



Short Communication

Hydrochlorothiazide: A savior to the heart or a foe to the skin?

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Hydrochlorothiazide (HCTZ), is a thiazide-type diuretic that has been used clinically for more than half a century. It works by inhibiting the sodium-chloride cotransporter system in the kidney's distal convoluted tubules, which results in its diuretic action as water follows the increased K^+ and Na^+ in the nephron [1]. Hydrochlorothiazide is a commonly prescribed diuretic and it is considered a first-line treatment for hypertension. The drug has gained a lot of popularity as it is affordable, potent, and capable to improve other conditions like cardiac failure and symptomatic edema. Hydrochlorothiazide, although commonly prescribed, has few conventional adverse effects such as electrolyte imbalances, hyperglycemia, hyperlipidemia, and hyperuricemia. Even then, authorities deemed it to be the principal recommendation for the treatment of hypertension [2]. HCZT may induce hypokalemia, hyponatremia, hypercalcemia, and hypomagnesemia, and it can also cause azotemia in individuals with renal impairment [3]. The guidelines for HCTZ dosage recommend 25 mg–100mg & 25–50 mg once a day orally for patients with edema and hypertension respectively [1].

However, a recent 2020 study published in the Journal of Clinical Medicine raised new, more serious concerns – it showed that hydrochlorothiazide exposure caused a statistically significant increase in the risk of skin cancer potentially due to the photosensitizing capability of thiazide diuretics [4]. Thereafter, two more case reports were published that further strengthened the association of hydrochlorothiazide to skin's squamous cell carcinoma [5].

Since 2010, there has been increased surveillance regarding the correlation of a few antihypertensive medications with increased risk of acquiring melanoma and other malignancies. The emphasis of experimental, partially multicentric investigations in dermatological science indicates the existence of angiotensin receptors in the skin and melanoma tissue and locoregional metastases, as well as the possibility of metastasis potentiation in preexisting melanoma cells. Although it

appears logical, it is uncertain to what degree these two experimental investigations have substantial clinical importance and may be regarded as a causative connection in the etiology of melanomas [6]. In vitro investigations in recent years have raised concerns regarding the potential function of angiotensin receptor blockers as carcinogens in connection to cutaneous melanoma, owing to the presence of angiotensin receptors in nevi and melanoma tissue [7].

Adalsteinsson JA et al. published a study in 2020 that concluded that the photosensitizing property of hydrochlorothiazide causes the production of free radicals and reactive oxygen species when exposed to ultraviolet radiation. As a result, mutations in the p53 and CDKN2A cell cycle regulators are increased, eventually leading to permanent UV damage. These free radicals subsequently result in neoplastic changes and give rise to keratinocyte carcinoma [8,9].

According to a cohort study published by Rouette J et al., HCZT was associated with an overall 50% increased risk of cutaneous squamous cell carcinoma (SCC), with females being at greater risk than males. However, when compared to other thiazide diuretics, HCZT was not associated with an overall increased risk of basal cell carcinoma (BCC) and melanoma [10]. The food and drug administration (FDA) recommends that clinicians inform their patients about the hazards of taking diuretics. This includes guiding patients to restrict their sun exposure and protect their skin by using broad-spectrum sunscreen and wearing protective clothing before going out in the sun. The FDA also advises patients who are on hydrochlorothiazide to get frequent testing for skin malignancies [11]. The FDA has approved drug label changes for hydrochlorothiazide (HCTZ) to forewarn healthcare professionals and patients of a slightly increased risk of non-melanoma skin cancer (basal cell skin cancer and squamous cell skin cancer) associated with HCTZ use and to encourage consumers to protect their skin from the sun [12]. Anuria and allergy to HCZT are two absolute contradictions. HCZT should not be prescribed to patients who have reported allergies to the

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Received 18 May 2022; Received in revised form 2 June 2022; Accepted 3 June 2022

Available online 9 June 2022

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use of sulfonamides-derived drugs. HCZT is a category B drug that can be administered throughout the gestational period. It is also secreted in breast milk but is reported to be safe to use during breastfeeding [13].

In light of these studies, the question still stands: Is Hydrochlorothiazide still safe to be considered as the first-line treatment for hypertension? The mentioned data is of chief importance to us because this drug is still widely used in different countries. Health workers should prescribe Hydrochlorothiazide with caution and should certainly rule out all the skin pathologies before prescribing this drug. If patients taking thiazides experience any sort of skin-related disturbances, they should seek immediate medical attention. Additionally, it is extremely important to promote precautionary strategies against sun exposure and frequent skin assessments to halt the mentioned deleterious consequences [14].

Ethics statement

The present study includes printed and published information; therefore, the formal ethical clearance was not applicable for this study.

Funding

None.

Annals of medicine and surgery

The following information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

Please state any conflicts of interest

NA.

Ethical approval

NA.

Consent

NA.

Author contribution

AK, P: conceived the idea, designed the study and drafted the manuscript.

AK, P, GK, SS, MMH: conducted literature search and created the illustrations.

AK, P, GK, SS, MMH: revised the manuscript critically and refined the illustrations.

AK, P, GK, SS, MMH: revised the final version of the manuscript critically and gave the final approval.

Registration of research studies

1. Name of the registry: NA
2. Unique Identifying number or registration ID: NA
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): NA

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Declaration of competing interest

The authors declare that there is no conflict of interests.

Acknowledgments

Not applicable.

References

- [1] M. Khoyi, D. Westfall, Hydrochlorothiazide. xPharm Compr Pharmacol Ref [Internet], 2021. Aug 10 [cited 2022 May 18];1–6. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK430766/>.
- [2] R. Kreutz, E.A.H. Algharably, A. Douros, Reviewing the effects of thiazide and thiazide-like diuretics as photosensitizing drugs on the risk of skin cancer [Internet], J. Hypertens. (2019 Oct 1) [cited 2022 May 18];37(10):1950–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/31145177/>.
- [3] A.D. Sinha, R. Agarwal, Thiazide diuretics in chronic kidney disease [Internet], Curr. Hypertens. Rep. (2015) [cited 2022 May 18];17(3). Available from: <https://pubmed.ncbi.nlm.nih.gov/25749608/>.
- [4] S.M. Lee, K. Kim, J. Yoon, S.K. Park, S. Moon, S.E. Lee, et al., Association between use of hydrochlorothiazide and nonmelanoma skin cancer: common data model cohort study in Asian population [Internet], J. Clin. Med. (2020 Sep 1) [cited 2022 May 18];9(9):1–11. Available from: <https://pubmed.ncbi.nlm.nih.gov/32916988/>.
- [5] A. Randhawa, G. Wylie, Severe widespread actinic damage and squamous cell carcinoma: could hydrochlorothiazide be implicated? A report of two cases [Internet], Br. J. Hosp. Med. (2020 Mar 2) [cited 2022 May 18];81(3). Available from: <https://pubmed.ncbi.nlm.nih.gov/32240009/>.
- [6] Tchernev G, Patterson JW. Telmisartan/hydrochlorothiazide-induced Nevus-Associated Cutaneous Melanoma: First Report in the Medical Literature. <https://doi.org/10.1080/1751243320211890581> [Internet]. 2021 [cited 2022 May 18];14(3):289–93. Available from: <https://www.tandfonline.com/doi/abs/10.1080/17512433.2021.1890581>.
- [7] D.N. Olschewski, V. Hofschroer, N. Nielsen, D.G. Seidler, A. Schwab, C. Stock, The angiotensin II type 1 receptor Antagonist Losartan Affects NHE1-dependent melanoma cell behavior [Internet], Cell. Physiol. Biochem. (2018 Apr 1) [cited 2022 May 18];45(6):2560–76. Available from: <https://pubmed.ncbi.nlm.nih.gov/29558744/>.
- [8] J.A. Adalsteinsson, S. Muzumdar, R. Waldman, C. Hu, R. Wu, D. Ratner, et al., Association between hydrochlorothiazide and the risk of in situ and invasive squamous cell skin carcinoma and basal cell carcinoma: a population-based case-control study [Internet], J. Am. Acad. Dermatol. (2021 Mar 1) [cited 2022 May 18];84(3):669–75. Available from: <https://pubmed.ncbi.nlm.nih.gov/32791082/>.
- [9] J.B. Loureiro, M. Abrantes, P.A. Oliveira, L. Saraiva, P53 in skin cancer: from a master player to a privileged target for prevention and therapy [Internet], Biochim. Biophys. Acta Rev. Canc (2020 Dec 1) [cited 2022 May 18];1874(2). Available from: <https://pubmed.ncbi.nlm.nih.gov/32980466/>.
- [10] J. Rouette, H. Yin, A. Pottgård, K. Nirantharakumar, L. Azoulay, Use of hydrochlorothiazide and risk of melanoma and nonmelanoma skin cancer [Internet], Drug Saf. (2021 Feb 1) [cited 2022 May 18];44(2):245–54. Available from: <https://pubmed.ncbi.nlm.nih.gov/33104975/>.
- [11] Hydrochlorothiazide and Skin Cancer [Internet]. [cited 2022 May 18]. Available from: <https://www.austinhospital.com/skin-cancer-prevention/hydrochlorothiazide-and-skin-cancer-is-there-a-connection/>.
- [12] FDA Approves Label Changes to Hydrochlorothiazide to Describe Small Risk of Non-melanoma Skin Cancer | FDA [Internet]. [cited 2022 May 18]. Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-label-changes-hydrochlorothiazide-describe-small-risk-non-melanoma-skin-cancer>.
- [13] National Toxicology Program. Toxicology and Carcinogenesis Studies of Hydrochlorothiazide (CAS No. 58-93-5) in F344/N Rats and B6C3F1 Mice (Feed Studies). Natl Toxicol Program Tech Rep Ser [Internet]. 1989 Jul [cited 2022 May 18];357:1–194. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12695784>.
- [14] P.M. Garrido, J. Borges-Costa, Hydrochlorothiazide treatment and risk of non-melanoma skin cancer: review of the literature [Internet], Rev. Port. Cardiol. (2020 Mar 1) [cited 2022 May 18];39(3):163–70. Available from: <https://pubmed.ncbi.nlm.nih.gov/32354458/>.