et al., 1983). A recent claims-based study from Detroit, Michigan, found that warts were more commonly diagnosed in Caucasians (22.6%) than in African Americans (5.7%) (Henderson *et al.*, 2012). A previous study of the determinants of sexually transmitted infections found that Caucasians were more likely than African Americans to have venereal warts (Short *et al.*, 1984). Furthermore, a recent prevalence study of warts in Caucasian Dutch schoolchildren aged 4–12 years showed that one-third of the children had warts (van Haalen *et al.*, 2009). This suggests that the incidence described in the United States may actually be lower than that in other countries owing to the mixture of racial and ethnic groups in our population.

The strengths of this study include being a large-scale, US population–based survey with minimal selection bias, and controlling for confounding demographic variables in multivariate models. However, the study also has some limitations. Warts and comorbidities were assessed by caregiver report, which have not been fully validated. The appearance of common warts is reasonably characteristic, and lay recognition can be assumed to be good. Another concern about self/parental-reported warts is potential reporting bias, where subjects with higher socioeconomic status may have better overall health and be more motivated to seek out care for warts. Future studies are needed to validate the accuracy of self/caregiver report and determine the ideal survey instrument for the epidemiologic study of these disorders.

The peak age of warts occurring at 9–10 years and common presence in teenagers may relate to school attendance and exposures from peer groups. School- and family-based transmissions have been cited as a leading cause of disease (van Haalen *et al.*, 2009). Age-specific physical activity and sports participation, particularly swimming pool use (Penso-Assathiany *et al.*, 1999) and use of communal showers (Johnson, 1995), have been linked to transmission of warts. Racial/ethnic and socioeconomic disparities may affect age-specific activities and pool use. Future studies are warranted to determine the role of age-specific physical activities and local environment on the US prevalence of warts.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

The results of this study were presented in part at the 2013 International Investigative Dermatology meeting in Edinburgh, Scotland.

Author contributions

Manuscript authorship: JI Silverberg, NB Silverberg; data analysis and interpretation: JI Silverberg, NB Silverberg; and statistical analysis: JI Silverberg.

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Risk of Rosacea in Patients with Diabetes Using Insulin or Oral Antidiabetic Drugs

Journal of Investigative Dermatology (2013) **133,** 2790–2793; doi:10.1038/jid.2013.225; published online 27 June 2013

TO THE EDITOR

Rosacea is a chronic facial skin disease with a presumed key vasodilatory component (Steinhoff *et al.*, 2011), whereas diabetes mellitus (DM) is associated with impaired vasodilation congruent with the degree of endothelial dysfunction. Insulin is a physiologic regulator of the vascular tone, but in the insulin-resistant state insulin increases vasoconstriction (Browne *et al.*, 2003; Kim *et al.*, 2006; Rask-Madsen and King, 2007; Cade, 2008; Barrett *et al.*, 2009; Ko *et al.*, 2010). Using the UK-based General

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; GPRD, General Practice Research Database; $HbA1_c$, hemoglobin $A1_c$; ISAC, Independent Scientific Advisory Committee; MHRA, Medicines and Healthcare Products Regulatory Agency; NSAID, nonsteroidal anti-inflammatory drug; OAD, oral antidiabetic drug; OR, odds ratio

Accepted article preview online 8 May 2013; published online 27 June 2013

Table 1. Distribution of diagnosed DM stratified by $HbA1_c$ values and disease duration

	Rosacea cases, no. ($n=53,927$)	(%)[1]	Rosacea-free controls, no. ($n=53,927$)	(%)[1]	OR crude	(95% CI)	OR adj[2]	(95% CI)
No diagnosed DM[1]	52,241	(96.9)	51,885	(96.2)	1.00	(ref.)	1.00	(ref.)
Diagnosed DM	1,686	(3.1)	2,042	(3.8)	0.81	(0.76–0.87)	0.80	(0.74–0.85)
Diagnosed DM by $HbA1_c$ (%)								
0–7.5	880	(1.6)	971	(1.8)	0.89	(0.81–0.98)	0.87	(0.79–0.96)
7.6–10.9	519	(1.0)	684	(1.3)	0.75	(0.67–0.84)	0.73	(0.65–0.82)
⩾11	58	(0.1)	101	(0.2)	0.57	(0.41–0.78)	0.57	(0.41–0.79)
NA	229	(0.4)	286	(0.5)	0.79	(0.66–0.94)	0.78	(0.65–0.94)
Diagnosed DM by treatment duration (years)								
Untreated	444	(0.8)	439	(0.8)	1.00	(0.87–1.14)	0.96	(0.84–1.10)
<1	135	(0.3)	170	(0.3)	0.79	(0.63–0.99)	0.78	(0.62–0.98)
1–3	288	(0.5)	325	(0.6)	0.87	(0.74–1.02)	0.85	(0.72–1.00)
3–5	252	(0.5)	312	(0.6)	0.79	(0.67–0.94)	0.80	(0.68–0.95)
5–10	368	(0.7)	503	(0.9)	0.72	(0.63–0.82)	0.71	(0.62–0.81)
⩾10	199	(0.4)	293	(0.5)	0.67	(0.55–0.80)	0.64	(0.54–0.78)

Abbreviations: adj, adjusted; CI, confidence interval; DM, diabetes mellitus; $HbA1_c$, hemoglobin $A1_c$; NA, no answer; OR, odds ratio; ref., reference.
[1]Percentages are rounded to nearest decimal.
[2]OR adjusted for smoking, body mass index, and alcohol consumption.

Practice Research Database (GPRD; Khan *et al.*, 2010), we conducted a large population-based case–control analysis, including patients with a first-time rosacea diagnosis (index date) between January 1995 and September 2009. We excluded patients with recorded alcoholism (explicit medical Read-code), cancer, or HIV, and patients with <3 years of recorded active history before the index date. Patients with diagnosed rhinophyma or ocular rosacea in the absence of another record of facial rosacea were excluded. We randomly matched one control to each case on age, sex, general practice, calendar time, and number of previous years of history in the database, and applied the same exclusion criteria to controls as to cases. The study protocol was approved by the ISAC (Independent Scientific Advisory Committee) for MHRA (Medicines and Healthcare Products Regulatory Agency) database research. Disease exposure was defined as a DM diagnosis (validity proven elsewhere; Khan *et al.*, 2010; Van Staa and Abenhaim, 1994) before the index date. Among DM patients, we captured the last hemoglobin $A1_c$ ($HbA1_c$) value before the index date, stratified into four categories (none, ⩽7.5%, 7.6–10.9%, or ⩾11%). DM duration was stratified into six categories by the number of years between the first recorded prescription of any antidiabetic drug and the index date (no treatment, <1, 1–3, 3–5, 5–10, and 10+ years), sub-stratified by $HbA1_c$ levels (⩽7.5% or >7.5%). We analyzed antidiabetic drug use (insulin vs. other antidiabetic drugs) stratified by timing (⩽ or >180 days before the index date) and duration of use (number of prescriptions before the index date). Within a mutually exclusive drug use model among diagnosed diabetics, we assessed insulin exposure (irrespective of any oral antidiabetic drug (OAD) use) and OAD exposure alone (no insulin exposure at any time), stratified by timing and duration of drug use and by $HbA1_c$ levels. We conducted multivariate conditional logistic regression analyses using SAS statistical software (version 9.3, SAS Institute, Cary, NC), and calculated odds ratios (ORs) with 95% confidence intervals (CIs). We adjusted all ORs for smoking (non, current, ex, unknown), alcohol consumption (0, 1–4, 5–9, 10–14, 15–24, or 25+ units per week, unknown), and body mass index (BMI, <18.5, 18.5–24.9, 25.0–29.9, or $+30\,kg\,m^{-2}$, unknown). Because other potential confounders, i.e., depression, cardiovascular diseases (hypertension, myocardial infarction, hyperlipidemia, heart failure, ischemic heart disease, ischemic stroke/transient ischemic attack), cardiovascular drugs (calcium channel blockers, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, statins, acetylsalicylic acid (anticlotting dosage), vitamin K antagonists, and diuretics), systemic steroids, and nonsteroidal anti-inflammatory drugs (NSAIDs) did not alter the relative risk estimates for the association between DM or insulin and rosacea by ⩾10%, we did not include them in the final model.

The study population's demographics and methodology including limitations have been described in detail elsewhere (Spoendlin *et al.*, 2012). Of the 53,927 rosacea cases and the same number of controls, 1,686 (3.1%) cases and 2,042 (3.8%) controls had a recorded DM diagnosis revealing an OR of 0.80 (95% CI 0.74–0.85), which further decreased with increasing $HbA1_c$ values (OR 0.57, 95% CI 0.41–0.79,

Table 2. Mutually exclusive antidiabetic drug use stratified by timing and duration of drug exposure and by $HbA1_c$ values

	Rosacea cases, no. ($n=53,927$)	(%)[1]	Rosacea-free controls, no. ($n=53,927$)	(%)[1]	OR crude	(95% CI)	OR adj[2]	(95% CI)
No DM	52,241	(96.9)	51,885	(96.2)	1.00	(ref.)	1.00	(ref.)
Diagnosed DM untreated	444	(0.8)	439	(0.8)	1.00	(0.88–1.14)	0.96	(0.84–1.10)
Diagnosed DM, $HbA1_c \leqslant 7.5$								
Current insulin 1–39 (± OAD[3])	52	(0.1)	73	(0.1)	0.70	(0.49–1.00)	0.67	(0.47–0.96)
Current insulin 40+ (± OAD[3])	37	(0.1)	54	(0.1)	0.68	(0.44–1.03)	0.69	(0.45–1.05)
Past insulin use (± OAD[3])	9	(0.0)	16	(0.0)	0.56	(0.25–1.27)	0.55	(0.24–1.24)
Current OAD[3] only, 1–19	154	(0.3)	175	(0.3)	0.87	(0.70–1.08)	0.84	(0.67–1.04)
Current OAD only, 20–39	125	(0.2)	143	(0.3)	0.86	(0.67–1.10)	0.85	(0.67–1.09)
Current OAD only, 40+	184	(0.3)	195	(0.4)	0.92	(0.75–1.13)	0.92	(0.75–1.13)
Past OAD use only	20	(0.0)	32	(0.1)	0.59	(0.34–1.04)	0.62	(0.35–1.09)
Diagnosed DM, $HbA1_c > 7.5$								
Current insulin 1–39(± OAD[3])	118	(0.2)	160	(0.3)	0.72	(0.57–0.92)	0.72	(0.57–0.92)
Current insulin 40+ (± OAD[3])	119	(0.2)	160	(0.3)	0.73	(0.58–0.93)	0.69	(0.55–0.88)
Past insulin use (± OAD[3])	7	(0.0)	14	(0.0)	0.48	(0.20–1.20)	0.43	(0.17–1.07)
Current OAD[3] only, 1–19	103	(0.2)	138	(0.3)	0.74	(0.57–0.95)	0.72	(0.55–0.93)
Current OAD only, 20–39	76	(0.1)	83	(0.2)	0.91	(0.66–1.24)	0.90	(0.65–1.23)
Current OAD only, 40+	118	(0.2)	159	(0.3)	0.73	(0.58–0.93)	0.73	(0.57–0.92)
Past OAD use only	3	(0.0)	29	(0.1)	0.10	(0.03–0.33)	0.11	(0.03–0.36)
Treated DM, $HbA1_c$ not recorded	117	(0.2)	172	(0.3)	0.67	(0.53–0.85)	0.67	(0.52–0.85)

Abbreviations: CI, confidence interval; DM, diabetes mellitus; $HbA1_c$, hemoglobin $A1_c$; OAD, oral antidiabetic drug; OR, odds ratio; ref., reference.
[1]Percentages are rounded to the nearest decimal.
[2]Adjusted for smoking, body mass index, and alcohol consumption.
[3]OADs include biguanides, sulfonylureas, thiazolidinediones, glinides, α-glucosidase inhibitors, and incretin-mimetics.

$HbA1_c$ ⩾11%) and with increasing disease duration (OR 0.64, 95% CI 0.54–0.78, disease duration ⩾10 years; Table 1). At earlier disease stages, we observed decreased ORs in poorly controlled diabetics ($HbA1_c$ >7.5%), whereas a disease history of ⩾5 years revealed decreased ORs irrespective of blood glucose control (Supplementary Table S2 online). Exposure to any antidiabetic drug was associated with a decreased OR of 0.76 (95% CI 0.71–0.83). The prevalence of insulin exposure was higher in controls (1.1%) than in cases (0.7%), yielding an OR of 0.75 (95% OR 0.65–0.85), unchanged across strata of timing and duration of insulin exposure. OAD exposure was also slightly more prevalent in controls (2.6%) than in cases (2.1%, OR 0.83, 95% CI 0.76–0.91), again independent of timing and duration of drug exposure (Supplementary Table S1 online). The mutually exclusive drug use model (Table 2) yielded significantly decreased ORs for insulin users, irrespective of $HbA1_c$ control. OAD use in the absence of insulin was associated with decreased ORs at $HbA1_c$ levels >7.5%, but non-significant results at $HbA1_c$ levels ⩽7.5%.

Our findings suggest a decreased rosacea risk in DM patients at an advanced disease state, i.e., in patients with high $HbA1_c$ levels and/or long disease duration. The underlying mechanism remains to be clarified; we hypothesize a reciprocal link of the two diseases via the degree of endothelial dysfunction and thus impaired vasodilation. Extrinsic insulin exposure revealed significantly decreased ORs, irrespective of $HbA1_c$ control, whereas OAD use yielded decreased ORs in poorly controlled diabetics only. This might reflect an additional insulin effect on the rosacea risk, but it could also depict a proxy for disease duration and/or severity. As insulin is used in diabetic patients only, we cannot disentangle the role of insulin from the underlying disease within this observational study. Most diabetic patients were coded with a DM subtype–unspecific code (66.6% cases, 68.3% controls), but as ORs were decreased in insulin users and in poorly controlled OAD users, a subtype-independent effect seems likely, especially as endothelial damage and diabetic microvascular complications are presumably driven by shared mechanisms caused by hyperglycemia in both DM subtypes (The Diabetes Control and Complications Trial Research Group, 1993; UKPDS Group, 1998; Browne *et al.*, 2003; Schalkwijk and Stehouwer, 2005; Rask-Madsen and King, 2007; Cade, 2008). Our study provides evidence for a significantly

reduced rosacea risk in diabetics at an advanced disease stage. This is, to our knowledge, a previously unreported finding, but some residual confounding or chance cannot entirely be ruled out. Whether insulin enhances this effect *per se* or whether it reflects a proxy for disease severity remains unclear.

CONFLICT OF INTEREST

JJV is an employee at Galderma, France. The other authors state no conflict of interest.

ACKNOWLEDGMENTS

This study was supported by an unconditional grant by Galderma, France.

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This study was conducted in Basel, Switzerland.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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A Mutation-Independent Therapeutic Strategy for Dominant Dystrophic Epidermolysis Bullosa

Journal of Investigative Dermatology (2013) **133,** 2793–2796; doi:10.1038/jid.2013.241; published online 11 July 2013

TO THE EDITOR

Dominant dystrophic epidermolysis bullosa (DDEB) is a rare genetic blistering skin disorder with no known cure. The disorder is caused by mutations in the *COL7A1* gene leading to weakened α1(VII) (collagen VII) homotrimers, whose function is to knit epidermal and dermal skin layers together (Parente *et al.*, 1991; McGrath *et al.*, 1993). Over 60 *COL7A1* mutations have been implicated in DDEB, making this disorder, similar to many other dominant disorders, extremely heterogenous (Nakamura *et al.*, 2004).

A gene therapy strategy for DDEB involving suppression of mutant *COL7A1* transcripts using allele-specific RNA interference (RNAi) molecules targeting a mutation site has been adopted *in vitro* (Pendaries *et al.*, 2012). This informative study demonstrated potent and specific RNAi-mediated allele-specific suppression of a *COL7A1* splice-site mutation in cells; similar levels of RNAi specificity have been obtained by others (Hickerson *et al.*, 2008; Lindahl *et al.*, 2008; Atkinson *et al.*, 2011). In contrast, for many *COL7A1* mutations and indeed other target genes, allele-specific RNAi suppression has not been achieved (de Yñigo-Mojado *et al.*, 2011; Pendaries *et al.*, 2012 and Morgan *et al.*, unpublished data).

Given the vast array of *COL7A1* mutations implicated in DDEB, the development of RNAi-mediated mutation-specific therapies targeting each mutant is not technically/economically feasible. In this study, we have addressed the substantial problem of DDEB-associated mutational heterogeneity and have tested four mutation-independent small interfering RNAs (siRNAs; si1-si4) targeting different regions of the *COL7A1*

Abbreviations: DDEB, dominant dystrophic epidermolysis bullosa; NT, nontargeting negative control RNAi; R, replacement COL7A1 gene; RNAi, RNA interference; siRNA, small interfering RNA

Accepted article preview online 6 June 2013; published online 11 July 2013