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Patients With Neurogenic Lower Urinary Tract Dysfunction Following Spinal Cord Injury Are at Increased Risk of Developing Type 2 Diabetes Mellitus

A Population-Based Cohort Study

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Abstract: To investigate whether patients with neurogenic lower urinary tract dysfunction (NLUTD) following spinal cord injury (SCI) are at increased risk of developing type 2 diabetes mellitus (T2DM).

The retrospective cohort study used a subset of the Taiwan National Health Insurance Research Database (NHIRD) comprising information on 2 million beneficiaries randomly sampled from the general population. A total of 3515 patients with newly diagnosed SCI were identified during the period of 2001 to 2008. Among them, 170 developed NLUTD following SCI. The control group was consisted of 656 patients without NLUTD over the study period randomly selected by matching NLUTD cases on the date of NLUTD incidence, age, sex, and duration since diagnosis of SCI. The study groups were then followed to the end of 2009. T2DM was the end-point.

The incidence rate ratios of T2DM were higher in the NLUTD group than in the control group (4.94 vs. 2.61 per 10,000 person-years), representing an adjusted hazard ratio (AHR) of 1.70 (95% confidence interval [CI] 1.11–2.61). Age-specific AHR was significantly elevated only in patients aged $>=60$ years (AHR = 2.52 (95% CI 1.35–4.70)).

This study showed that the NLUTD following SCI may significantly increase the risk of developing T2DM.

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Abbreviations: AHR = adjusted hazard ratio, BTX-A = botulinum toxin A, CI = confidence interval, CRP = C-reactive protein, ICD-9-CM = International Classification of Diseases Ninth Revision Clinical Modification, IRR = incidence rate ratio, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NLUTD = neurogenic lower urinary tract dysfunction, SCI = spinal cord injury.

INTRODUCTION

Studies have shown a strong association between spinal cord injury (SCI) and the development of type 2 diabetes mellitus.[1,2] The incidence of type 2 diabetes in SCI patients ranges from 10% to 22%.[3–5] Diabetes in SCI patients is associated with poorer quality of life and a greater incidence of slow-healing foot sores.[4] Thus, identification and management of risk factors for type 2 diabetes in patients with SCI is crucial.

Neurogenic lower urinary tract dysfunction (NLUTD) has a significant effect on the quality of life of patients with SCI.[6] The reported prevalence of NLUTD in patients with SCI ranges from 17.5% to 88%.[7–9] Current evidence indicates that the adverse effects of bladder function depend on the phase and severity of SCI.[6] NLUTD after SCI can be divided into 2 phases: a period of spinal shock and a chronic phase.[6] The consequences of spinal shock immediately follow the injury and are characterized by detrusor areflexia,[6] which usually resolves within 3 months.[10] Symptoms, including neurogenic detrusor overactivity, detrusor-sphincter dyssynergia, and areflexic neurogenic bladder, are observed in the chronic phase.[11,12] The alterations of the neurogenic bladder, including significant deficits in bladder tight junction proteins and sustained bladder uroepithelium ulceration, leave the bladder vulnerable to chronic inflammation.[13,14]

Diabetes progression is also associated with the inflammatory process.[15] Therefore, the authors conducted a population-based cohort study to investigate whether NLUTD increases the risk of type 2 diabetes in patients with SCI.

METHODS

Data Source

Patients in this population-based cohort study were retrospectively collected from the Taiwan National Health Insurance

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W-CL designed the study, did statistical analyses, drafted the initial manuscript, and revised important content. T-SK designed the study and drafted the initial manuscript. Y-CL and P-CH participated in study design and interpretation of results. F-WL performed data mining and contributed to data analyses. C-YL designed the study, contributed to interpretation of results and revision for important content. C-YL is the guarantor of this work, has full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.
T-SK and C-YL contributed equally to this article.
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Research Database, which consists of standard computerized claims documents submitted by medical institutions seeking reimbursement through the National Health Insurance (NHI) Program. The NHI program provides the medical needs for more than 23 million people, representing more than 98% of the population in Taiwan, and records clinical diagnoses according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.[16] This study used a subset of the National Health Insurance Research Database (NHIRD) managed by the Collaboration Center of Health Information Application, which is supervised by the Department of Statistics, Ministry of Health and Welfare. The subset of the NHIRD comprises information on 2 million beneficiaries randomly sampled from the general population. This cohort was followed longitudinally from 2000 to 2009. This random sample has been verified by the Department of Statistics to be representative of the entire Taiwanese population with respect to age, sex, and geographical distribution of residence. To ensure the accuracy of the databases, the National Health Insurance Administration performs quarterly reviews on a random sample of every 50 ambulatory and inpatient claims. This study was approved by the Institutional Review Board of the National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University (Approval No.: A-ER-104-056). Access to the research data was approved by the Review Committee of the National Health Research Institute.

Study Design and Patient Identification

All patients ≥20 years of age with newly diagnosed SCI without evidence of spinal bone injury (ICD-9-CM code 952.x) or vertebral column fractures (ICD-9-CM code 806.x)[9,17] at index hospitalization during the period January 1, 2001 to December 31, 2008 were identified from the NHI database (n = 3515). To ensure that patients had new onset SCI, patients admitted for SCI or who sought ambulatory care for SCI in 2000 were excluded (n = 428).

Patients were also excluded if they died or withdrew from the NHI program within the first 6 months after diagnosis of SCI (n = 346); if they had comorbidities that have been found to predispose patients to the development of NLUTD,[18,19] including nephritis, nephrotic syndrome or nephrosis (ICD-9-CM codes 580-589), multiple sclerosis (ICD-9-CM code 340), disorders of the prostate (ICD-9-CM codes 600-602), genital prolapse or fistula (ICD-9-CM codes 618-619), Parkinson disease (ICD-9-CM code 332), cerebrovascular disease (ICD-9-CM codes 430-438), or cancer (ICD-9-CM codes 140-239), within 1 year prior to SCI (n = 352); and if they had a history of urinary dysfunction, defined as any disorder of the bladder (ICD-9-CM code 596), symptoms involving the urinary system (ICD-9-CM code 788), receipt of urinary catheterization treatment, or receipt of medication for neurogenic urinary dysfunction (eg, alpha blockers or anticholinergic agents) within 3 months prior to SCI onset (n = 61). The levels of SCI were classified as cervical SCI (ICD-9-CM codes 952.0, 806.0-1) and noncervical SCI (ICD-9-CM codes 952.x, with the exception of 952.0, and 806.x, with the exception of 806.0-1), which included thoracic, lumbar, and other spinal cord injuries as defined previously.[2,4,9]

Selection of NLUTD and Non-NLUTD Groups

Patients with newly diagnosed SCI who developed NLUTD during the follow-up period and who fulfilled the following criteria were included in the NLUTD group: a diagnosis of functional disorders of the bladder or symptoms of urinary incontinence (ICD-9-CM codes 596.5 or 788.3); urinary catheterization; or treatment with alpha blockers (the Anatomical Therapeutic Chemical code G04CA), cholinergic agents (the Anatomical Therapeutic Chemical code N07AB02 (bethanechol)), or anticholinergic agents (the Anatomical Therapeutic Chemical codes G04BD (urinary antispasmodics), and N06AA02 (imipramine)).[9,20] The above-mentioned diagnoses, procedures, or treatments had to persist for at least 3 months.[9,10,20] Patients with NLUTD also had to be free from any diagnosis of diabetes (ICD-9-CM code: 250) prior to the date of developing NLUTD, which was considered the index date. A total of 170 patients with NLUTD were identified.

Each patient in the NLUTD group was matched to 4 randomly selected patients without NLUTD on index date, age (± 5 years), sex, and duration (in years) since diagnosis of SCI. All patients selected for inclusion in the non-NLUTD group also had to be free from a history of diabetes prior to the index date. A total of 656 patients were selected for inclusion in the non-NLUTD group. Patients in both groups were then linked to the ambulatory care and inpatient medical claims database to identify possible episodes of diagnosis of type 2 diabetes (ICD-9-CM codes: 250.x0 or 250.x2) during the period 2001 to 2009.[2,21] A flowchart illustrating the cohort identification process and follow-up of study subjects is presented in Figure 1.

Statistical Methods

Differences between NLUTD and non-NLUTD groups were assessed using the independent *t* test for continuous variables and the χ^2 test for nominal variables. Poisson regression modeling was used to estimate incidence rate ratios (IRR) of type 2 diabetes. The adjusted hazard ratio (AHR) of type 2 diabetes incidence was estimated using Cox proportional

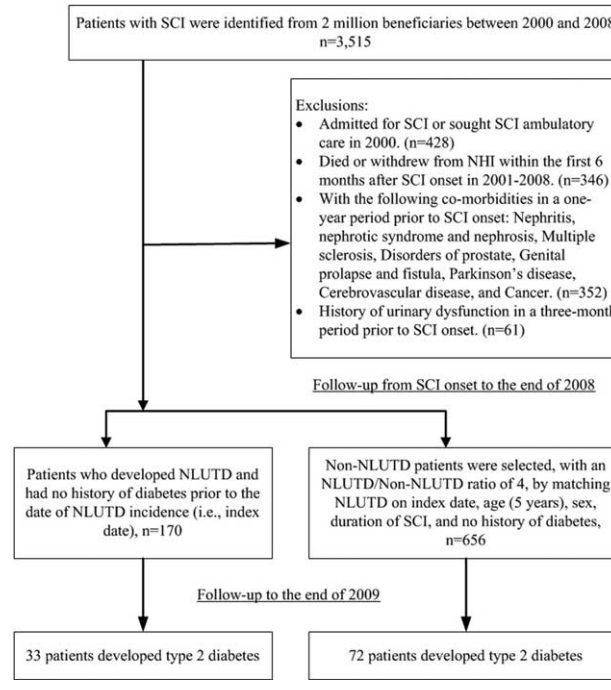

FIGURE 1. Flowchart illustrating the cohort identification process and follow-up of study subjects.

hazard regression models with adjustment for potential confounders, including sex, age, level of SCI, insurance premium, urbanization level, and selected comorbidities.[22] Comorbidities that appeared in medical claims in the 1-year period prior to the index date that were considered in the analysis included hypertension (ICD-9-CM codes 401-405), hyperlipidemia (ICD-9-CM code 272), coronary heart disease (ICD-9-CM codes 410-414), liver disorder (ICD-9-CM codes 570-573), and congestive heart failure (ICD-9-CM code 428). These selected comorbidities have been found to pose an increased risk of type 2 diabetes in persons with SCI.[4] Type 2 diabetes-free survival curves were plotted using the Kaplan–Meier method, and differences between the survival curves were tested by the log-rank test. A P value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed with the statistical package SAS (Version 9.3, SAS Institute, Cary, NC).

RESULTS

Age and sex were comparably distributed between the 2 groups. The 2 most common subtypes of SCI in the NLUTD and non-NLUTD groups were cervical injury (47.6% vs. 63.0%) and lumbar injury (24.7% vs. 19.1%) (Table 1). Patients in the non-NLUTD group had significantly higher insurance premiums than those in the NLUTD group, and patients in the NLUTD group had a significantly longer hospital stay at the time of SCI onset (16.5 vs 11.1 days) despite the fact that distributions of comorbidities were similar between the 2 study groups (Table 1).

During a maximum of 9 years of follow-up, 33 patients (33/170, 19.4%) in the NLUTD group and 72 patients (72/656, 11.0%) in the non-NLUTD group developed type 2 diabetes, representing an IRR of 4.94 per 10,000 person-years (95% confidence interval [CI] 3.25–6.62) and 2.61 per 10,000 person-years (95% CI 2.01–3.21), respectively. Compared with patients without NLUTD, patients with NLUTD had a significantly increased AHR for type 2 diabetes (1.70; 95% CI 1.11–2.61) (Table 2). Because there was a significant interaction between NLUTD and age ($P < 0.001$), we performed stratified analyses to estimate age-specific hazard ratios. The stratified analyses showed that increased AHR of type 2 diabetes was only observed in patients with NLUTD aged $\geq$60 years (2.52; 95% CI 1.35–4.70) (Table 2).

The Kaplan–Meier curves revealed that the type 2 diabetes-free survival rate was significantly higher in the non-

TABLE 1. Patient Characteristics at Baseline

Characteristic	Non-NLUTD Group N = 656	NLUTD Group N = 170	*P* Value
Age, mean (SD), yr	55.3 (18.1)	58.0 (17.5)	0.084
Age group			0.653
20–39	128 (19.5%)	32 (18.8%)	
40–59	244 (37.2%)	61 (35.9%)	
60–79	231 (35.2%)	58 (34.1%)	
>=80	53 (8.1%)	19 (11.2%)	
Mean follow-up period, yr	4.21	3.93	
Sex			0.915
Female	171 (26.1%)	45 (26.5%)	
Male	485 (73.9%)	125 (73.5%)	
Level of SCI			< 0.001
Cervical	413 (63.0%)	81 (47.6%)	
Thoracic	76 (11.6%)	23 (13.5%)	
Lumbar	125 (19.1%)	42 (24.7%)	
Other	42 (6.4%)	24 (14.1%)	
Urbanization status			0.217
Urban	264 (40.2%)	81 (47.6%)	
Satellite	169 (25.8%)	39 (22.9%)	
Rural	223 (34.0%)	50 (29.4%)	
Insurance premium			<0.001
Dependent	179 (27.3%)	43 (25.3%)	
<Median (19,200 NTD*)	137 (20.9%)	61 (35.9%)	
>=Median	340 (51.8%)	66 (38.8%)	
Comorbid conditions	204 (31.1%)	63 (37.1%)	0.139
Hypertension (401–405)	132 (20.1%)	44 (25.9%)	0.102
Hyperlipidemia (272)	49 (7.5%)	13 (7.6%)	0.938
Coronary heart disease (410–414)	49 (7.5%)	18 (10.6%)	0.184
Liver disorder (570–573)	48 (7.3%)	19 (11.2%)	0.1005
Congestive heart failure (428)	16 (2.4%)	5 (2.9%)	0.7109
Length of hospital stay (SD), days	11.1 (13.7)	16.5 (16.6)	<0.001

NLUTD = neurogenic lower urinary tract dysfunction; SCI = spinal cord injury; SD = standard deviation.
* NTD: New Taiwan Dollars; 1 USD ≅ 31.0 NTD.

TABLE 2. Overall and Age-Specific Incidence Densities and Relative Hazards of Type 2 Diabetes in the NLUTD and Non-NLUTD Groups

	NLUTD Group		Non-NLUTD Group			
Variables	No. Events	IRR[‡,§] (95% CI[‡,§])	No. Events	IRR[‡,§] (95% CI[‡,§])	Crude HR[‡] (95% CI[‡])	Adjusted HR[‡] (95% CI[‡])
Age, yr						
20–39	4	2.23 (0.60–5.70)	5	6.75 (2.18–15.76)	3.30 (0.89–12.29)	3.32 (0.80–13.71)[*]
40–59	10	3.89 (1.48–6.29)	35	3.33 (2.22–4.43)	1.16 (0.58–2.35)	1.24 (0.60–2.54)[*]
>=60	19	8.22 (4.52–11.91)	32	3.30 (2.16–4.45)	2.68 (1.50–4.77)	2.52 (1.35–4.70)[*]
Overall	33	4.94 (3.25–6.62)	72	2.61 (2.01–3.21)	1.89 (1.25–2.86)	1.70 (1.11–2.61)[†]

NLUTD = neurogenic lower urinary tract dysfunction.
[*] Based on Cox proportional hazard regression with adjustment for all variables, with the exception of sex.
[†] Based on Cox proportional hazard regression with adjustment for age, sex, type of SCI, urbanization status, insurance premium, length of stay, and comorbidity.
[‡] IRR = incidence rate ratio, per 10,000 person-years; CI = confidence interval; HR = hazard ratio.
[§] Based on Poisson assumption.

NLUTD group than in the NLUTD group (*P* for log-rank test, 0.0037) (Figure 2).

DISCUSSION AND CONCLUSIONS

The key findings of this retrospective cohort study included: the IRR of type 2 diabetes in NLUTD patients was 4.94 per 10,000 person-years; patients with NLUTD were more likely than non-NLUTD patients to develop type 2 diabetes by a magnitude of 70%; and the age of SCI patients appeared to modify the risk of developing type 2 diabetes, with those aged ≥60 years being at the greatest risk. Patients aged less than 60 years were also at elevated risk of type 2 diabetes; however, there were no significant differences in risk estimates between patients aged 20 to 40 years and those aged 40 to 60 years. The lack of significance was most likely due to the small sample size of NLUTD patients in these age groups.

The alterations of NLUTD, including significant deficits in bladder tight junction proteins and sustained bladder uroepithelium ulceration, leave the bladder vulnerable to chronic inflammation.[13,14] In addition, patients with NLUTD typically have elevated serum C-reactive protein (CRP) levels.[23] CRP, which is considered a general biomarker of acute or chronic inflammation, is an acute phase protein that is stimulated by proinflammatory cytokines, particularly IL-6 and TNF-α.[24] Moreover, inflammation may be associated with the development of insulin resistance and type 2 diabetes in patients with SCI.[25] The above-mentioned biochemical and physiological changes may be responsible for the relationship between NLUTD and risk of type 2 diabetes noted in this study.

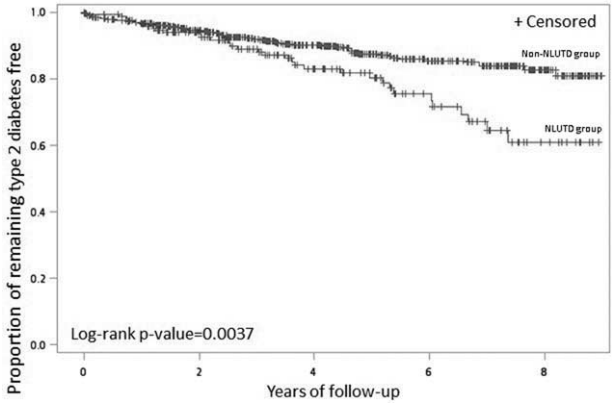

FIGURE 2. Comparison of Kaplan–Meier survival estimates of type 2 diabetes onset between the 2 study groups.

The authors also found variation in age-specific relative hazards of type 2 diabetes in association with NLUTD, with the highest risk observed in patients aged ≥60 years. These results suggest that age plays a significant role in moderating the effect of NLUTD on type 2 diabetes onset. Previous studies[1,2] have also reported higher relative risk of type 2 diabetes in older SCI patients, although those studies did not specify the risk factors responsible for such phenomena. Inflammation associated with NLUTD is characterized by neutrophil influx into the bladder after SCI.[14] Phagocytic leukocytes contain nicotinamide-adenine dinucleotide phosphate oxidase, an enzyme that reduces molecular oxygen to superoxide anion, which may increase oxidative stress in the bladder. Aikawa et al[26] found that the cause of bladder contractile dysfunction associated with aging may be a loss of antioxidant mechanisms resulting in progressive oxidative damage to bladder smooth muscle and the contractile apparatus. This could explain our finding that older SCI patients with NLUTD have a higher relative hazard of type 2 diabetes.

The goals of bladder management in SCI patients include preservation of the upper urinary tract and renal function, avoidance of urological complications, and improvement of patients' quality of life by restoring independence and continence.[6] Based on the findings in this study, reducing chronic inflammation of the bladder should be included as a key issue in bladder management to decrease the incidence of new onset type 2 diabetes in SCI patients. Lucioni et al[27] found that the application of botulinum toxin A (BTX-A) inhibits the release of sensory neurotransmitters in bladder preparations isolated from rats with both acute injury and chronic inflammation, suggesting a potential clinical benefit of BTX-A in the treatment of bladder inflammation. Injecting BTX-A into the detrusor sphincter also has been found to significantly improve bladder emptying, thereby allowing for the discontinuation of catheter usage in individuals with SCI.[28] However, detrusor

BTX-A injection for NLUTD has only been covered by the Taiwan NHI program since 2014; therefore, the authors were unable to include this treatment as a pharmacologic alternative in our analysis. Further longitudinal studies are needed to investigate the potential benefit of detrusor BTX-A injection.

The strengths of this study include its large sample size and long follow-up period. In addition, ascertainment of NLUTD was not merely made by diagnostic codes, but also supported by information on prescriptions and procedures. Also, the design of this study involved an unbiased participant selection process. Because participation in the NHI is mandatory and all residents of Taiwan can access low-cost health care, referral bias is considered low and the follow-up compliance rate high.

This study does have a number of limitations, however. First, the NHIRD provides ICD-9-CM diagnostic codes but not detailed information on risk factors for type 2 diabetes, such as physical inactivity, hemoglobin A1C level, body mass index, and family history of type 2 diabetes.[1] Nonetheless, the mobility status of SCI patients has been shown to be related to injury level, diabetes, hypertension, and high serum cholesterol.[29] Because information on physical activity was not available from the NHI claims, the authors adjusted for it using the level of SCI and comorbidities including hypertension and hyperlipidemia.[29] Second, the NHIRD does not accurately distinguish between complete and incomplete spinal cord injuries. The severity of SCI has been shown to be related to the level and completeness of SCI[2] and to be among the factors strongly related to risk of depression onset,[30] which in turns leads to onset of type 2 diabetes.[21] The authors adjusted for the level of SCI and hospital length of stay associated with first-time admission for SCI to account for the potential confounding effect of SCI severity.[2,9]

Third, the authors used ICD-9-CM codes to determine type 2 diabetes, which might entail certain degrees of misclassification. Therefore, some of the patients including in this study may have been misclassified. Nonetheless, because of the large sample size, the rate of misclassification would be statistically low, and hence would not affect the results. Fourth, the authors excluded from the analyses all patients who died early or withdrew from the NHI program within 6 months after SCI. Finally, several types of NLUTD can occur following SCI onset, including neurogenic detrusor overactivity, detrusor-sphincter dyssynergia, and areflexic neurogenic bladder.[12,13] However, due to the limited sample size, the authors were unable to perform analyses that examined the relationship between specific types of NLUTD and risk of type 2 diabetes.

In conclusions, this cohort study found that NLUTD is significantly associated with an increased risk of developing type 2 diabetes in SCI patients. Interventional programs that may effectively reduce the risk of type 2 diabetes onset should be considered and administered to SCI patients who develop NLUTD.

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