Multifactorial Drivers of Chronic Kidney Disease of Unknown Etiology (CKDu): A Review of Cadmium Exposure, Ultraviolet B B Radiation, and the Potential Role of Vitamin D Toxicity

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ABSTRACT

There are many research studies conducted to determine the cause/origin of CKDu for preventing this increasingly occurring disease, particularly among poor farmers. The disease is known to be multifactorial with heat stress enduring period > 3 months, but there is difficulty in distinguishing between harsher environments than endemic locations. This study identified that the likely cause is UVB actuating Vitamin D Toxicity (VDT), thus affecting the kidneys. Hence, a focused literature review was undertaken to find the links between cadmium (Cd), calcium, fluoride, enzymes, inhibitions, and the like. Moreover, 2nd law of thermodynamics was applied to determine the entropy differences between cold and hot source. The mean values of climate models were obtained from one publication on radiative forcing (RF) in the tropopause of 1.28 Wm^{-2} and climate feedback (CF) 0.25 $Wm^{-2}K^{-1}$. The energy of RF was used to determine entropy value $S_{RF(UVB)}$ at $T_2 = 230K$ as mean atmospheric temperature and the maximum temperature, T_1 at locations. It was then equated to the energy value of UVB, $Q_{CF_{(UVB)}}$ to be found between 1/273 and $1/T_1$. It was also validated using CF. The endemic location resulted 3.697 Wm^{-2} at 303K, and low RH compared to 3.239 Wm^{-2} at 311 K high RH. Although there is much comfort in endemic location, the chances of VDT or heat stress are higher more so with Cd inhibition of enzyme 7-dehydrocholesterol reductase (DHCR7), which is crucial for cholesterol synthesis. Instead, 7-dehydrocholesterol in excess switches more to form VDT, causing symptomatic hypercalcemia. Cadmium can disrupt vitamin D metabolism, contributing to osteomalacia and osteoporosis, actuating hypercalciuria, an indirect marker of low-level cadmium exposure. The kidneys, already compromised due to cadmium (Cd) accumulation and reabsorption during systemic distribution, ultimately eliminate Cd via the urine. Notably, no significant Cd accumulation is observed in end-stage renal tissues. Further basic research is required to elucidate the VDT in response to UVB exposure.

KEYWORDS: *Cadmium, Ckdu, Climate Feedback, Hypercalcemia, Vitamin D Toxicity (Vdt), Uvb, Radiative Forcing, 7-Dehydrocholesterol Reductase (Dhcr7)*

INTRODUCTION

Chronic kidney disease (CKD) is a global health problem with an increasing number of cases. CKD is defined as abnormalities of kidney structure or function, present for >3 months with health implications [1]. Hewageegana et al. (2024) [2] did undertake an extensive review on the unknown etiology of CKDu. They have reviewed papers on most aspects of possible causes and narrowed down to heat stress with multifactorial illnesses, but not conclusive because the neighbouring Northern Province in Sri Lanka is much harsher than the affected locations. Multifactorial illnesses may seem plausible with the number of publications on heavy metal contaminants, medical health issues like non-communicable diseases, social behaviour, and poor food intake [2-7].

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Cadmium is one of the key toxicants causing CKDu as reported by [8]. According to the findings, cadmium is responsible for the mobility of calcium, thus causing hypercalcemia and hypercalciuria with excessive exposure to ultraviolet B radiation (UVB). Vitamin D Toxicity (VDT) is very rare occurrence [9], but it could be one of the triggering factors. It is a hypothesis, but it could very well be valid because there is excess UVB, particularly in the tropical belt with increased radiative forcing. The other logical argument is UVB, if in excess, will heat the skin surface very quickly, leading to accelerated perspiration and dehydration, which is a known factor affecting CKDu [10].The researchers in this study have been involved in climate modelling, and they are able to distinguish between a high incidence of UVB in the affected locations as opposed to harsher environments with less intensity in the neighbouring Northern Province. This study was conducted to conduct a targeted review of publications on cadmium to derive adequate evidence for in-depth research on the effect of UVB exposure on VDT or heat stress.

MATERIALS AND METHODS

A focused literature review was undertaken to determine the influence of gastrointestinal absorption of heavy metals (HM) on organ failure, specifically examining the interaction of cadmium and metallothioneins, cadmium, and calcium, fluoride, heat stress, VDT, switching between vitamin D production and cholesterol synthesis, and the mechanism of bone damage. Studies directly related to temperature were reviewed to determine the relationship to energy received from UVB radiation. Such that, the second law of thermodynamics was used to explain the energy levels received at different temperatures in dry and humid conditions.

By the Clausius definition, if an amount of heat (Q) flows into a large heat reservoir at temperature (T) above absolute zero, then the entropy (S) increase is:

$$\Delta S = Q/T. \quad (1)$$

Whenever, ΔS is the same between energies, Eq. (1) can be written as:

$$\frac{Q_1}{T_1} = \frac{Q_2}{T_2} \quad (1a)$$

And between two reservoirs of hot and cold, Eq. (1) can be expressed as:

$$\Delta S = Q\left(\frac{1}{T_2} - \frac{1}{T_1}\right) \quad (2)$$

Where $T_1 > T_2$, [11, 12].

The radiative forcing (RF) values and climate feedback were obtained from literature [13], as given in Table 1.

Table 1. A comparison of radiative perturbations (Wm^{-2}) at the tropopause and the associated climate feedback ($Wm^{-2}K^{-1}$) [13]

Values of Climate Models	**Radiative Forcing Tropopause (Wm^{-2})**	**Climate Feedback ($Wm^{-2}K^{-1}$)**	**Climate Feedback * ($Wm^{-2}K^{-1}$)**
Mean	1.28	0.25	0.17
Std. dev	0.40	0.07	0.05
Min	0.68	0.16	0.12
Max	2.24	0.40	0.28

*Adjusted value given by [13]

Not all the radiative forcing is UVB because most of the entropy buildup is from the climate feedback of long-wave radiation. The direct reflectance from stratospheric water vapour in the lower stratosphere is responsible for UVB, and it can be calculated considering the average atmospheric temperature. According to [14], the average atmospheric temperature over time must have reduced from 254.6 K, but that reduction is not known. This phenomenon is reflected in several of the models developed over the years, since [14] tabulated NASA as 254.6, the Heat Transfer Model as 251.7 K, and the American Chemical Society Layer Model as 242.3 K. This reduction explains the movement of gas molecules upwards into the lower

stratosphere from the top of the troposphere within the ozone layer. We decided to use a value of 230 K that was obtained from unpublished works of the authors to calculate the plausible UVB received at 30 ºC and 38 ºC, representing Giradurukotte (endemic CKDu) and Northern Province. It was compared with 254.6 K, representing 1990 values. The minimum temperatures can be determined by considering Eq. (2). Such that the entropy of radiative forcing (S_{RF}) is:

$$S_{RF} = Q_{CF}\left(\frac{1}{T_2} - \frac{1}{T_1}\right) \text{ in } Wm^{-2}K^{-1}. \quad (3)$$

And Q_{CF} is the energy of climate feedback, since the entropy of climate feedback (S_{CF}) is:

$$S_{CF} = \frac{Q_{CF}}{T_1} \quad Wm^{-2}K^{-1}. \quad (3a)$$

T_2 is the minimum temperature and T_1 is the maximum temperature of a location at a given time. It can be postulated that Q_{RF} (energy of radiative forcing) being positioned in the Stratospheric Water Vapor (SWV) region, it will be at the assumed temperature of 230 K. The energy of S_{RF} is within S_{CF}, thus considering Eq. (3a), we can write that:

$$S_{RF} = \frac{Q_{RF}}{T_1} \text{ in } Wm^{-2}K^{-1}. \quad (4)$$

Combining Eq. (3) with Eq. (4), we get:

$$T_2 = \frac{Q_{CF}.T_1}{(Q_{RF}+Q_{CF})} \quad \text{in K} \quad (5)$$

In an activated state due to UVB radiation, the temperature T_1 will increase, depending on how cold the source temperature would be. In this instance, it is the assumed average atmospheric temperature (T_A),

T_A = 230K. Such that the average entropy of radiative forcing (S'_{RF}):

$$S'_{RF} = \frac{Q_{RF}}{T_A} \text{ in } Wm^{-2}K^{-1}. \quad (6)$$

It is at a higher entropy value since $S'_{RF} > S_{RF}$. We can write Eq. (3) at an elevated temperature, T'_1:

$$S'_{RF} = Q_{CF}\left(\frac{1}{T_2} - \frac{1}{T'_1}\right) \text{ in } Wm^{-2}K^{-1}. \quad (7)$$

Since T_2 was found from Eq. (5), $T'_1 = \frac{Q_{CF}}{\left(\frac{Q_{CF}}{T_2} - S'_{RF}\right)}$ in K. (8)

Therefore, the entropy of UVB can be derived from the difference between the activated maximum temperature and the maximum temperature at the location.

$$S_{RF(UVB)} = Q_{CF}\left(\frac{1}{T_1} - \frac{1}{T'_1}\right) \text{ in } Wm^{-2}K^{-1}. \quad (9)$$

It can be validated by considering only Q_{RF} with the low temperature of the average atmospheric temperature and the maximum temperature at the location. Hence, the entropy of radiative forcing in terms of UVB ($S_{RF(UVB)}$) can be written as:

$$S_{RF(UVB)} = Q_{RF}\left(\frac{1}{T_A} - \frac{1}{T_1}\right) \text{ in } Wm^{-2}K^{-1}. \quad (10)$$

Where, T_A is the average atmospheric temperature and T_1 is the ambient temperature at locations.

To determine the energy of UVB, $Q_{CF_{(UVB)}}$ at the location, the entropy of UVB should then be expressed in terms of the entropy of non-condensable climate feedback UVB component, stated as:

$$S_{RF(UVB)} = Q_{CF_{(UVB)}}\left(\frac{1}{273} - \frac{1}{T_1}\right) \text{ in } Wm^{-2}K^{-1}. \quad (11)$$

It leads to $Q_{CF_{(UVB)}} = \frac{S_{RF(UVB)}}{\left(\frac{1}{273} - \frac{1}{T_1}\right)}$ in Wm^{-2} (11a)

There are basically four cases, where $T_2 = 230K$ and $T_1 = 311$K and 303K.

And $T_2 = 254.6\ K$ and $T_1 = 311\ K\ and\ 303\ K$

Both Q_{RF} and Q_{CF} were modified to resemble radiative forcing and climate feedback values in 1990 by considering that,

$$Q_{RF2} = Q_{RF}.\frac{230}{254.6} \quad (12)$$

$$S_{CF2} = \frac{Q_{RF2}}{Q_{RF}} . S_{CF} \quad (13)$$

The implications of increasing energy levels over time are discussed, as well as high microbial activity. In lieu of the complexities surrounding the disease, the paper focuses on precautionary measures to reduce and prevent CKDu cases. Also, going beyond preventive steps, a research study is proposed to quantify the findings of this review.

Results anD Discussion

3.1 Bioelement Interactions in Cd Toxicity

Organometallic compounds can cross biological membranes more easily than inorganic heavy metal compounds because inorganics entry into living systems is often more limited by factors like solubility and bioavailability. Organometallics pose a higher risk of toxicity because of bioaccumulation due to their increased lipophilicity and potential for metabolic transformation into more toxic forms [15]. Trihalomethanes (THM) interfere with essential biometals like zinc, magnesium, selenium, calcium, and iron, altering their homeostasis and also impairing their biological functions [16-19], paving the way for heavy metal entry. Gastrointestinal absorption of Cd metal is determined in the diet by the content of these essential elements, along with vitamins, polyphenols, antioxidants, and other active biomolecules. The enhanced intake of some bioelements may prevent the absorption and the toxic effects of Cd, while the deficiency of some of these biologically active substances can increase gastrointestinal absorption and the accumulation of Cd in the body [17,19, 20 -22].

3.1.1 Cadmium and Metallothioneins

Genchi et al. (2020) [17] clearly explain the dysfunction of the kidney by cadmium. Metallothioneins (MTs) are ubiquitous low molecular weight proteins (MW 7–8 KDa). Their name is related to the occurrence of several divalent metal ions (Fe, Co, Ni, Cu, Zn, Ag, Cd, Hg, Pb) in the isolated material (metallo-) and the high –SH (cysteine) content of the protein (-thionein). Metallothionein was first identified in the kidney cortex of equines as a Cd-binding protein that is responsible for the accumulation of Cd in the tissues. The mammalian MT is made up of 61–68 amino acid residues, 18–23 of which are cysteines. MT is a unique protein that is very rich in thiol groups.

In the human body, high levels of this protein are synthesized in the liver and kidney, and their production depends on the presence of dietary minerals, such as Zn, Cu, and Se, as well as the amino acids histidine and cysteine. After absorption, Cd is delivered to the liver via endogenous intestinal MTs. Then hepatic Cd-MT gradually redistributes this metal to the kidneys, which are the main target organ for Cd toxicity. After being released from the liver, Cd bound to MTs is distributed to other organs. In the kidney, Cd undergoes glomerular filtration, from where it is reabsorbed intracellularly from renal tubular cells. In the latter, Cd is cleaved from MTs and Cd^{2+} ions are re-excreted into the tubular fluid; finally, Cd is eliminated in the urine. An acidic medium, such as that present in lysosomes (pH 4.5–5.5), promotes the dissociation of Cd from a Cd-MT complex. Cd-MT shows very low toxicity to fetuses and the central nervous system compared with other heavy metals because it does not easily cross the placental and hemato-encephalic barriers. Cd is mainly eliminated through the urine, even if the amount of Cd excreted daily in urine is very low. This low excretion corresponds to the Cd biological half-life of more than 25–30 years [17, 23-24].

High levels of cadmium and fluoride, and complex interactions between the ratio of dissolved sodium and calcium in the presence of fluoride have been hypothesized to cause CKDu in endemic areas of Sri Lanka [25]. Cadmium may also act directly on bone. Animal studies have shown cadmium to stimulate the formation and activity of osteoclasts, breaking down the collagen matrix in bone. Osteoporosis is the main cause of fractures in post-menopausal women, a common occurrence worldwide, giving rise to disability and a high cost to health services. In bones, cadmium can disrupt vitamin D metabolism, contributing to osteomalacia (softening of the bones) and osteoporosis (weakening of the bones) [26]. The identification of

cadmium, an environmental pollutant, as one causal factor is highly significant in helping to control the incidence of this complex condition [27].

3.2 UVB and VDT

Hewageegana et al. (2024) [2] have touched on an important issue: heat stress. In the text, they state that chronic occupational heat stress and dehydration are now thought to be the key etiologic factors for CKDu [10]. Chronic dehydration is a promoting factor for the development of crystal nephropathy [28]. In Central America, the main focus of attention for research in CKDu is dehydration and heat stress, but it has been paid less attention in Asia [29], including Sri Lanka. The possible pathophysiological mechanism of CKD in chronic dehydration includes sub-clinical rhabdomyolysis, hyperuricemia and hyperuricosuria, hyperosmolarity, and vasopressin effects [2]. Hard water in the CKDu prevailing area makes the water unpalatable [28], and as a result, people drink less, which causes dehydration in a vicious cycle. The dehydration hypothesis, however, cannot fully elucidate the low disease prevalence in the neighboring Northern province of Sri Lanka, where the conditions are warmer and drier than the endemic areas [30]. It is hypothesized in this study that UVB levels tend to be higher under low humidity like in the affected areas, than humid high-temperature locations referred to in the Northern Province. However, the relationship is complex; lower humidity generally allows more UVB radiation to reach the Earth's surface [31]. In Central America, the CKDu endemic is called Mesoamerican Nephropathy (MeN), and men working with heavy physical labor in warm areas near the Pacific Ocean often develop the disease.

Vitamin D is produced in the skin when 7-dehydrocholesterol is converted to cholecalciferol (vitamin D_3) by UVB radiation. Overexposure to vitamin D produces symptomatic hypercalcemia, an abnormally high level of calcium in the blood with possible weakness, fatigue, depression, confusion, stupor or coma, polyuria, nephrolithiasis, renal failure, ectopic calcification, conjunctivitis, fever, chills, anorexia, nausea, vomiting, and constipation [32]. Vitamin D Toxicity (VDT) normally encountered by excessive vitamin D intake. Overexposure to ultraviolet B (UVB) radiation is less common than toxicity from supplements [33].

Becklund et al. (2009) [33] explain that vitamin D toxicity and hypercalcemia do not typically occur upon exposure to sunlight because of several factors that limit the endogenous production of vitamin D. These factors include the photochemical conversion of previtamin D_3 into biologically inert compounds, skin pigmentation, and latitude. Thus, the levels of $1,25(OH)_2D_3$ required to suppress experimental autoimmune encephalomyelitis (EAE) are well above those that can be produced naturally upon exposure to sunlight. Furthermore, results from their laboratory suggest that hypercalcemia is more than simply an unfortunate consequence of $1,25(OH)_2D_3$ treatment and may play an essential role in the immunosuppressive effects of $1,25(OH)_2D_3$. It is notable that the conversion of 7-dehydrocholesterol to cholesterol, the final step of cholesterol synthesis in the Kandutsch-Russell pathway, is catalysed by the enzyme 7-dehydrocholesterol reductase (DHCR7). 7-dehydrocholesterol is also a precursor of vitamin D, switching between cholesterol synthesis [34]. Although not explicitly detailed, cadmium can inhibit the enzyme 7-dehydrocholesterol reductase (DHCR7), which is crucial for cholesterol synthesis. According to [35], inhibition leads to an accumulation of 7-dehydrocholesterol (7-DHC) and a reduction in cholesterol production. The altered sterol profile can have various consequences, including potential effects on cellular signalling, membrane structure, and susceptibility to oxidative stress. We can postulate that excess of 7-dehydrocholesterol will increase vitamin D production, leading to toxic levels. It is reported that in CKD patients, cholesterol synthesis can be affected, leading to dyslipidemia [36].

3.3 Mechanism of Bone Damage

Cadmium disrupts bone metabolism in many ways, with the worst appearing to be from impairing key kidney functions and directly damaging the osteoblasts. Vitamin D, whether from diet or production in the skin, must be first hydroxylated in the

liver and then undergo a second hydroxylation in the kidneys to produce its most active form, calcitriol ($1,25(OH)_2D_3$). Cadmium poisons the kidney enzyme that converts 25(OH)D to $1,25(OH)_2D_3$. Cadmium also damages the kidneys' ability to excrete toxins and to reabsorb important molecules and minerals. This results in increased loss of calcium in the urine. In fact, hypercalciuria is an indirect marker of low-level cadmium exposure. Cadmium inhibits the activity of alkaline phosphatase, which is produced by osteoblasts and is needed to deposit calcium into newly formed bone. Cadmium also decreases bone's collagen content by stimulating the formation and activity of osteoclasts, which break down the collagen matrix in bone as part of normal remodelling. Finally, cadmium activates gene expression of "toxic response" pathways in bone cells, which further stimulates osteoclast bone resorption [37]. Bone damage, specifically renal osteodystrophy, is a common complication in CKDu patients in Sri Lanka. This condition arises because the kidneys, when damaged, struggle to regulate mineral and bone metabolism, leading to various bone problems. In CKDu patients, bone pain and fractures are common symptoms, and the severity of bone damage can impact quality of life and mortality. A common symptom, often associated with the weakening of bones [38].

In a mathematical and biochemical point of view, both time and rate are involved in the progress of the multifactorial illness. Perhaps VDT triggers further malfunctioning of the kidney in a vicious cycle by hypercalcemia condition to activate even low levels of cadmium stored in the bones to release more calcium and even phosphorus. At latter stages of the patients, vitamin D levels become low but the effectiveness may become redundant. Evidently, Vitamin D treatment in CKDu patients involves supplementing with active vitamin D analogues or calcitriol, especially in later stages of CKD, to address secondary hyperparathyroidism. These analogues help regulate calcium and phosphate metabolism, reducing the risk of bone complications and cardiovascular issues. Nutritional vitamin D supplements are also used to address vitamin D deficiency and insufficiency in the general population with CKD [39].

CLIMATE CHANGE

A rise of the incidence of CKD was reported from the dry zone of the country in the 1990s [2] and the number of CKDu patients in Sri Lanka is increasing, particularly in the North Central Province. According to data from 2020, a total of 164,000 individuals were diagnosed with CKD. Furthermore, a comprehensive study indicates that approximately 10% of the population in Sri Lanka is afflicted by kidney-related ailments. There has been a notable increase in the burden of CKD in the country in the last two decades, with the identification of CKD cases among a population residing in the North Central Province, specifically in the Anuradhapura and Polonnaruwa districts. The occurrence of CKD in these regions varies between 5% and 15% [40].

Such an increase could be related to climate change because UVB radiation is increasing directly from Stratospheric Water Vapor in the ozone layer. The increase in activated water vapour is expressed in terms of radiative forcing of the atmospheric perturbations and radiated to the Earth in the form of climate feedbacks (CF). The increase in water vapour in the lower stratosphere causes elevated levels of UV radiation to the Earth otherwise be reflected from the ozone layer. A study conducted to compare atmospheric modelling of atmospheric perturbations resulting in climate feedback shows vast variations, but the mean values given in Table 2 by this research could be used to comprehend the differences between unaffected high-humidity locations to those of multifactorial regions with high incidence of CKDu.

The results of the study analysis given in Table 2 show that there is a difference in the lower maximum temperature location, like Giradurukotte to that of a higher temperature location in the Northern Province. The energy of UVB received at the lower maximum temperature is 14.16% more than in the higher maximum temperature and 8.70% higher in 1990. 17.27% increase can be expected if the maximum temperature rises to 40 ^oC, 313K. The values can be validated by applying Eq. (10).

Table 2. show the radiative force and climate feedback obtained from [13] and the modified values to simulate 1990 conditions at assumed average atmospheric temperatures and likely prevailed value in 1990 for location temperatures of

311K and 303K and the derived minimum and maximum temperatures, UVB entropy component of radiative forcing and UVB energy component of climate feedback at the two locations and hypothetical values of them in 1990

Q_{RF} (Wm^{-2})	S_{CF} ($Wm^{-2}K^{-1}$)	Q_{CF} (Wm^{-2})	T_A (K)	T_1 (K)	T_2 (K)	T_1' (K)	$S_{RF(UVB)}$ ($Wm^{-2}K^{-1}$)	$Q_{CF(UVB)}$ (Wm^{-2})
1.28	0.25	77.75	230	311	305.96	312.81	0.00145	3.239
1.28	0.25	75.75	230	303	297.97	304.63	0.00134	3.697
1.16	0.23	70.24	254.6	311	305.96	312.14	0.00082	1.840
1.16	0.23	68.43	254.6	303	297.97	303.98	0.00073	2.000

The climate feedback values for UVB were derived from the average model predictions; however, specific values for tropical locations can be much more than 3.697 Wm^{-2}. The extent of endemic locations is becoming more as reported by [2], because of the increasing radiative forcing and climate feedback year after year. The relationship between UVB radiation, humidity, and wind is complex. Generally, UVB levels are higher when humidity is low and wind is high. This is because low humidity allows more solar radiation, including UVB, to reach the Earth's surface, and high wind speeds can reduce the amount of water vapor in the atmosphere, further contributing to higher UVB levels. However, monsoon rains with high winds increase humidity in coastal locations compared to inland landmasses. UVB radiation intensity is generally higher in conditions of low humidity. This is because high humidity can lead to the formation of water droplets in the atmosphere, which scatter and reduce the amount of direct solar radiation reaching the surface, including UVB. In other words, the energy level of 3.239 Wm^{-2} given in Table 2 will reduce further with high humidity, giving normal values of UVB for absorption by the skin. Low humidity, therefore, allows more UVB radiation to reach the Earth's surface [31]. Farmers tend to work long hours under low humidity and windy conditions rather than high humidity and low wind conditions. Farmers' perceptions of climate change should be viewed to find better solutions, like conservation farming.

3.5 Synthesis in Developing Hypothesis

Metallothioneins play a protective role in neutralizing the toxicity of heavy metals. They prevent cellular damage. It is not an enzyme but can conjugate HMs. They transport HM into different parts of the body, thus leaving behind HMs in the dissociation reactions. Vitamin D is a nutrient the body needs, along with calcium, to build bones and keep them healthy. The body can absorb calcium only if it has enough vitamin D. Calcium is a major part of the bones. Cadmium can disrupt vitamin D metabolism in bones, thus causing hypercalcemia. Vitamin D also has many other uses in the body. It supports immune health and helps keep muscles and brain cells working.

In cholesterol synthesis, 7-dehydrocholesterol is indeed a key intermediate. When 7-dehydrocholesterol levels are high, the enzyme 7-dehydrocholesterol reductase (DHCR7) facilitates its conversion into cholesterol, thus continuing the cholesterol synthesis pathway [41] . Boland and Tatonetti (2016) [41] found that Cd and including a metabolite of arsenic, As inhibits enzyme (DHCR7). When there is inhibition of the enzyme (DHCR7), there will be a build-up of high level of 7-dehydrocholesterol, and in the presence of high UVB, there will be an excess of vitamin D. It is postulated that VDT conditions are of short durations because 7-dehydrocholesterol productions are suppressed over time. Individuals with inhibited or deficient enzyme DHCR7 will likely indicate low vitamin D levels as reported in Colombo and Kandy in Sri Lanka. It is expected that individuals with low vitamin D will get hydrated rapidly, causing oxidative stress. Under excessive exposure to UVB, individuals become feeble, experiencing both heat stress and VDT. Farmers become even more susceptible

to excess calcium in water, with catalytic reactions of fluoride causing rapid kidney failure.

CONCLUSION

The study distinguished the endemic region with higher UVB levels at lower temperatures than the adjoining region, signaling the possibility of VDT. It may be an additional influence in the multifactorial clinical conditions causing CKDu. The key factor being cadmium accumulation in the kidney and bones, which dysfunction the kidney and creates other health issues. Cadmium found in the urine of CKDu patients is a sign of excess levels in the body. In the presence of calcium or fluoride or both, cadmium in excess causes hypercalcemia and hypercalciuria in the affected patients. VDT also shows the same symptoms because VDT productions are more with less cholesterol synthesis. The worst-case scenario is when the manifestation of VDT with excess cadmium and calcium, catalyzed by fluoride, can lead to various adverse effects, including cellular damage and dysfunction of the kidneys. Most times, the poor health conditions of the farmers with weakened kidneys due to cadmium (Cd) exposure, exacerbated by UVB radiation, can lead to hypercalcemia and impaired cholesterol synthesis. Cd, even at low levels, can form complexes with calcium in the bones, disrupting calcium balance and potentially causing hypercalcemia. This, coupled with impaired kidney function, can lead to bone damage and reduced calcium levels, which are further compounded by a condition of low cholesterol synthesis. Basic research on UVB triggering VDT should be undertaken to prevent CKDu and find new management practices for affected patients.

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