Hydrochlorothiazide Use and Increased Squamous Cell Carcinoma Burden in a High-Risk Mohs Population: A Cross-Sectional Study

It is becoming increasingly clear from epidemiological, in vitro, and in vivo research that hydrochlorothiazide (HCTZ) enhances the photocarcinogenic effect of ultraviolet radiation and risk of cutaneous squamous cell carcinoma (SCC) in non-Hispanic whites.[1–3]

We conducted a 3-month single-center cross-sectional study for the purpose of determining whether HCTZ use was associated with increased SCC burden at the Mohs micrographic surgery (MMS) unit of Florida State University College of Medicine (FSUCOM), Tallahassee,

TABLE 1. Demographic Characteristics of the Total Cohort

	HCTZ (n = *174*)	*Non-HCTZ* (n = *629*)	p
Age, mean (SD)	74.6 (9.4)	73.0 (12.7)	.12
Sex			
Male	116 (66.7)	404 (64.2)	.49
Female	57 (33)	225 (36)	
High-burden SCC vs general Mohs, no. (%)			
High-burden SCC	58 (33.3)	138 (21.9)	<.01
General Mohs	116 (66.7)	491 (78.1)	
Combination hypertension therapy, no. (% of HCTZ use)			
Yes	112 (64)	*N*/A	
No (HCTZ alone)	62 (36)	*N*/A	
Smoking, no. (%)			
Yes	92 (52.9)	260 (41.3)	<.01
No	82 (47)	369 (59)	
Immunosuppressed,* no. (%)			
Yes	12 (6.9)	31 (4.9)	.31
No	162 (93.1)	598 (95.1)	
Average number of skin cancers per patient, mean			
SCC	24.5	14.4	<.001
SCCis	15.8	9.2	<.001
BCC	10.1	7.3	.06
BCC:SCC ratio	1.0: 2.5	1.0: 2.0	
Location of invasive SCC (not including SCCis), no.			
Scalp	354 (8.3)	633 (7.0)	.45
Face, total	1,368 (32.1)	3,591 (39.6)	
Forehead	215 (5.0)	578 (6.4)	.95
Eyelid	15 (0.4)	48 (0.5)	.45
Cheek	372 (8.7)	609 (6.7)	.56
Nose	124 (2.9)	427 (4.7)	.94
Ears	175 (4.1)	558 (6.2)	.33
Lip	53 (1.2)	134 (1.5)	.49
Other facial sites	414 (9.7)	1,237 (13.7)	.39
Neck	218 (5.1)	564 (6.2)	.31
Forearms	565 (13.2)	1,226 (13.5)	.06
Hands	548 (12.8)	919 (10.1)	<.01
Other body sites	1,212 (28.4)	2,122 (23.4)	.01
Total all sites	4,265	9,055	<.001

*Defined as organ transplant recipient, long-term corticosteroid use defined as continuous use for ≥1 year.

NMSC, nonmelanoma skin cancer; SCC, squamous cell carcinoma; SCCis, squamous cell carcinoma in situ; BCC, basal cell carcinoma; HTCZ, hydrochlorothiazide.

ISSN: 1076-0512 • Dermatol Surg 2019;00:1–4 •

Florida. Patients with a history of invasive SCC treated by the study's primary investigator (A.B.C.) and high-risk skin cancer management team within the 3-month study period were included in the study. We chose to define increased SCC burden (high-burden SCC) as Mohs patients with a lifetime history of ≥20 invasive cSCC and general Mohs patients (non-high-burden) as those with <20 lifetime cSCC. We did not include actinic keratosis (AK) with transition to squamous cell carcinoma in situ (SCCis) or AK with small foci of SCCis in determining high-burden SCC.

Data were analyzed with STATA (version 14.2) using descriptive models; an independent *t*-test was used for continuous normally distributed variables and a chi-squared test for binary variables, reported with *p*-values, comparing the risk factors in the 2 groups, "HCTZ users" and "non-HCTZ users."

A logistic regression analysis was performed for the total cohort to determine whether the use of HCTZ was a predictor of being in the "high-burden SCC" Mohs group, adjusted for age, sex, and smoking. A secondary logistic regression based on survey data was conducted with adjustments for the following covariates: age, sex, smoking, organ transplant recipient, use of tanning bed, outdoor exposure, skin type, and use of immunosuppressants. Additional subanalyses, reported with odds ratios (ORs), were conducted excluding individuals with organ transplant, immunosuppressant use, and high-risk skin type (Fitzpatrick I). Patients with HIV were excluded from all regression analyses.

Inclusion criteria resulted in a total cohort of 803 patients with a combined lifetime history of 19,632 NMSC and 11,163 MMS cases over a 30-year period from 1984 to 2014. All patients were white (n = 803), 520 men, 283 women, and the mean age (SD) was 74.6 (9.4) for HCTZ users and 73.0 (12.7) for nonusers. Hydrochlorothiazide users (n = 174) were more likely than nonusers (n = 629) to be classified as high-burden SCC (≥20 lifetime SCC; 33.3% vs 21.9%; $p < .01$). Hydrochlorothiazide users had a higher percentage of SCC (71.0% vs 66.4%; $p < .001$) and had a higher number of SCC per patient, (24.5 vs 14.4) compared with nonusers. The ratio of BCC to SCC was 1.0:2.5 and 1.0:2.0 for HCTZ and non-HCTZ users, respectively (Table 1).

The use of HCTZ was found to be a predictor of being in the high-burden SCC Mohs group OR 1.71 (95%

TABLE 2. Logistic Regression Analysis: Use of Hydrochlorothiazide (HCTZ) as a Predictor of Being in the "High-Burden SCC Group" Compared With the "General Group," Reported in Odds Ratio With 95% Confidence Intervals

	No. of Persons Exposed to HCTZ	*Total No. of Persons in the Cohort*	*OR 95% CI*
Full cohort			
Crude data	174	803	1.76 (1.22–2.55)
Adjusted for age, sex, and smoking	174	803	1.71 (1.17–2.51)
Survey data			
Crude data	102	406	1.79 (1.12–2.85)
Adjusted for age, sex, and smoking	102	406	1.80 (1.11–2.90)
Full model*	102	406	1.84 (1.13–3.00)
Expanded model†	102	406	2.21 (1.26–3.89)
Supplementary analyses (on survey data)			
Expanded model‡	91	371	2.03 (1.21–3.38)
Excluding high-risk skin types§	67	262	2.27 (1.20–4.31)

*Adjusted for age, sex, smoking, organ transplant recipients, use of tanning bed, outdoor exposure, skin type, and use of immunosuppressants.

†Adjusted for age, sex, smoking, skin type, use of immunosuppressants, exposure to radiation, organ transplant recipients, carcinogenic exposure, PUVA or UVB treatment, outdoor exposure to sun light, use of tanning beds, and hypertension.

‡Excluding individuals with organ transplant and users of immunosuppressants.

§Expanded model, excluding individuals with high-risk skin type (Fitzpatrick I).

CI, confidence interval; SCC, squamous cell carcinoma.

TABLE 3. Mohs Surgery Patient Demographics, Anatomical Locations, Histology, and Increased Subclinical Extension

	HCTZ Users (n = *168*)	*Non-HCTZ Users* (n = *596*)	p
Patient demographics			
Age, mean (SD)	74.7 (9.4)	73.0 (12.6)	.1
Sex			
Male (%)	114 (68)	389 (65)	.53
Female (%)	54 (32)	207 (34.7)	
High-burden SCC vs general Mohs, no. of patients (%)			
High-burden SCC	35 (20.8)	93 (15.6)	.11
General Mohs	133 (79.2)	503 (84.4)	
	HCTZ Users Mohs Surgery Sites, SCC (n = *2,528*)	*Non-HCTZ Users Mohs Surgery Sites, SCC* (n = *5,562*)	p
Mohs Surgery Sites			
High-burden SCC vs general Mohs, no. of SCC sites (%)			
High-burden SCC	1866 (73.8)	3,821 (68.7)	<.01
General Mohs	662 (26.2)	1741 (31.3)	
Location of SCC, no. (%)			
Scalp	253 (10.0)	413 (7.4)	.39
Forehead	128 (5.1)	406 (7.3)	.94
Lid	9 (0.4)	37 (0.7)	.09
Cheek	158 (6.3)	541 (9.7)	.88
Nose	90 (3.6)	341 (6.1)	.48
Ears	165 (6.5)	483 (8.7)	.64
Lip	46 (1.8)	106 (1.9)	.13
Other facial sites	281 (11.1)	973 (17.5)	.8
Neck	119 (4.7)	267 (4.8)	<.05
Forearms	281 (11.1)	624 (11.2)	.42
Hands	314 (12.4)	529 (9.5)	<.01
Other body	684 (27.1)	842 (15.1)	<.05
Total # SCC treated with Mohs surgery	2,528	5,562	
% of total Mohs cases that were SCC	76.3	70.9	
Increased subclinical extension, SCC (%)			
ISE (>equal to 3 Mohs stages)	344 (13.6)	884 (15.9)	.28
No ISE	2,184	4,678	

HCTZ, hydrochlorothiazide; ISE, increased subclinical extension; SCC, squamous cell carcinoma.

confidence interval [CI]; 1.17–2.51) for the total cohort using logistic regression analysis adjusted for age, sex, and smoking. After adjusting for age, sex, skin type, immunosuppressant use, solid organ transplant recipient, radiation therapy, carcinogenic exposure, treatment with PUVA or UVB, outdoor exposure to UV light, the use of tanning beds, and smoking, HCTZ use was found to be a predictor of being in the high-burden SCC group OR 2.22 (95% CI; 1.26–3.89) (Table 2).

Ninety five percent ($n = 765$) of the total cohort was treated with MMS at least once. All patients who treated with MMS met Mohs appropriate use criteria (score 7–9).[4] Statistically significant differences between HCTZ and non-HCTZ users were discovered: a higher percent were high-burden SCC (73.8 vs 68.7, $p < .01$); a higher percent of MMS-treated SCC were located on the hands (12.4 vs 9.5, $p < .01$) and "other body" site (27.1 vs 15.1, $p < .05$); a slightly lower percent of MMS-treated SCC were located on the neck (4.7 vs 4.8, $p < .05$). There were no statistically significant differences between the 2 groups for other anatomical locations or the presence of increased subclinical extension (Table 3). As part of our field-therapy optimization protocol, patients with diffuse sun damage and/or ill-defined SCC borders are aggressively treated preoperatively with 5-flourouracil or photodynamic therapy before Mohs surgery likely

decreasing the incidence of ISE. There was a lack of a statistically significant difference between the 2 groups with regard to SCC at sun-exposed anatomical locations other than the hands, which may be expected with HCTZ use. Patients identified as high-burden cSCC (high-risk) are treated more frequently with field therapies such as 5-flourouracil and photodynamic therapy on sun-exposed and sun-damaged anatomical locations such as the head and neck, as often as every 3 to 6 months and minimally annually.

Limitations of our study include an inability to account for total dose and duration of HCTZ use, duration of immunosuppression, and an inability to adjust for every confounding variable.

Together, this clinical data along with large statistical cohorts from countries with robust data sets add to the growing body of evidence for a link between HCTZ use and cutaneous SCC.

References

1. Arnspang S, Gaist D, Johannesdottir Schmidt SA, Holmich LR, et al. Hydrochlorothiazide use and risk of non-melanoma skin cancer: a nationwide case-control study from Denmark. J Am Acad Dermatol 2017;78:673–81.
2. Pottegård A, Hallas J, Olesen M, Svendsen MT, et al. Hydrochlorothiazide use is strongly associated with risk of lip cancer. J Intern Med 2017;282:322–31.
3. Nardone B, Majewski S, Kim AS, Kiguradze T, et al. Melanoma and non-melanoma skin cancer associated with angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers and thiazides: a matched cohort study. Drug Saf 2017;40:249–55.
4. Connolly SM, Baker DR, Coldiron BM, Fazio MJ, et al. AAD/ACMS/ASDSA/ASMS 2012 appropriate use criteria for Mohs micrographic surgery: a report of the American Academy of Dermatology, American College of Mohs surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs surgery. Dermatol Surg 2012;38:1582–603.

Sae Han, BS
Department of Sociomedical Sciences
Columbia University Mailman
School of Public Health
New York City, New York

Christopher M. Wolfe, DO
Lauren Angnardo, BS
Division of Dermatology
Mohs Micrographic Surgery Unit
Florida State University College of Medicine
Tallahassee, Florida

Sidsel Arnspang Pedersen, MD
Department of Public Health
Clinical Pharmacology and Pharmacy
University of Southern Denmark
Odense, Denmark
Department of Neurology
Odense University Hospital
Odense, Denmark
Department of Clinical Research
Faculty of Health Science
University of Southern Denmark
Odense, Denmark

David Gaist, MD, PhD
Department of Neurology
Odense University Hospital
Odense, Denmark
Department of Clinical Research
Faculty of Health Science
University of Southern Denmark
Odense, Denmark

Anton Pottegård, PhD
Department of Public Health
Clinical Pharmacology and Pharmacy
University of Southern Denmark
Odense, Denmark

Armand B. Cognetta Jr, MD
Division of Dermatology
Mohs Micrographic Surgery Unit
Florida State University College of Medicine
Tallahassee, Florida

The authors have indicated no significant interest with commercial supporters.