Keio University School of Medicine, Tokyo, Japan.[b]

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Reprint requests: Keitaro Fukuda, MD, PhD, Department of Dermatology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160-8582, Japan

E-mail: kei_fu@keio.jp

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Biotin interference in routine laboratory tests: A bibliometric analysis

To the Editor: Biotin (vitamin B_7), a cofactor in metabolic pathways, is often recommended to promote hair, skin, and nail growth. Biotin can interfere with routine laboratory tests that use biotin-streptavidin binding,[1] leading to misdiagnosis and even death.[2] A US Food and Drug Administration (FDA) warning on biotin interference was issued in 2017.[3] In a survey-based study, 60% of physicians were knowledgeable about biotin interference with thyroid/troponin tests, with most unaware of interactions with hepatitis, HIV, beta-human chorionic gonadotropin and vitamin D tests (S.R. Lipner, unpublished data, April 2020). This study aimed to characterize the biotin laboratory interference literature and frequency of reported laboratory interactions.

Web of Science (WOS) and SCOPUS were searched for term *biotin interference* alone and in combination with *troponin*, *thyroid*, *HCG*, *hepatitis*, *HIV*, and *vitamin D*. Results were analyzed for publications per year, research subject, Altmetric score, citation averages, and *h*-indices.

The search for *biotin interference* yielded 101 and 99 results in WOS and SCOPUS, respectively, with greater than 90% overlap and 109 unique publications. *Biotin interference* and *thyroid* was most frequent (71), followed by *troponin* (24) (Table I). Case reports/series showed that thyroid, parathyroid hormone, and troponin interference affected 39 (8 in patients with multiple sclerosis taking an average dose of 300 mg/day), 3, and 3 unique patients, respectively.

Biotin interference was first described in 1995, with a sharp increase in publications in 2017. Search results were most often published in clinical laboratory technology and biochemistry journals (Table I). The *h*-index, a metric of the cumulative impact of articles weighted to correct for highly cited articles, was 15 for the term *biotin interference*, 6 for *biotin interference* and *troponin*, and 10 for *biotin interference* and *thyroid* (Table I).

The top 20 most cited *biotin interference* publications were cited 11 to 62 times, with Altmetric scores, a measure of media attention of a publication, of 1 to 72. The most common theme was thyroid disease, in 6 of 20 (30%) (Table II). On average, publications with more citations did not correlate with higher Altmetric scores.

Our study shows that there were few publications on biotin interference before 2017, a spike in 2017 (likely prompting the 2017 FDA warning), and low *h*-index (<20) and media attention scores. These data are consistent with an Altmetric study on biotin literature after the FDA alert, showing that this warning was rarely mentioned and generally not published in high-impact journals.[4] Furthermore, the most highly cited articles were published in biochemistry or laboratory medicine journals, as opposed to medicine journals. Therefore, these biotin articles are more likely to be read by basic science researchers rather than dermatologists.

This bibliometric analysis of the biotin literature showed that there were relatively few search results and relatively low impact of publications regarding laboratory interference. Taken together, our study may explain the lack of physician awareness of the FDA warning regarding the risks of recommending biotin. Therefore, there is a need for more literature targeted toward dermatologists detailing the potential interference of biotin on various assays, especially those besides thyroid panels and

Table I. Characteristics of biotin literature*

Year, research subjects, citation report	Search result characteristics						
	biotin	biotin + thyroid	biotin + troponin	biotin + HCG	biotin + hepatitis	biotin + vitamin D	biotin + HIV
Total, n	109	71	24	4	4	3	1
Year, n							
2020	15	15	6		3		1
2019	27	21	8	2		1	
2018	27	21	6	1			
2017	23	9	3	1	1	2	
2016	5	3					
2006-2015	5	2	1				
2005-1995	7						
Research subjects, n (%)							
Laboratory technology/ biochemistry	45 (41)	24 (34)	15 (63)	3 (75)	1 (25)	2 (67)	1 (100)
Endocrinology	16 (15)	7 (10)	1 (4)	—	—	—	—
Medicine	12 (11)	30 (42)	6 (25)	—	2 (50)	1 (33)	—
Pathology	11 (10)	4 (17)	1 (4)	—	1 (25)	—	—
Dermatology	2 (2)	1 (1)	1 (4)	—	—	—	—
Neurology	6 (6)	2 (3)	—	—	—	—	—
Other	17 (16)	5 (7)	—	—	—	—	—
Citation report, n	—	—	—	—	—	—	—
h-Index	15	10	6	3	0	2	0
Average citations per item	7.16	11.14	7.38	6	0	29.33	
Sum of times cited	723	390	118	18	0	88	
Number of citing articles	258	193	91	16	0	74	

*The unique results of searches for *biotin interference* and the combination of *biotin interference* and other search words on WOS and SCOPUS. The number of relevant results is categorized by year published, research area, *h*-index of publications, and citation report. The percentages of results in each research area (as determined by the database) are listed.

troponins. Increased awareness of the potential negative effects of this increasingly popular and easily available supplement may be potentially lifesaving.

Bukhtawar Waqas, BA,[a] and Shari R. Lipner, MD, PhD[b]

Weill Cornell Medicine, New York, New York[a]; Department of Dermatology, Weill Cornell Medicine, New York, New York.[b]

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Correspondence to: Shari R. Lipner, MD, PhD, 1305 York Ave, 9th Floor, New York, NY 10021

E-mail: shl9032@med.cornell.edu

Table II. Top 20 most-cited articles on *biotin interference*[*]

Most-cited articles	Title	Year	Authors	Journal	Journal impact factor	Total times cited	Altmetric score
1	Factitious Graves' Disease Due to Biotin Immunoassay Interference—A Case and Review of the Literature	2016	Elston MS, Sehgal S, Du Toit S, Yarndley T, Conaglen JV	*Journal of Clinical Endocrinology & Metabolism*	5.6	62	17
2	High-Dose Biotin Therapy Leading to False Biochemical Endocrine Profiles: Validation of a Simple Method to Overcome Biotin Interference	2017	Piketty ML, Prie D, Sedel F, Bernard D, Hercend C, Chanson P, Souberbielle JC	*Clinical Chemistry and Laboratory Medicine*	3.6	49	10
3	Misdiagnosis of Graves' Disease With Apparent Severe Hyperthyroidism in a Patient Taking Biotin Megadoses	2016	Barbesino G	*Thyroid*	7.8	46	13
4	Positive and Negative Interference in Immunoassays Following Biotin Ingestion: A Pharmacokinetic Study	2012	Wijeratne NG, Doery JC, Lu ZX	*Pathology*	3.2	42	1
5	Association of Biotin Ingestion With Performance of Hormone and Nonhormone Assays in Healthy Adults	2017	Li D, Radulescu A, Shrestha RT, Root M, Karger AB, Killeen AA, Hodges JS, Fan SL, Ferguson A, Garg U, Sokoll LJ, Burmeister LA	*JAMA*	51.3	41	72
6	False Biochemical Diagnosis of Hyperthyroidism in Streptavidin-Biotin-Based Immunoassays: The Problem of Biotin Intake and Related Interferences	2017	Piketty ML, Polak M, Flechtner I, Gonzales-Briceno L, Souberbielle JC	*Clinical Chemistry and Laboratory Medicine*	3.6	42	1
7	Biotin Interference on TSH and Free Thyroid Hormone Measurement	2012	Kwok JSS, Chan HIS, Chan MHM	*Pathology*	3.2	41	1
8	Biotin Interference With Routine Clinical Immunoassays: Understand the Causes and Mitigate the Risks	2017	Samarasinghe S, Meah F, Singh V, Basit A, Emanuele N, Emanuele MA, Mazhari A, Holmes EW	*Endocrine Practice*	3.8	34	2
9	Interference by Biotin Therapy on Measurement of TSH and FT4 by Enzyme Immunoassay on Boehringer Mannheim ES700 Analyser	1996	Henry JG, Sobki S, Arafat N	*Annals of Clinical Biochemistry*	1.9	30	N/A
10	Characterization of the Scope and Magnitude of Biotin Interference in Susceptible Roche Elecsys Competitive and Sandwich Immunoassays	2018	Trambas C, Lu Z, Yen TN, Sikaris K	*Annals of Clinical Biochemistry*	1.9	29	10

Continued

Table II. Cont'd

Most-cited articles	Title	Year	Authors	Journal	Journal impact factor	Total times cited	Altmetric score
11	Falsely Low Parathyroid Hormone Secondary to Biotin Interference: A Case Series	2013	Waghray A, Milas M, Nyalakonda K, Siperstein AE	*Endocrine Practice*	3.8	22	6
12	Evaluation of Biotin Interference on Immunoassays: New Data for Troponin I, Digoxin, NT-Pro-BNP, and Progesterone	2016	Willeman T, Casez O, Faure P, Gauchez AS	*Clinical Chemistry and Laboratory Medicine*	3.6	19	2
13	Biotin Interference in Immunoassays Mimicking Subclinical Graves' Disease and Hyperestrogenism: A Case Series	2017	Batista MC, Ferreira CES, Faulhaber ACL, Hidal JT, Lottenberg SA, Mangueira CLP	*Clinical Chemistry and Laboratory Medicine*	3.6	18	N/A
14	Prevalence of Biotin Supplement Usage in Outpatients and Plasma Biotin Concentrations in Patients Presenting to the Emergency Department	2018	Katzman BM, Lueke AJ, Donato LJ, Jaffe AS, Baumann NA	*Clinical Biochemistry*	2.4	17	13
15	Biotin: From Nutrition to Therapeutics	2017	Mock DM	*Journal of Nutrition*	3.6	20	3
16	Biotin Interference in Clinical Immunoassays: A Cause for Concern	2017	Holmes EW, Samarasinghe S, Emanuele MA, Meah F	*Archives of Pathology & Laboratory Medicine*	4.2	16	1
17	Free and Bound Biotin Molecules in Helminths: A Source of Artifacts for Avidin Biotin-Based Immunoassays	1996	Romaris F, Iglesias R, Garcia LO, Leiro J, Santamarina MT, Paniagua E, Ubeira FM	*Parasitology Research*	2.1	13	N/A
18	Comprehensive Assessment of Biotin Interference in Immunoassays	2018	Li JL, Wagar EA, Meng QH	*Clinica Chimica Acta*	2.7	12	1
19	Biotin-Containing Proteins of the Insect Nervous System, a Potential Source of Interference With Immunocytochemical Localization Procedures	1995	Ziegler R, Engler DL, Davis NT	*Insect Biochemistry and Molecular Biology*	3.6	13	N/A
20	Rethinking Biotin Therapy for Hair, Nail, and Skin Disorders	2018	Lipner SR	*Journal of the American Academy of Dermatology*	7.1	11	14

*The top 20 most cited papers resulting from a search of *biotin interference*, categorized by year published, author, journal, total times cited, and Altmetric score.

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The effect of intradermal botulinum toxin on androgenetic alopecia and its possible mechanism

To the Editor: Dihydrotestosterone (DHT) induces transforming growth factor β1 (TGF-β1) in dermal papilla cells (DPCs) to suppress follicular epithelial cell growth. Thus, TGF-β1 is one of the key players in androgenetic alopecia (AGA), and its antagonist may prevent AGA.[1] Botulinum toxin type A (BTX) may inhibit TGF-β1 secretion from DPCs as it does with scar tissue fibroblasts,[2] which share the mesenchymal origin. Recently, BTX has been effective for the treatment of AGA.[3,4]

Here, we evaluated the efficacy and safety of intradermal injection of BTX (Nabota, Daewoong Pharmaceutical Co, Seoul, Korea) in AGA and its relationship with TGF-β1.

Patients with AGA were enrolled according to the basic and specific classification.[5] Patients undergoing treatment with finasteride, minoxidil, or supplements that affect hair growth were excluded. This study was approved by the institutional review board. The participants received intradermal BTX injections every 4 weeks for 24 weeks. A total of 30 units of BTX were injected at 20 different sites on the balding scalp in each treatment session.

The expression of TGF-β1 from cultured DPCs under 10^{-9}mol/L DHT was evaluated by reverse transcription polymerase chain reaction analysis. Suppression of DHT-induced TGF-β1 secretion from DPCs by BTX (2.5 U/10^6 cells) was assessed by immunofluorescence staining. The doses of BTX in the in vitro study were selected on the basis of a previous report investigating the effect of BTX (2.5 U/10^6 cells) on TGF-β1 secretion from the fibroblasts.[2]

This study comprised 18 male patients with a mean age of 49.00 ± 6.50 years. In an unblinded phototrichogram image analysis (Lead M Corp, Seoul, Korea), the mean ± standard deviation of hairs per square centimeter at weeks 0, 12, and 24 were 129.61 ± 28.05, 129.11 ± 28.80, and 136.22 ± 33.05, respectively. The number of hairs significantly increased at week 24 ($P = .012$) but not at week 12 ($P = .803$). Comparison of the pre- and posttreatment photographs showed significant improvement at week 24 ($P = .031$) (Fig 1). DHT upregulated the TGF-β1 expression of DPCs in 96 hours, whereas BTX downregulated the TGF-β1 expression in 96 hours (Fig 2). No serious adverse events or changes in laboratory parameters were reported.

DHT-induced synthesis of paracrine mediators (Dkk-1, interleukin 6, TGF-β1) in balding DPCs may play a role in AGA and represent alternative treatment targets.[1,6] However, clinical studies targeting these paracrine mediators have not been reported. In our in vitro study, BTX successfully abrogated DHT-induced secretion of TGF-β1 from DPC. Intradermal injection of BTX was effective against AGA by inhibiting TGF-β1 secretion in the hair bulb, which is thought to suppress follicular keratinocyte growth and changes in the hair cycle.[1] Previous studies reported the use of intramuscular BTX injections to treat AGA without elucidating the exact underlying mechanism.[3,4] Considering the diffusion of the injected liquid BTX and scalp anatomy, even the intramuscular injection[3,4] may indirectly inhibit the secretion of TGF-β1 from DPCs in the hair bulb. Advanced AGA or older age may have adversely influenced our treatment outcome.

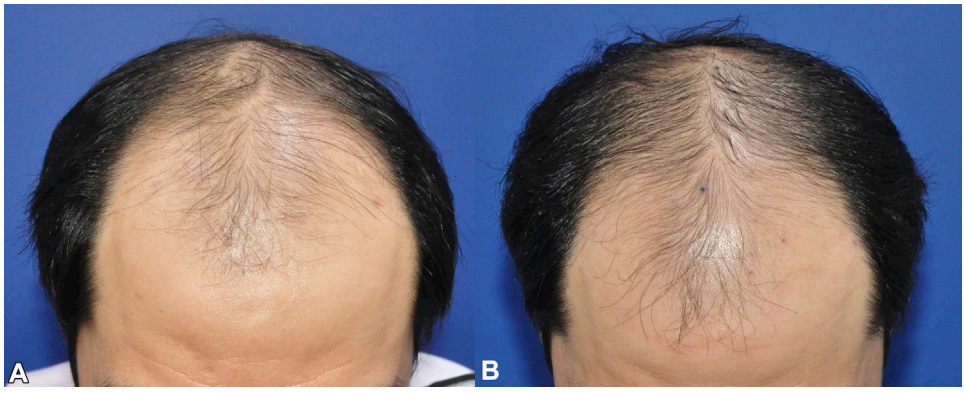

Fig 1. Comparison of pretreatment and posttreatment clinical images. **A**, Baseline photography and (**B**) improvement after 6 months of treatment are shown.