The American Journal of Surgery (2014) 208, 811-816

The American Journal of Surgery®

Clinical Science

Splenectomy in trauma patients is associated with an increased risk of postoperative type II diabetes: a nationwide population-based study

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KEYWORDS:
Splenectomy;
Postoperative diabetes;
Trauma

Abstract

BACKGROUND: Animal studies indicate that splenocytes may act as precursors of β-islet secretory cells in the pancreas. This study aimed to assess the risk of postoperative type II diabetes after splenectomy in trauma patients.

METHODS: We used data from the Taiwan National Health Insurance hospitalized claims. Study 1 included 3,723 patients receiving splenectomy and 3,723 matched patients receiving other types of abdominal surgery. Study 2 included 5,996 patients with spleen injury and 5,996 matched patients with other types of abdominal injury. The hazard ratio for diabetes was estimated using the matched Cox proportional hazard regression model.

RESULTS: In trauma patients after surgery, those who received splenectomy had a 2-fold higher risk of diabetes compared with patients without splenectomy after a 3-year follow-up period. In the nonoperative group, there was no difference in diabetes risk between patients with splenic injury and those with other types of injury.

CONCLUSIONS: Splenectomy was associated with an increased risk of postoperative type II diabetes in trauma patients. Thus, there may be a role for the spleen in the development of diabetes.

The spleen is known to play an important role in both immune and circulatory functions. Reports have also suggested that the spleen may serve as a source of adult multipotent stem cells, which could act as precursors of β-islet secretory cells in the pancreas.[1,2] Moreover, clinical studies assessing the operative management for chronic pancreatitis have revealed that patients who received splenectomy with pancreatectomy developed postoperative diabetes at a higher rate than those who received spleen-preserving pancreatectomy.[3,4] Furthermore, traumatic splenectomy has been associated with

Supported by the Taiwan Department of Health Clinical Trial and Research Center for Excellence (DOH102-TD-B-111-004) and the Taiwan Department of Health Cancer Research Center for Excellence (DOH102-TD-C-111-005).

The authors declare no conflicts of interest.

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Manuscript received April 12, 2013; revised manuscript November 19, 2013

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http://dx.doi.org/10.1016/j.amjsurg.2014.03.003

hyperglycemia after long-term follow-up,[5] which indicates that there might be an association between splenectomy and the development of postoperative adult onset diabetes.

Trauma patients may represent an appropriate study population for investigating the association between splenectomy and postoperative diabetes because trauma patients receiving splenectomy are distinct from those who receive splenectomy because of hematologic diseases. To assess the effect of splenectomy on postoperative diabetes in trauma patients, we conducted this nationwide population-based cohort study using the Taiwan Longitudinal Health Insurance Database and hypothesized that splenectomy would be associated with a higher incidence of postoperative diabetes.

Patients and Methods

Method

Data source. The Taiwan National Health Insurance program was set up by the Bureau of Health Insurance in 1995 and this program has covered over 99% of the entire population in Taiwan. For research use, the National Health Research Institutes set up the Longitudinal Health Insurance Database in 2000, which contains one million randomly selected subjects from the registry for beneficiaries in 2000 and includes all of these patients' medical claims from 1996 to 2010. For the privacy protection of patients, the identification information was scrambled cryptographically before the data were released for research use. This study was approved by the ethical review board of China Medical University in Taiwan.

Study population. We selected 15,462 patients with newly diagnosed spleen injury (SI, International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] 865) between 1998 and 2010 from the hospital records and we defined the diagnosis date of SI as the entry date. Subjects demonstrating a history of diabetes mellitus (DM, ICD-9-CM 250, $n = 5{,}175$) before the entry date, those with other types of abdominal surgery (ICD-9-CM 863 and 864; treatment codes 45.9, 50, and 54, $n = 249$), and those who received splenectomy with pancreatectomy (treatment codes 52 and 41.5, $n = 314$) before the occurrence of type II DM (ICD-9-CM 250.x0 and 250.x2) were excluded. Our study sample included a total of 9,719 patients with SI, who were classified in the splenectomy group ($n = 3{,}723$) or non-splenectomy group ($n = 5{,}996$).

The control group consisted of 30,413 patients with other types of abdominal injury (ICD-9-CM 863 and 864), who were diagnosed between 1998 and 2010, and the date of diagnosis was considered the entry date. We excluded 2,660 patients with a history of DM and 4,686 patients with spleen or pancreatic injury before the occurrence of type II DM. The patients with other types of abdominal injury were grouped into surgery ($n = 8{,}018$) and nonsurgery groups ($n = 15{,}049$). To identify the level of injury severity in these trauma patients, we considered major trauma as rated 16 or more in the Injury Severity Score. In Taiwan, patients who suffer from major trauma and score 16 or more receive a certificate from the National Health Insurance Program for waiver of the copayment.

We conducted individual matching for the study and control cohorts based on age, sex, and the presence of hypertension (ICD-9-CM 401–405) and hyperlipidemia (ICD-9-CM 270). There were 2 studies included in this manuscript. Study 1, which was designed for the surgery subjects, included 3,723 patients who received splenectomy and 3,723 matched patients who received other types of abdominal surgery. Study 2, which was designed for the nonsurgery subjects, consisted of 5,996 patients with SI and 5,996 matched patients with other types of abdominal injury. The flow chart displayed in Fig. 1 shows our sampling method.

Statistical analysis. The chi-square test and Wilcoxon test were used to test the categorical and continuous variables between the SI and non-SI cohorts in both studies. The study cohorts were followed from baseline to the occurrence of type II DM, withdrawal from the insurance program, or the end of 2010. The SI to non-SI hazard ratios (HRs) and 95% confidence intervals for DM were estimated using matched Cox proportional hazard regression. We further divided the follow-up period into 3 time periods: within 1 year, 2 to 3 years, and more than 3 years. Kaplan–Meier analysis was used to generate the cumulative incidence of DM between the SI and non-SI cohorts. All statistical analyses were performed using SAS 9.1 software for Windows (SAS Institute, Cary, NC) and the significance level was set at .05.

Results

Study 1 for surgical patients compared SI patients who received splenectomy with non-SI patients who received other types of abdominal surgery.

The study subjects were dominated by men and more than half of the patients receiving operations were older than 30 years of age. There were no significant differences in age, sex, follow-up years, or the prevalence of hypertension, hyperlipidemia, and major trauma between patients with and without SI (Table 1). The average follow-up time was 5.91 and 5.96 years for the SI group and the non-SI group, respectively. After 13 years of follow-up, the incidence rates of DM in the surgery group were 6.68 and 5.36 per 1,000 person-years in patients with and without SI, respectively (Table 3). After adjusting for all covariates, patients who received splenectomy had a 2-fold greater risk of diabetes compared with patients without splenectomy after a 3-year follow-up period (adjusted hazard ratio [aHR] = 2.00, 95% confidence interval = 1.20 to 3.34). Among men and participants younger than 50 years of age, patients who received splenectomy also had a higher risk for DM

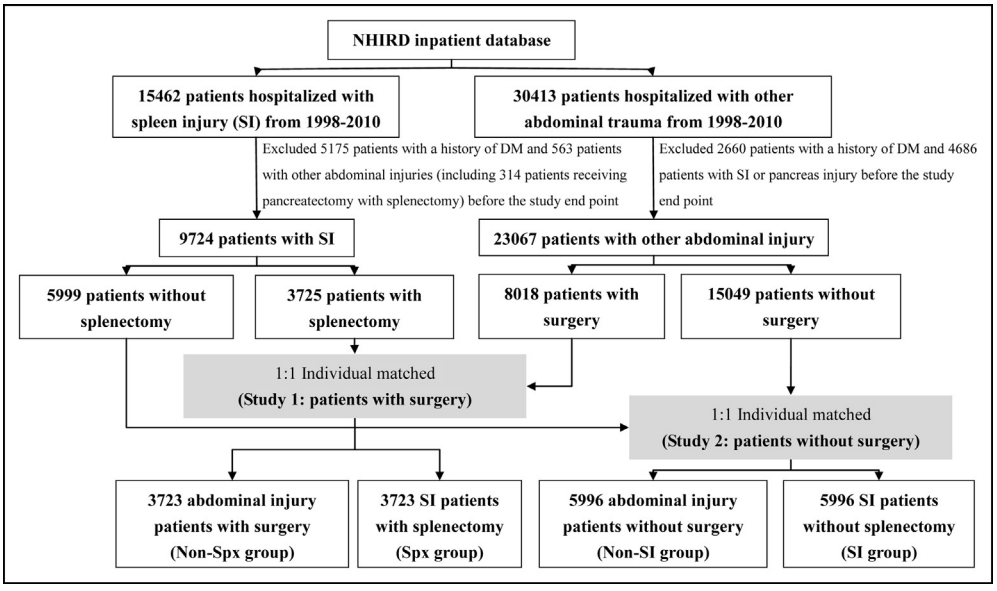

Figure 1 Flow chart showing the study subject selection process.

(aHR = 1.89 in men; aHR = 1.79 in the subgroup aged <50 years).

Study 2 for nonsurgical patients compared SI patients who did not receive surgery with non-SI patients who did not receive surgery.

Among the nonsurgical subjects, no differences in age, sex, study period, or comorbidities were observed between the SI and non-SI cohorts (Table 2). The average follow-up time was 5.46 and 5.30 years for the SI group and the non-SI group, respectively. Overall, the incidence rates of DM were 5.65 and 5.63 per 1,000 person-years in the SI group and non-SI group, respectively (Table 3). We found no difference in the DM risk between SI and non-SI patients among patient subgroups with different follow-up durations. In addition, no difference in the incidence of developing diabetes was observed between patients with SI and patients with other types of abdominal injuries (Fig. 2B).

Comments

The spleen is known to play an important role in human immunity. Clinical observations indicate that patients who receive splenectomy with pancreatectomy are more likely to develop postoperative diabetes compared with those who receive spleen-preserving pancreatectomy.[3] Additionally, traumatic splenectomy

Table 1 Demographics of spleen injury patients and non-spleen injury patients in the surgery group (study 1)

	With surgery				
	Spx (n = 3,723)		Non-spx (n = 3,723)		
	n	%	n	%	P value
Age (years)					>.99
<30	1,773	47.6	1,773	47.6	
30–49	1,125	30.2	1,125	30.2	
≥50	825	22.2	825	22.2	
Mean (SD)	35.8	(18.0)	35.6	(18.0)	.84*
Male	2,719	73.0	2,719	73.0	>.99
Follow-up (year), mean (SD)	5.91	(3.95)	5.96	(3.75)	.82*
Comorbidity					
Hypertension	120	3.22	120	3.22	>.99
Hyperlipidemia	52	1.40	52	1.40	>.99
Major trauma†	460	12.4	460	12.4	>.99

Chi-square test, spx group compared with non-spx group.
SD = standard deviation; spx = splenectomy.
*Wilcoxon test, spx group compared with non-spx group.
†Major trauma: Injury Severity Score rated ≥16.

Table 2 Demographics of spleen injury patients and non-spleen injury patients in the nonsurgery group (study 2)

	Without surgery				
	SI (n = 5,996)		Non-SI (n = 5,996)		
	n	%	n	%	P value
Age (years)					>.99
<30	3,145	52.5	3,145	52.5	
30–49	1,690	28.2	1,690	28.2	
≥50	1,161	19.4	1,161	19.4	
Mean (SD)	33.4	(18.0)	33.3	(18.8)	.96*
Male	4,248	70.9	4,248	70.9	>.99
Follow-up (year), mean (SD)	5.46	(3.75)	5.30	(3.75)	.01*
Comorbidity					
Hypertension	195	3.25	195	3.25	>.99
Hyperlipidemia	81	1.35	81	1.35	>.99
Major trauma†	432	7.20	432	7.20	>.99

Chi-square test, SI group compared with the non-SI group.
SD = standard deviation; SI = spleen injury.
*Wilcoxon test, SI group compared with the non-SI group.
†Major trauma: Injury Severity Score rated ≥16.

has been associated with hyperglycemia after long-term follow-up.[5] Furthermore, children who receive splenectomy for severe thalassaemia have been shown to have an increased incidence of glucose intolerance.[6] Therefore, the current evidence supports the association between splenectomy and type II DM.

Our study findings indicated that patients who received splenectomy had a 2-fold greater risk of developing DM compared with patients without splenectomy after a 3-year follow-up period. This result suggests that splenectomy may be associated with an increased risk of postoperative diabetes after long-term follow-up.

The spleen is thought to harbor pancreatic stem cells, as cells within the spleen demonstrate close inter-relationships with stem cells during embryonic development.[7,8] In particular, it has been reported that the splenic mesenchyme buds off from the pancreatic mesenchyme during early development.[9] Additional evidence for this close relationship between cell types came from a study that used PTF1-p48 gene knockout mice; although these mice are born without an exocrine pancreas, functional islets were found in the spleen and these animals showed normoglycemia.[10] In addition, it has been reported that human adult spleens uniquely possess a reservoir of multilineage adult stem cells that

Table 3 Incidence and hazard ratio of DM for spleen injury patients and non-spleen injury patients, stratified by sex, age, and follow-up duration

	Study 1 (surgical group)					Study 2 (nonsurgical group)				
	Spx		Non-spx			SI		Non-SI		
	Case	IR	Case	IR	HR (95% CI)	Case	IR	Case	IR	HR (95% CI)
Overall	147	6.68	119	5.36	1.59 (1.13–2.24)*	185	5.65	179	5.63	.98 (.75–1.29)
Sex										
Male	112	6.99	79	4.90	1.89 (1.26–2.83)*	136	5.88	145	6.44	.96 (.70–1.32)
Female	35	5.84	40	6.55	1.00 (.52–1.92)	49	5.10	34	3.67	1.04 (.60–1.80)
Age (years)										
<50	76	4.14	56	3.05	1.79 (1.12–2.84)†	105	3.82	81	3.04	1.23 (.84–1.80)
>50	71	19.33	63	16.43	1.39 (.84–2.29)	80	15.29	98	19.24	.77 (.52–1.14)
Follow-up (years)										
1	27	8.08	19	6.00	1.40 (.72–2.72)	32	5.82	34	6.26	.94 (.56–1.55)
2–3	36	6.22	21	3.77	1.24 (.65–2.34)	43	4.66	45	4.98	.82 (.57–1.47)
>3	84	6.52	79	5.86	2.00 (1.20–3.34)*	110	6.11	100	5.78	1.08 (.69–1.68)

Adjusted for age, sex, hypertension, hyperlipidemia, and major trauma.
CI = confidence interval; DM = diabetes mellitus; HR = hazards ratio; IR = incidence rate per 1,000 person-years; SI = spleen injury; spx = splenectomy.
*$p < .01$
†$p < .05$

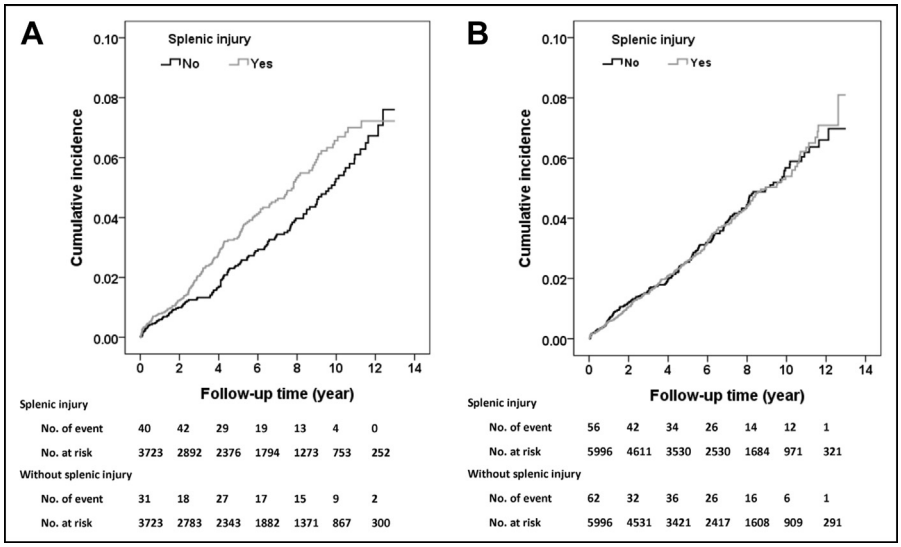

Figure 2 Cumulative incidence of type II DM for (A) study 1 and (B) study 2.

express the developmental transcription factor HOX11.[11,12] HOX11 stem cells demonstrate low levels of lineage restriction and are essential for organogenesis of the spleen and the development of the pancreas, cochlea, hindbrain, and other organs.[12] Furthermore, a previous study proposed that spleen stem cells may act as precursors for β-islet secretory cells in the pancreas.[2] Specifically, these rodent studies revealed that splenocytes could enhance the neogenesis of pancreatic β-islet secretory cells,[2] indicating that the spleen may play an important role in the endocrine function of the pancreas.

Patients who receive other types of abdominal surgery (eg, for bowel injury) rather than splenectomy may experience a similar degree of perioperative stress, which may result in hormonal and/or metabolic changes as well as the development of diabetes. In this study, we compared the risk of developing DM between both study groups that received surgery to evaluate whether receiving surgery affected the development of DM. Moreover, we assumed that there was no difference in surgical stress between the group receiving splenectomy and the group receiving other types of abdominal surgery.

It is not uncommon to observe hyperglycemia after traumatic insults or in cases of critical illness. For example, diabetes in cases of critical illness may be attributed to acute insulin resistance.[13] Jiang et al[14] reported that macrophages may play a role in maintenance of the insulin-resistant state and the development of critical illness diabetes in rodent model. Moreover, there is also evidence that hyperglycemia is predictive of outcome in critically ill trauma patients.[15] However, this result was mostly indicative of the short-term effects rather than long-term effects of trauma and injury, indicating that the acute stress associated with trauma may not play a role in the development of hyperglycemia in long-term follow-up patients. Therefore, we presumed that the development of postoperative diabetes after more than 3 years of follow-up may have been because of removal of the spleen.

The spleen is one of the most vulnerable solid organs in the abdominal cavity and spleen injuries are managed using both surgical and nonsurgical approaches.[16] As a result, the application of nonsurgical management for spleen salvage in blunt splenic injury patients with hemodynamic stability has been widely accepted and has become a trend of standard treatment in recent decades. However, some centers still tend to perform surgeries for higher grade splenic injuries.[17] This study indicated that splenectomy was associated with an increased risk of postoperative DM. Therefore, our findings may provide additional evidence supporting the nonoperative approach for spleen salvage in the management of splenic injuries.

It has been proposed that the development of type II DM (also termed adult-onset DM) may be because of islet replication declination with human ageing.[18] However, there remains a debate as to whether adult-onset DM is because of β-cells themselves or another tissue that may influence β-cell proliferation in a cell nonautonomous manner.[19] For example, Conboy et al[20] reported that cell nonautonomous factors may play a major role in the regulation of stem-cell ageing in muscle systems. It has also been suggested that the spleen could serve as a source of new islets for transplantation in children, which may demonstrate the potential to reverse diabetes.[21] Therefore, it is possible that removal of the spleen may disrupt the nonautonomous regulation pathway and increase the risk of adult-onset diabetes.

It has been proposed that the central nervous system may regulate innate immune responses via the vagus nerve. Termed the cholinergic anti-inflammatory pathway, this mechanism involves vagus nerve stimulation followed by the inhibition of proinflammatory cytokine release.[22] Using an animal model, the study by Huston[23] suggested that the cholinergic pathway may be closely related to the spleen via the branching of the vagus nerve and indicated that splenectomy may inactivate the cholinergic pathway during

endotoxemia and sepsis. These findings suggested that the spleen plays an important role in the inflammatory reflex or neurohumoral control of inflammation mediated by the vagus nerve.[24] Therefore, future studies should examine the potential associations between long-term diabetes and the failure to inhibit proinflammatory cytokine production via the vagus nerve after splenectomy.

To our knowledge, this was the 1st large cohort study to investigate the association between splenectomy and the development of DM using population data. However, we recognize several limitations of this study, including its retrospective nature, modest sample size, and the probable bias in case selection, which may have restricted our analytical conclusions. In addition, we acknowledge that the lack of data on risk factors such as obesity and smoking represents another limitation. Another flaw of this study was the paucity of data on short-term glycemic control near the time of surgery, in which stress hormone response (eg, epinephrine, cortisol) may represent an important harbinger. Therefore, additional multi-institutional trials or randomized experimental studies should be performed with predefined enrollment criteria for a better understanding of this association and its mechanism.

In conclusion, our study results showed that splenectomy in trauma patients is associated with a long-term increased risk of postoperative type II diabetes. This finding may be partially attributed to the role of the spleen in the endocrine function of the pancreas and as a mediator of neurohumoral control. Future studies are warranted to investigate this proposed relationship and the underlying mechanisms. Additionally, our results may provide evidence in support of clinical spleen salvage for the management of splenic injuries.

Acknowledgments

Dr Yen-Jung Chang is the guarantor of this work and, as such, has full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Shih-Chi Wu contributed to the study design and wrote the manuscript. Chih-Yuan Fu researched the data and reviewed the manuscript. Chih-Hsin Muo researched the data and wrote the manuscript. Yen-Jung Chang contributed to the study design and reviewed/edited the manuscript.

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