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Incidence and Prognosis of Psoriasis and Psoriatic Arthritis in Patients Undergoing Bariatric Surgery

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IMPORTANCE Psoriasis and obesity are strongly linked, and weight loss appears to improve psoriasis symptoms and severity. Bariatric surgery may induce remission of psoriasis, but data are limited to small studies and case series.

OBJECTIVE To examine the incidence and prognosis of psoriasis and psoriatic arthritis in patients undergoing bariatric surgery (gastric bypass and gastric banding).

DESIGN, SETTING, AND PARTICIPANTS This population-based cohort study used individual-level linkage of administrative and public health registers in Denmark. All Danish citizens who received gastric bypass or gastric banding between January 1, 1997, and December 31, 2012, were included in the study. Data analysis was performed from February 4 to April 14, 2016.

MAIN OUTCOMES AND MEASURES The outcomes were incident (new-onset) psoriasis or psoriatic arthritis, or progression to severe psoriasis. Incidence rates per 1000 person-years were calculated, and crude and adjusted hazard ratios (HRs) were estimated by Cox regression models and presented with 95% CIs. The HRs were obtained by comparing the risk in the cohort of patients presurgery and postsurgery, with the presurgery groups serving as the reference groups.

RESULTS We identified 12 364 and 1071 patients receiving gastric bypass and gastric banding, respectively. The gastric bypass subset was composed of 9480 (76.7%) women and 2884 (23.3%) men at the study start; the mean (SD) age of these patients was 27.8 (10.1) years at the study start and 41.0 (10.0) years at the time of surgery. The gastric banding subset was composed of 800 (74.7%) women and 271 (25.3) men; the mean (SD) age of these patients was 32.3 (10.1) years at the study start and 41.7 (10.0) years at the time of surgery. Adjusted HRs of psoriasis were 0.52 (95% CI, 0.33-0.81) and 1.23 (95% CI, 0.40-3.75) for gastric bypass and gastric banding, respectively. Similarly, adjusted HRs of progression to severe psoriasis were 0.44 (95% CI, 0.23-0.86) and 1.18 (95% CI, 0.12-11.49) for gastric bypass and gastric banding, respectively. Adjusted HRs of psoriatic arthritis were 0.29 (95% CI, 0.12-0.71) and 0.53 (95% CI, 0.08-3.56) for gastric bypass and gastric banding, respectively.

CONCLUSIONS AND RELEVANCE Gastric bypass was associated with a significantly reduced risk and improved prognosis of psoriasis and psoriatic arthritis, whereas gastric banding was not. This finding may be caused by the postoperative differences in nutrient intake and/or weight loss as well as differences in the secretion of hormones that potentially modulate inflammation.

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Psoriasis is a chronic inflammatory disease of which the exact cause is not fully understood, but both genetic and environmental factors have been implicated in its onset and progression.[1] The prevalence is approximately 2% to 3% in Europe and up to 9% in some Nordic countries.[2] Psoriasis is characterized by localized or widespread thick, raised, silvery white scaling and pruritic plaques. It is also a systemic disease that affects joints, vasculature, and other tissues.[1,3] Approximately one-third of patients with psoriasis develop psoriatic arthritis, and patients with severe psoriasis have a shortened life expectancy (most likely because of cardiovascular disease).[1,3] Obesity is significantly and independently associated with the presence and severity of psoriasis,[4] likely as a result of obesity-induced, systemic low-grade inflammation.[5,6] Obese patients show a slowed response to antipsoriatic therapy,[7] so weight loss has been suggested as a potential therapeutic option for patients with psoriasis.[8,9]

Gastric banding is considered a purely restrictive procedure that involves the laparoscopic placement of an adjustable band around the cardia of the stomach, creating an approximately 15-mL proximal pouch. However, gastric bypass, in particular Roux-en-Y gastric bypass, is the favored surgical treatment for patients who are morbidly obese and accounts for more than 95% of bariatric surgical procedures in Denmark (in accordance with national and international guidelines).[10] In this procedure, the stomach is divided into a small proximal pouch from which ingested nutrients are diverted to the jejunum with a Roux-en-Y gastrojejunostomy and thus bypass a large segment of the proximal small bowel. Gastric bypass results in robust and sustained weight loss. Interestingly, the procedure also causes a rapid improvement of the glucose tolerance in patients with type 2 diabetes (or even complete remission of the diabetic state), even before any significant weight loss has occurred.[11] This phenomenon is most likely mediated by multifarious factors. One of the most well-described factors is the rerouting of ingested nutrients directly from the stomach to the distal part of the small intestine where there are abundant enteroendocrine cells that secrete the insulinotropic, glucagonostatic, and appetite-reducing hormone glucagon-like peptide-1 (GLP-1).

Research has suggested that bariatric surgery has antipsoriatic effects, as evidenced by some patients who are in complete remission of psoriasis after undergoing gastric bypass, but these data are limited to small studies and case series; even less is known about the effects of gastric banding.[12-15] Therefore, we examined the incidence and prognosis of psoriasis and psoriatic arthritis in patients treated with gastric bypass or gastric banding. We identified a nationwide Danish cohort and observed them for a maximum of 16 years.

Key Points

Question Does bariatric surgery affect the risk and prognosis of psoriasis?

Findings In a population-based cohort study, gastric bypass was associated with reduced risk and improved prognosis of psoriasis and psoriatic arthritis, whereas gastric banding was not.

Meaning The results may be due to postoperative differences in nutrient intake and/or weight loss, but differences in the secretion of hormones that potentially modulate inflammation may also play a role.

Methods

Data Sources and Study Population

In Denmark, the population-based health registry provides an opportunity to perform a population-based cohort study. Each citizen is assigned a unique civil registration number at birth or on immigration, allowing for unambiguous linkage among all population-based administrative and health registries in the country.[16] The Danish National Health Service provides all residents with tax-supported health care that includes unrestricted access to hospitals and general practitioners. Information on all patients admitted to Danish hospitals is stored in the Danish National Patient Register, in accordance with the Danish version of *the International Classification of Diseases*; hospital-based treatments, such as surgical procedures, are recorded by treatment procedure (Sundhedsvæsnets Klassifikation System [SKS]) codes.[17] In addition, all pharmacy-dispensed prescriptions in the country are recorded in the Register of Medicinal Product Statistics, and all drugs are classified according to the Anatomical Therapeutic Chemical Classification System.[18]

Using data from the Danish National Patient Registry, we identified all patients who received bariatric surgery, including gastric bypass (SKS code KJDF1) and gastric banding (SKS code KJDF2), between January 1, 1997, and December 31, 2012. All patients were included at the study start (January 1, 1997) and followed up until migration, death from any cause, the occurrence of an endpoint, or December 2012, whichever came first. Patients with psoriatic disease prior to study start were excluded to enable examination of incident (new-onset) cases of psoriasis or psoriatic arthritis.

Covariates (ie, alcohol abuse and diabetes, smoking, and socioeconomic status) were assessed up to 5 years prior to study start or surgery, as appropriate. Information on tax-reported household income was obtained from Statistics Denmark to calculate an age-standardized index of socioeconomic status between 0 (lowest group) and 4 (highest group) on the basis of mean gross annual income. Diabetes was defined by either a hospital diagnosis or use of glucose-lowering drugs. Collection of proxy data on smoking history and alcohol abuse was performed as described previously.[19,20] The end points were the first occurrence of psoriasis or psoriatic arthritis and the classification of psoriasis as a severe disease. Patients were classified with severe psoriasis when they received systemic antipsoriatic therapy (biological drugs, cyclosporine, psoralens, retinoids, or methotrexate). A previous study described and validated this method for psoriasis identification and severity classification with a sensitivity of 98%.[19] The end points were analyzed separately, and the occurrence of an end point in one analysis (eg, risk of psoriasis) did not result in censoring in the other analysis (eg, risk of psoriatic arthritis). We followed recommendations from Strengthening the Reporting of

Table 1. Characteristics of the Study Population[a]

Characteristic	Gastric Bypass (n = 12 364)		Gastric Banding (n = 1071)	
	At Study Start	At Time of Surgery	At Study Start	At Time of Surgery
Sex				
Women	9480 (76.7)		800 (74.7)	
Men	2884 (23.3)		271 (25.3)	
Age, mean (SD)	27.8 (10.1)	41.0 (10.0)	32.3 (10.1)	41.7 (10.0)
Socioeconomic status				
Lowest income group	2492 (20.2)	2472 (20.0)	218 (20.4)	215 (20.1)
Below-average income group	2468 (20.0)	2473 (20.0)	213 (19.9)	214 (20.0)
Average income group	2468 (20.0)	2473 (20.0)	214 (20.0)	214 (20.0)
Above-average income group	2468 (20.0)	2473 (20.0)	213 (19.9)	214 (20.0)
Highest income group	2468 (20.0)	2473 (20.0)	213 (19.9)	214 (20.0)
Alcohol abuse	96 (0.8)	93 (0.8)	14 (1.3)	13 (1.2)
Diabetes	142 (1.2)	2271 (18.4)	18 (1.7)	191 (17.8)
Smoking	926 (7.5)	1850 (15.0)	56 (5.2)	174 (16.3)

[a] Data are given as number (percentage) unless otherwise noted.

Observational Studies in Epidemiology to conduct and report this study.[21]

This study was approved by the Danish Data Protection Agency. Danish law does not require ethical approval or written patient consent when nationwide registries are used for registry studies. Data analysis was performed from February 4 to April 14, 2016.

Statistical Analysis

We described patient characteristics with means (SDs) for continuous variables, and frequencies and percentages for categorical variables. To ensure accurate registration of time at risk, we included surgery status as a time-dependent variable. This means patients, before surgery, contributed risk time in the presurgery groups and, after surgery, allocated risk time to the postsurgery groups. Consequently, events (diagnosis of psoriasis or psoriatic arthritis) that occurred before the surgery date were allocated to the presurgery groups, and events that occurred after the surgery date were allocated to the postsurgery groups. However, if a patient was diagnosed with psoriasis in the presurgery group, this individual was censored and did not contribute risk time in the postsurgery groups during the analysis of incident psoriasis. Rather than use a healthy (eg, general population) comparison group, we compared the risk in the same group of individuals presurgery and postsurgery because the direct effect of the intervention can be observed with minimal risk of introducing bias that occurs because of between-group (eg, demographic) differences. Throughout this article, the presurgery groups constitute the reference groups.

We used SAS, version 9.4 (SAS Institute Inc), and STATA, version 13 (StataCorp), to summarize incidence rates per 1000 person-years. We also used Cox proportional hazards regression models to obtain hazard ratios (HRs) for the risk of any psoriasis, severe psoriasis, and psoriatic arthritis. The HRs were calculated as crude, age-adjusted and sex-adjusted, and fully adjusted (ie, age, sex, alcohol abuse, and socioeconomic, smoking, and diabetes status were considered). These covariates were chosen a priori because they are independently associated with psoriasis. Alcohol abuse data as well as smoking and diabetes status were continually updated throughout the study. The Cox proportional hazards assumption was tested and found to be valid. All statistical tests were conducted using a level of significance of .05, and results were reported with 95% CIs, where applicable. Because the Danish Data Protection Agency does not permit the presentation of data on groups composed of fewer than 3 individuals, the results of 1 or 2 events or individuals are described as "fewer than 3" and derived results are shown as approximations.

Results

The study comprised 12 364 patients undergoing gastric bypass and 1071 patients undergoing gastric banding between January 1, 1997, and December 31, 2012. There was a female predominance in both cohorts. Patient characteristics are shown in **Table 1**.

From study start until the time of surgery, there were 272 (2.2%) and 16 (1.5%) cases of incident psoriasis in the gastric bypass and gastric banding groups, respectively, including 84 (0.8%) and fewer than 3 cases of severe psoriasis, respectively. Before bariatric surgery, there were 56 patients (0.5%) in the gastric bypass group and 3 patients (0.3%) in the gastric banding group who developed psoriatic arthritis. After bariatric surgery, there were 49 (0.5%) and 15 (1.4%) cases of incident psoriasis in the gastric bypass and gastric banding groups, respectively, including 20 (0.0%) and 5 (0.5%) cases of severe psoriasis, respectively, and 11 (0.1%) and 6 (0.6%) cases of incident psoriatic arthritis, respectively. Follow-up time and incidence rates per 1000 person-years are shown in **Table 2**. There was a significantly decreased risk of psoriasis (adjusted HR, 0.52; 95% CI, 0.33-0.81), severe psoriasis (adjusted HR, 0.44; 95% CI, 0.23-0.86), and psoriatic arthritis (adjusted HR, 0.29; 95% CI, 0.12-0.71) in patients following gastric bypass. Interestingly, there were no significant differences in risk of psoriasis (adjusted HR, 1.23; 95% CI, 0.40-

Table 2. Summary of Follow-up Time, Number of Events, and Event Rates per 1000 Person-years

Characteristic	Gastric Bypass		Gastric Banding	
	Presurgery	Postsurgery	Presurgery	Postsurgery
Any psoriasis				
Person-years	158 404.6	33 175.8	9939.1	6724.1
No.of events	272	49	16	15
Incidence rate per 1000 person-years (95% CI)	1.72 (1.52-1.93)	1.48 (1.12-1.95)	1.61 (0.99-2.63)	2.23 (1.34-3.70)
Severe psoriasis				
Person-years	159 529.2	33 729.6	10 000.5	6848.4
No. of events	84	20	<3[a]	5
Incidence rate per 1000 person-years (95% CI)	0.59 (0.43-0.65)	0.53 (0.38-0.92)	<0.30 (0.05-0.80)	0.73 (0.30-1.75)
Psoriatic arthritis				
Person-years	159 652.1	33 823.2	9999.4	6844.4
No. of events	56	11	3	6
Incidence rate per 1000 person-years (95% CI)	0.35 (0.27-0.46)	0.33 (0.18-0.59)	0.30 (0.10-0.93)	0.88 (0.39-1.95)

[a] Because the Danish Data Protection Agency does not permit presentation of data on groups composed of fewer than 3 individuals, results of 1 or 2 events or individuals are described as "<3" and derived results are shown as approximations.

Table 3. Crude and Adjusted Hazard Ratios of Psoriasis, Severe Psoriasis, and Psoriatic Arthritis in Patients Undergoing Bariatric Surgery

Characteristic	Crude		Age Adjusted and Sex Adjusted		Fully Adjusted[a]	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Gastric bypass						
Any psoriasis	0.54 (0.34-0.84)	.006	0.52 (0.32-0.81)	.004	0.52 (0.33-0.81)	.004
Severe psoriasis	0.45 (0.23-0.88)	.02	0.44 (0.22-0.73)	.02	0.44 (0.23-0.86)	.02
Psoriatic arthritis	0.31 (0.13-0.76)	.01	0.30 (0.12-0.73)	.01	0.29 (0.12-0.71)	.01
Gastric banding						
Any psoriasis	1.42 (0.47-4.30)	.54	1.23 (0.41-3.74)	.71	1.23 (0.40-3.75)	.72
Severe psoriasis	1.32 (0.14-12.11)	.81	1.28 (0.14-11.85)	.83	1.18 (0.12-11.48)	.89
Psoriatic arthritis	0.62 (0.10-3.89)	.61	0.58 (0.09-3.68)	.57	0.53 (0.08-3.56)	.52

[a] Fully adjusted considered age, sex, alcohol abuse, and socioeconomic, smoking, and diabetes status.

3.75), severe psoriasis (adjusted HR, 1.18; 95% CI, 0.12-11.48), or psoriatic arthritis (adjusted HR, 0.53; 95% CI, 0.08-3.56) following gastric banding (**Table 3**).

Discussion

In this nationwide study of patients undergoing bariatric surgery, gastric bypass was associated with a significantly reduced risk and progression of psoriasis and psoriatic arthritis whereas gastric banding was not. To date, this is the largest study to examine the effect of bariatric surgery on psoriatic disease, and our results suggest that the type of bariatric procedure is important for the antipsoriatic effects associated with surgical weight loss therapy; gastric bypass stands out as a bariatric procedure with antipsoriatic effects. One of the features that distinguishes gastric bypass from gastric banding is the dramatically changed secretory profile of a number of gut hormones released during meal intake (eg, GLP-1). According to our results, these postoperative hormonal changes may, in addition to the weight loss, be important for the antipsoriatic effect of gastric bypass. Both gastric bypass and gastric banding have been shown to lead to sustained weight loss, suggesting that the observed differences in our study might be caused by factors other than weight loss.[22]

It is well established that obesity is a risk factor for psoriasis and psoriatic arthritis,[4,23] and obese patients with psoriatic disease are less likely than leaner individuals with psoriatic disease to achieve a satisfactory treatment response.[8] Similarly, numerous studies suggest that a low-calorie diet is associated with greater improvement in objective disease measurements, such as the Psoriasis Area and Severity Index and the Dermatology Life Quality Index.[8] Previously, a study of 33 morbidly obese patients found an improvement of psoriasis symptoms in 39.4% of patients after bariatric surgery. Interestingly, and in potential agreement with our findings, more patients who underwent gastric bypass reported improvements compared with those who received nonbypass procedures (ie, sleeve gastrectomy or laparoscopic adjustable gastric banding).[12] Similarly, Hossler et al[24] found that, following

bariatric surgery, 21 of 34 patients showed improvement in their psoriasis and patients tended to need less systemic antipsoriatic therapy. To date, available evidence regarding gastric bypass in the context of psoriasis is limited to these small studies and case series, and even less is known about the effect of gastric banding on psoriasis. Therefore, our study of 12 364 patients undergoing gastric bypass and 1071 patients undergoing gastric banding expands the existing literature by suggesting important differences in psoriasis outcome and prognosis following these procedures.

Both gastric bypass and gastric banding lead to weight loss and improvements in certain obesity-related comorbidities, but gastric bypass also elicits endocrine changes. The procedure increases postprandial secretion of the gut-derived hormone GLP-1, which is renowned for lowering glucose (because of its insulinotropic and glucagonostatic effects) and reducing appetite (because it activates GLP-1 receptors in the brain), whereas gastric banding does not.[25] Patients who are glucose intolerant see improvements of their glucose and insulin levels within days after gastric bypass, seemingly uncorrelated with postsurgical weight loss.[11] Such apparent changes are believed to be caused by the rerouting of ingested nutrients, bypassing a large segment of the proximal small bowel and entering the distal part of the jejunum directly.[26] Postprandial GLP-1 plasma levels increase 20-fold following gastric bypass, but not after gastric banding.[25,27] It has been suggested that the antipsoriatic effects of weight loss could be explained, at least in part, by increased GLP-1 levels.[28] Along this line, some but not all studies have demonstrated improvements in psoriasis following treatment with liraglutide, a GLP-1 receptor agonist used in treatment of type 2 diabetes and obesity.[29-31] Interestingly, GLP-1 has demonstrated anti-inflammatory effects in vitro and in vivo,[32,33] with down-regulation of tumor necrosis factor and the nuclear factor κβ pathway.[34,35] Indeed, tumor necrosis factor and nuclear factor κβ are crucial in the initiation and maintenance of the inflammatory cycle in psoriasis,[36] and it is tempting to speculate if the antipsoriatic effects observed in our study is, in part, mediated by decreased systemic inflammation because of GLP-1.

Important strengths of the study include the high accuracy of the nationwide registries as well as the available information on household income, which minimized bias regarding sex, age, comorbidity, and/or socioeconomic status. In addition, the statistical adjustments for covariates for which data were continually updated during follow-up, as well as the length and accuracy of follow-up, add credibility to our findings.

Limitations

Several limitations and strengths apply to the interpretation of our results. Because of the observational nature of our study, we cannot determine causality. We lacked information on presurgical and postsurgical body weight, and whether the observed effect is due, in part, to postsurgical differences in GLP-1 response; whether the findings are mainly due to differences in weight loss, lifestyle factors, or other mechanisms requires further examination. Some but not all studies have suggested that sustained weight loss may be greater for gastric bypass than gastric banding. Moreover, the Danish population is predominantly of Caucasian descent, which may limit extrapolation of the results to other ethnicities. Furthermore, the sample sizes and absolute number of events were limited, and the risk estimates should be interpreted accordingly.

Conclusions

In conclusion, gastric bypass was associated with a significantly reduced risk and improved prognosis of psoriasis and psoriatic arthritis, whereas gastric banding was not. Although speculative, these findings may be the result of postoperative differences in weight loss and nutrient uptake as well as differences in the postsurgical secretion of a number of gut hormones, including GLP-1.

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Correction: This article was corrected on March 7, 2018, to fix the heading for the last column of data in Table 2 so that it reads "Postsurgery" instead of "Presurgery."

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Study concept and design: Egeberg, Sørensen, Skov.
Acquisition, analysis, or interpretation of data: Egeberg, Gislason, Knop.
Drafting of the manuscript: Egeberg.
Critical revision of the manuscript for important intellectual content: All authors.
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