relationship between serum 25(OH)D concentrations and the presence and/or severity of NAFLD.[85] Nakano et al. showed that artificial sunlight and vitamin D supplementation significantly reduced the severity of NAFLD in Lewis rats.[86] Additionally, artificial sunlight alleviated hepatitis and fibrogenesis, but not steatosis, in Zucker fa/fa rats,[86] the best known and most widely used rat model of genetic obesity without hyperglycemia.[87] Furthermore, vitamin D supplementation reduced the severity of NAFLD and suppressed circulating TNF-α levels, a critical factor in the development of NAFLD, in mice fed a high-fat diet.[54] A recent study in mice also reported that hepatic steatosis induced by a high-fat diet or methionine/choline-deficient diet (MCD) was markedly exacerbated in liver-specific vitamin D receptor (VDR)-knockout mice; the protective effect of vitamin D supplementation on NAFLD was weakened.[88] The study further revealed a mechanism of vitamin D through the interaction between VDR and hepatocyte nuclear factor 4 α (HNF4α) in NAFLD mice.[88] In rat allografts, calcitriol (the active form of vitamin D) decreased hepatocyte apoptosis,[89] which promoted liver fibrogenesis and aggravated NAFLD.[90] A recent review highlighted the potential advantages of vitamin D supplementation in patients with NAFLD, particularly in those with mild-to-moderate liver impairment and shorter disease duration.[91] These results indicated that UVB-induced vitamin D might help prevent and delay the progression of hepatic steatosis.

6 | DISCUSSION

Sun exposure has been observed to reduce the mortality rates associated with cardiovascular and metabolic disorders.[6] UV-induced vitamin D and NO play significant roles in this phenomenon, as illustrated in Figure 1. Table 1 summarizes recent rodent studies examining the impact of UV on cardiovascular and metabolic disorders. These studies reveal that UV lights with different spectral properties can be beneficial in preventing disease symptoms. Notably, both solar UV (comprising 4% UVB and 96% UVA) and broadband UV (65% UVB) prevented metabolic disorders in a NO-dependent manner,[33,79] indicating that both UVA-induced and UVB-induced NO can be integral to these processes, albeit through different mechanisms. UVA radiation triggers a rapid release of NO through a non-enzymatic reaction, while UVB radiation increases NO production by enhancing iNOS activity, a process much slower than the former. It has been shown that vitamin D can inhibit hepatic inflammation, a significant contributor to NAFLD, by suppressing hepatocyte apoptosis and hepatic fibrosis.[85] UVB-induced vitamin D may benefit T1DM by downregulating autoimmunity, primarily through the direct or indirect regulation of cells that activate autoreactive T and B lymphocytes.[92] Additionally, UV-induced vitamin D is crucial for other health benefits, such as colorectal cancer prevention[93] and respiratory tract infection resistance.[94] Beyond NO and vitamin D, chronic UV exposure may influence mood and memory by increasing levels of β-endorphin[95] and corticosterone.[96] Additionally, there may be other unappreciated but important mechanisms that are yet to be discovered, such as appetite regulation and thermogenesis.

In conclusion, although UV exposure causes photoaging and skin cancer, it has significant advantages in regulating cardiovascular and metabolic diseases. UV-induced NO circulates in the bloodstreams, counteracting hypertension, obesity, T2DM, and NAFLD. Simultaneously, vitamin D, specifically produced in the skin by UVB exposure, modulates immunity and inflammation, alleviating T1DM and NAFLD. Adequate UV exposure is pivotal for maintaining a healthy balance. Further research is warranted to determine how we harness the positive effects of UV radiation while mitigating its detrimental outcomes.

AUTHOR CONTRIBUTIONS

Dong Hun Lee created the work's concept and design. Qing-Ling Quan wrote the manuscript. Kyeong-No Yoon, Ji Su Lee, Eun Ju Kim and Dong Hun Lee revised, co-wrote, and edited the manuscript. All authors have given their final approval.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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