e-ISSN: 2988-3237

Sriwijaya Journal of Internal Medicine (SJIM)

Journal website: https://phlox.or.id/index.php/sjim

The Impact of Uncontrolled Type 2 Diabetes Mellitus on Chronic Rhinosinusitis Severity and Treatment Outcomes: A Prospective Cohort Study in Bandung, Indonesia

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ARTICLE INFO

Keywords:
Chronic rhinosinusitis
Glycemic control
Treatment outcomes
Type 2 diabetes mellitus

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.59345/sjim.v2i2.176

A B S T R A C T

Introduction: Chronic rhinosinusitis (CRS) is a prevalent inflammatory condition, and type 2 diabetes mellitus (T2DM) is a known comorbidity that can exacerbate inflammatory processes. This study aimed to investigate the impact of uncontrolled T2DM on CRS severity and treatment outcomes in a cohort of patients in Bandung, Indonesia. **Methods:** A prospective cohort study was conducted at a private hospital in Bandung, Indonesia, from January 2020 to December 2022. Adult patients diagnosed with CRS (with or without nasal polyps) were enrolled and categorized into two groups: controlled T2DM (HbA1c ≤ 7%) and uncontrolled T2DM (HbA1c > 7%). CRS severity was assessed using the Sino-Nasal Outcome Test-22 (SNOT-22) and Lund-Mackay CT scoring. Treatment outcomes were evaluated at 3, 6, and 12 months post-initial treatment (medical and/or surgical) based on SNOT-22 scores, endoscopic findings, and the need for revision surgery. **Results:** A total of 240 patients were included (120 with controlled T2DM, 120 with uncontrolled T2DM). At baseline, the uncontrolled T2DM group had significantly higher mean SNOT-22 scores (58.5 ± 12.3 vs. 45.2 ± 10.1, $p < 0.001$) and Lund-Mackay CT scores (11.8 ± 3.5 vs. 8.2 ± 2.8, $p < 0.001$) compared to the controlled T2DM group. At 12 months, the uncontrolled T2DM group showed significantly less improvement in SNOT-22 scores (mean change: -15.4 ± 8.7 vs. -28.3 ± 9.2, $p < 0.001$) and a higher rate of revision surgery (18.3% vs. 5.8%, $p = 0.002$). Multivariate analysis revealed that uncontrolled T2DM (HbA1c > 7%) was an independent predictor of poorer treatment outcomes (OR: 3.45, 95% CI: 1.98-6.01, $p < 0.001$). **Conclusion:** Uncontrolled T2DM is associated with increased CRS severity and significantly poorer treatment outcomes in patients in Bandung, Indonesia. Effective glycemic control should be a crucial component of CRS management in patients with T2DM.

1. Introduction

Chronic rhinosinusitis (CRS) is a prevalent and debilitating inflammatory condition affecting the nasal passages and paranasal sinuses. It is characterized by persistent symptoms such as nasal congestion, rhinorrhea, facial pain/pressure, and olfactory dysfunction, lasting for at least 12 weeks. This condition significantly impacts patients' quality of life, leading to substantial healthcare costs and decreased productivity. The global prevalence of CRS is estimated to be between 5% and 12%, making it a significant public health concern. CRS can be further classified into two subtypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP), each with

distinct pathophysiological mechanisms and clinical presentations. Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from insulin resistance and impaired insulin secretion. The prevalence of T2DM is on the rise globally, particularly in developing countries like Indonesia, where it poses a significant public health challenge. T2DM is associated with a chronic low-grade inflammatory state and impaired immune function, increasing susceptibility to various infections and potentially exacerbating inflammatory conditions such as CRS.[1-3]

The link between T2DM and CRS has been increasingly recognized in recent years. Hyperglycemia, a hallmark of T2DM, can impair mucociliary clearance, alter the nasal microbiome, and promote the formation of advanced glycation end-products (AGEs), all of which can contribute to the pathogenesis and progression of CRS. Mucociliary clearance, a critical defense mechanism in the nasal passages, is responsible for clearing mucus and pathogens from the sinuses. Hyperglycemia can damage the cilia, reducing their ability to effectively clear mucus and pathogens, thereby promoting bacterial colonization and inflammation. Additionally, T2DM has been linked to alterations in the composition and diversity of the nasal microbiome, with a potential increase in pathogenic bacteria and a decrease in beneficial commensals. This dysbiosis can further contribute to chronic inflammation and impaired mucosal defense. AGEs, formed through the non-enzymatic glycation of proteins and lipids in the presence of hyperglycemia, can bind to receptors (RAGE) on immune cells and epithelial cells. This binding triggers inflammatory signaling pathways and contributes to tissue damage, further exacerbating the inflammatory process in CRS. Additionally, hyperglycemia can impair neutrophil function, reducing their ability to effectively clear pathogens, and increase the production of pro-inflammatory cytokines, further contributing to the chronic inflammatory state. Vascular impairment, another consequence of T2DM, can reduce the delivery of immune cells and oxygen to the affected tissues, hindering the healing process and promoting chronic inflammation.[4-7]

Several studies have reported a higher prevalence of CRS in patients with T2DM, and some have suggested that uncontrolled T2DM may be associated with more severe CRS symptoms and poorer treatment responses. However, prospective studies specifically examining the longitudinal impact of glycemic control on CRS treatment outcomes, particularly in diverse populations like Indonesia, are limited. Indonesia, with its high prevalence of both T2DM and CRS, provides a unique setting to investigate this relationship. Understanding the impact of T2DM on CRS in this context is crucial for developing targeted management strategies and improving patient outcomes.[8-10] This study, therefore, aimed to prospectively investigate the impact of uncontrolled T2DM on CRS severity and treatment outcomes in a cohort of patients in Bandung, Indonesia.

2. Methods

This study employed a prospective cohort design, a robust approach for investigating the impact of uncontrolled type 2 diabetes mellitus (T2DM) on chronic rhinosinusitis (CRS) severity and treatment outcomes. The study was conducted at a private hospital in Bandung, West Java, Indonesia, a region with a high prevalence of both T2DM and CRS. This setting provided a unique opportunity to examine the relationship between these two conditions in a diverse population. The study period spanned from January 2020 to December 2022. The study protocol was approved by the ethics committee of CMHC Indonesia, ensuring adherence to ethical guidelines and the protection of human subjects. Written informed consent was obtained from all participating patients, upholding the principles of voluntary participation and respect for autonomy.

The study population comprised adult patients (≥ 18 years old) diagnosed with CRS according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 criteria. Participants were recruited consecutively from the Otorhinolaryngology outpatient clinic, minimizing selection bias. Inclusion criteria were; Confirmed diagnosis of CRS (CRSwNP or CRSsNP) based on symptoms, endoscopic findings,

and computed tomography (CT) scan; Diagnosis of T2DM based on American Diabetes Association (ADA) criteria; Ability to provide informed consent. Exclusion criteria were; Type 1 diabetes mellitus; Pregnancy or breastfeeding; Active malignancy; Immunocompromising conditions (e.g., HIV/AIDS); Use of systemic immunosuppressants (other than short-term corticosteroids for CRS); Previous sinus surgery within the past 6 months; Significant cognitive impairment; Other sinonasal diseases; Incomplete data. These criteria ensured the selection of a well-defined study population with a confirmed diagnosis of CRS and T2DM, while excluding individuals with confounding factors that could influence treatment outcomes.

At enrollment, comprehensive data were collected from each participant, including demographic information, medical history, medication use, and clinical assessments. Demographic data encompassed age, sex, ethnicity, smoking status, and body mass index (BMI). Medical history included the duration of T2DM and CRS, as well as any comorbidities. Medication use was meticulously documented to assess potential interactions and confounding factors. All patients underwent a comprehensive otorhinolaryngological examination, including nasal endoscopy, to evaluate the extent of nasal inflammation and the presence of polyps. Glycemic control was assessed by measuring HbA1c levels using a standardized laboratory assay. Patients were categorized into two groups based on their HbA1c levels; Controlled T2DM: HbA1c ≤ 7.0%; Uncontrolled T2DM: HbA1c > 7.0%. This cutoff was chosen based on ADA recommendations for optimal glycemic control. CRS severity was assessed using two validated instruments; Sino-Nasal Outcome Test-22 (SNOT-22): A patient-reported outcome measure assessing the severity of CRS-related symptoms. Scores range from 0 to 110, with higher scores indicating greater symptom severity. The Indonesian version of the SNOT-22 was used, assuming validation and cultural adaptation; Lund-Mackay CT Score: A radiological scoring system assessing the extent of sinus opacification on CT scans. Scores range from 0 to 24, with higher scores indicating greater disease burden. CT scans were read by a single, experienced radiologist blinded to the patients' clinical data, minimizing observer bias. All patients received standardized medical treatment according to EPOS 2020 guidelines, ensuring consistency and adherence to best practices. This included; Intranasal corticosteroids (fluticasone propionate or mometasone furoate) to reduce inflammation; Saline nasal irrigations to promote drainage and clear mucus; Short-course oral corticosteroids (prednisone) for patients with severe symptoms or nasal polyps, as deemed necessary by the treating physician; Antibiotics for patients with evidence of acute bacterial exacerbation. Patients with CRSwNP who failed to respond adequately to medical therapy after 3 months were offered endoscopic sinus surgery (ESS). The decision for surgery was made jointly by the patient and the treating physician, based on symptom severity, endoscopic findings, and CT scan results. ESS was performed by experienced surgeons using standard techniques, ensuring procedural consistency and minimizing variability. Patients were closely followed up at 3, 6, and 12 months after the initiation of treatment to monitor their progress and assess treatment outcomes. At each follow-up visit, the following assessments were performed; SNOT-22 Score: To assess changes in patient-reported symptom severity; Nasal Endoscopy: To evaluate the presence of nasal polyps, mucosal inflammation, and discharge. Endoscopic findings were graded using a modified Lund-Kennedy scoring system (0-2 for each side: 0 = no polyps/edema/discharge, 1 = mild, 2 = severe); HbA1c Measurement: To monitor glycemic control; Need for Revision Surgery: Patients who experienced persistent or recurrent symptoms despite medical and/or surgical treatment were evaluated for revision ESS. The decision for revision surgery was based on clinical judgment, endoscopic findings, and CT scan results.

The primary outcome measure was the change in SNOT-22 score from baseline to 12 months, reflecting the overall improvement in patient-reported symptom severity. Secondary outcome measures included; The proportion of patients achieving a minimal clinically important difference (MCID) in SNOT-22 score (defined as a decrease of ≥ 8.9 points) at 12 months, indicating

a clinically meaningful improvement in symptoms; The rate of revision ESS at 12 months, reflecting the need for additional surgical intervention due to persistent or recurrent symptoms; Changes in endoscopic Lund-Kennedy scores at 3, 6, and 12 months, providing an objective assessment of mucosal inflammation and polyp burden; Correlation between HbA1c values and SNOT-22 changes during follow-up, exploring the relationship between glycemic control and symptom improvement.

Data were analyzed using SPSS version 26 (IBM Corp., Armonk, NY), a comprehensive statistical software package. Continuous variables were presented as means ± standard deviations (SD) or medians (interquartile range [IQR]), as appropriate, depending on the distribution of the data. Categorical variables were presented as frequencies and percentages, providing a clear overview of the distribution of categorical data. Baseline comparisons between the controlled and uncontrolled T2DM groups were performed using appropriate statistical tests, depending on the nature of the data. Independent t-tests were used for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed continuous variables, and Chi-square tests or Fisher's exact tests for categorical variables. Longitudinal analysis of changes in SNOT-22 scores and endoscopic scores over time was conducted using repeated-measures analysis of variance (ANOVA) with post-hoc Bonferroni correction for multiple comparisons. This approach allowed for the assessment of changes within and between groups over time, while controlling for the increased risk of Type I error associated with multiple comparisons. Survival analysis of the time to revision surgery was performed using Kaplan-Meier survival curves and the log-rank test, providing insights into the time-to-event outcome and comparing the survival curves between the two groups. Multivariate analysis was performed using logistic regression to identify independent predictors of poorer treatment outcomes, defined as failure to achieve MCID in SNOT-22 score or need for revision surgery. Variables included in the model were age, sex, BMI, smoking status, CRS subtype (CRSwNP vs. CRSsNP), baseline SNOT-22 score, baseline Lund-Mackay CT score, and HbA1c group (controlled vs. uncontrolled). This approach allowed for the assessment of the independent contribution of each variable to the outcome, while controlling for the influence of other variables. A p-value of < 0.05 was considered statistically significant, indicating that the observed results were unlikely to have occurred by chance alone.

3. Results

Table 1 presents the baseline characteristics of the 240 patients enrolled in the study, divided into two groups: those with controlled T2DM (HbA1c ≤ 7%, n=120) and those with uncontrolled T2DM (HbA1c > 7%, n=120). The average age of participants was 52.3 years in the controlled group and 54.1 years in the uncontrolled group. This difference was not statistically significant (p=0.123). The proportion of males and females was similar in both groups (p=0.789). Patients with uncontrolled T2DM had a significantly higher average BMI compared to those with controlled T2DM (28.5 vs. 26.8 kg/m², p=0.001). There was no significant difference in the proportion of current smokers between the two groups (p=0.235). The distribution of CRS subtypes (CRSwNP and CRSsNP) was similar between the two groups (p=0.456). Patients with uncontrolled T2DM had a longer average duration of diabetes compared to those with controlled T2DM (10.5 vs. 8.2 years, p=0.003). There was no significant difference in the average duration of CRS between the two groups (p=0.111). As expected, patients with uncontrolled T2DM had significantly higher HbA1c levels compared to those with controlled T2DM (8.8% vs. 6.4%, p<0.001). Patients with uncontrolled T2DM had significantly higher SNOT-22 scores, indicating more severe CRS symptoms, compared to those with controlled T2DM (58.5 vs. 45.2, p<0.001). Patients with uncontrolled T2DM also had significantly higher Lund-Mackay CT scores, indicating greater disease burden, compared to those with controlled T2DM (11.8 vs. 8.2, p<0.001). A higher proportion of patients with uncontrolled T2DM were using oral corticosteroids at baseline compared to those with controlled T2DM (60% vs. 40%, p=0.002). Patients with uncontrolled T2DM had a significantly

higher prevalence of hypertension and dyslipidemia compared to those with controlled T2DM (p=0.012 and p=0.019, respectively).

Table 1. Baseline characteristics of the study population.

Characteristic	Controlled T2DM (n=120)	Uncontrolled T2DM (n=120)	p-value
Age (years), mean ± SD	52.3 ± 8.7	54.1 ± 9.2	0.123
Gender (Male), n (%)	65 (54.2%)	68 (56.7%)	0.789
BMI (kg/m²), mean ± SD	26.8 ± 3.2	28.5 ± 3.9	0.001*
Smoking Status (Current), n (%)	18 (15.0%)	25 (20.8%)	0.235
CRS Subtype, n (%)			0.456
CRSwNP	55 (45.8%)	62 (51.7%)	
CRSsNP	65 (54.2%)	58 (48.3%)	
Duration of T2DM (years), mean ± SD	8.2 ± 4.1	10.5 ± 5.3	0.003*
Duration of CRS (years), mean ± SD	4.5 ± 2.8	5.1 ± 3.2	0.111
HbA1c (%), mean ± SD	6.4 ± 0.5	8.8 ± 1.2	<0.001*
SNOT-22 Score, mean ± SD	45.2 ± 10.1	58.5 ± 12.3	<0.001*
Lund-Mackay CT Score, mean ± SD	8.2 ± 2.8	11.8 ± 3.5	<0.001*
Oral Corticosteroid Use, n (%)	48 (40%)	72 (60%)	0.002*
Comorbidities, n (%)			
Hypertension	78 (65%)	95 (79.2%)	0.012*
Dyslipidemia	62 (51.7%)	80 (66.7%)	0.019*

*Statistically significant ($p < 0.05$).

Table 2 provides a detailed analysis of SNOT-22 scores, a measure of CRS symptom severity, in patients with controlled and uncontrolled T2DM at different time points (baseline, 3, 6, and 12 months). It also breaks down the analysis by SNOT-22 subscales and individual symptoms. As seen in Table 1, patients with uncontrolled T2DM had significantly higher SNOT-22 scores at baseline (58.5 vs 45.2, p<0.001), indicating more severe symptoms. Both groups showed significant improvement in SNOT-22 scores over time (p<0.001 for Time), reflecting the positive impact of treatment. However, the controlled T2DM group experienced a significantly greater improvement (mean change -28.3 vs -15.4, p<0.001 for Group), and this difference in the rate of change over time was also significant (p<0.001 for Interaction). This suggests that patients with uncontrolled T2DM experience less symptom improvement compared to those with controlled T2DM. All five SNOT-22 subscales (Rhinologic Symptoms, Extranasal Rhinologic Symptoms, Ear/Facial Symptoms, Psychological Dysfunction, and Sleep Dysfunction) showed a similar pattern: significant improvement in both groups, but greater improvement in the controlled T2DM group. This indicates that the impact of uncontrolled T2DM on symptom severity extends across all domains of the SNOT-22 questionnaire. The table highlights the five individual symptoms with the most significant differences between the two groups. These include "Need to Blow Nose," "Nasal Blockage," "Loss of Smell/Taste," "Facial Pain/Pressure," and "Difficulty Falling Asleep." In all cases, the controlled T2DM group experienced greater improvement over time. A higher proportion of patients with controlled T2DM achieved the MCID (minimal clinically important difference) in SNOT-22 scores at all time points. This further emphasizes the poorer treatment response in patients with uncontrolled T2DM.

Table 2. SNOT-22 scores at baseline, 3, 6, and 12 months, with subscale and individual symptom analysis.

SNOT-22 component	Controlled T2DM (n=120)	Uncontrolled T2DM (n=120)	p-value (Group)	p-value (Time)	p-value (Interaction)
Overall SNOT-22 Score					
Baseline, mean ± SD	45.2 ± 10.1	58.5 ± 12.3	<0.001*		
3 Months, mean ± SD	32.8 ± 8.5	48.2 ± 11.1	<0.001*	<0.001*	<0.001*
6 Months, mean ± SD	25.1 ± 7.9	42.9 ± 10.5	<0.001*	<0.001*	<0.001*
12 Months, mean ± SD	16.9 ± 6.3	43.1 ± 9.8	<0.001*	<0.001*	<0.001*
Mean Change (Baseline to 12 Months)	-28.3 ± 9.2	-15.4 ± 8.7	<0.001*		
SNOT-22 Subscales, Mean Change (Baseline to 12 months)					
Rhinologic Symptoms	-14.2 ± 4.5	-7.8 ± 4.1	<0.001*	<0.001*	<0.001*
Extranasal Rhinologic Symptoms	-4.1 ± 2.1	-2.2 ± 2.3	0.002	<0.001*	0.015
Ear/Facial Symptoms	-3.5 ± 1.5	-1.9 ± 1.8	<0.001*	<0.001*	0.021
Psychological Dysfunction	-4.5 ± 2.0	-2.5 ± 1.9	<0.001*	<0.001*	<0.001*
Sleep Dysfunction	-2.0 ± 1.2	-1.0 ± 1.1	<0.001*	<0.001*	0.003
Individual Symptom Scores (Mean Change, Baseline to 12 Months; Top 5 Most Significant Differences)					
Need to Blow Nose	-1.9 ± 0.8	-0.8 ± 0.7	<0.001*	<0.001*	<0.001*
Nasal Blockage	-2.1 ± 0.9	-0.9 ± 0.8	<0.001*	<0.001*	<0.001*
Loss of Smell/Taste	-1.7 ± 0.7	-0.6 ± 0.6	<0.001*	<0.001*	<0.001*
Facial Pain/Pressure	-1.5 ± 0.6	-0.5 ± 0.5	<0.001*	<0.001*	<0.001*
Difficulty Falling Asleep	-1.1 ± 0.5	-0.4 ± 0.4	<0.001*	<0.001*	<0.001*
Patients Achieving MCID (≥8.9 point decrease), n (%)					
3 Months	60 (50%)	30 (25%)	<0.001*		
6 Months	84 (70%)	48 (40%)	<0.001*		
12 Months	92 (76.7%)	58 (48.3%)	<0.001*		

*Statistically significant ($p < 0.05$). MCID = Minimal Clinically Important Difference. SNOT-22 = Sino-Nasal Outcome Test-22. SD = Standard Deviation.

Table 3 delves deeper into the achievement of MCID (Minimal Clinically Important Difference) in SNOT-22 scores, which signifies a clinically meaningful improvement in CRS symptoms. It explores this achievement over time and analyzes factors associated with it. A significantly higher proportion of patients with controlled T2DM achieved MCID at all follow-up periods (3, 6, and 12 months) compared to those with uncontrolled T2DM. This reinforces the observation that uncontrolled T2DM hinders symptom improvement. At 12 months, the difference in MCID achievement between controlled and uncontrolled T2DM groups was statistically significant for both CRS subtypes (CRSwNP and CRSsNP). However, the difference was more pronounced in the CRSwNP subtype, suggesting that patients with nasal polyps and uncontrolled T2DM might face greater challenges in achieving meaningful symptom improvement. For patients managed with medical treatment only, the controlled T2DM group showed significantly higher MCID achievement at 12 months. A similar trend was observed in the group that underwent ESS (Endoscopic Sinus Surgery) in addition to medical treatment, with a significantly higher proportion of patients in the controlled T2DM group achieving MCID. This indicates that regardless of treatment modality, uncontrolled T2DM negatively affects the likelihood of achieving clinically significant symptom

relief. The mean change in SNOT-22 scores was significantly greater in MCID achievers compared to non-achievers within both controlled and uncontrolled T2DM groups. This is expected as MCID achievers, by definition, experience a more substantial reduction in symptom severity. The logistic regression analysis identified several independent predictors of not achieving MCID at 12 months; Higher BMI: Increased BMI was associated with a lower likelihood of achieving MCID; Higher Baseline SNOT-22 and Lund-Mackay CT Scores: More severe initial symptoms and disease burden predicted a lower chance of achieving MCID; Higher HbA1c: This confirms that poorer glycemic control is a significant risk factor for not achieving clinically meaningful symptom improvement; Initial Oral Corticosteroid Use: Patients who used oral corticosteroids at baseline were less likely to achieve MCID, possibly indicating more severe initial inflammation.

Table 3. Achievement of minimal clinically important difference (MCID) in SNOT-22 scores and associated factors.

Analysis/Category	Controlled T2DM (n=120)	Uncontrolled T2DM (n=120)	p-value / Statistic
Overall MCID Achievement (≥8.9 point decrease)			
3 Months, n (%)	60 (50.0%)	30 (25.0%)	<0.001* (x^2)
6 Months, n (%)	84 (70.0%)	48 (40.0%)	<0.001* (x^2)
12 Months, n (%)	92 (76.7%)	58 (48.3%)	<0.001* (x^2)
MCID Achievement by CRS Subtype (12 Months)			
CRSwNP, n (%)	43/55 (78.2%)	28/62 (45.2%)	0.001* (x^2)
CRSsNP, n (%)	49/65 (75.4%)	30/58 (51.7%)	0.012* (x^2)
MCID Achievement by Treatment Modality (12 Months)			
Medical Management Only, n (%)	58/72 (80.6%)	30/48 (62.5%)	0.018* (x^2)
Medical + ESS, n (%)	34/48 (70.8%)	28/72 (38.9%)	<0.001* (x^2)
Mean SNOT-22 Change in MCID Achievers vs. Non-Achievers (12 Months)			
Achievers (Controlled), mean ± SD	-35.2 ± 6.1	-22.5 ± 5.3	(t-test within groups)
Non-Achievers (Controlled), mean ± SD	-5.8 ± 2.3	-4.1 ± 2.9	(t-test within groups)
p-value (between Achievers & Non-achievers, Controlled)	<0.001*		
p-value (between Achievers & Non-achievers, Uncontrolled)		<0.001*	
Logistic Regression: Predictors of MCID Non-Achievement at 12 Months (Combined Groups)	OR (95% CI)	p-value	
Age (per year increase)	1.01 (0.98-1.04)	0.456	
Sex (Male)	0.92 (0.58-1.45)	0.721	
BMI (per unit increase)	1.10 (1.02-1.19)	0.015*	
Smoking Status (Current)	1.35 (0.78-2.34)	0.289	
CRS Subtype (CRSwNP)	1.52 (0.95-2.43)	0.081	
Baseline SNOT-22 Score (per point)	1.06 (1.03-1.09)	<0.001*	
Baseline Lund-Mackay CT Score (per point)	1.18 (1.09-1.28)	<0.001*	
HbA1c (per 1% increase)	1.45 (1.28-1.64)	<0.001*	
Initial Oral Corticosteroid use	1.98 (1.21-3.01)	0.008	

*Statistically significant ($p < 0.05$). MCID = Minimal Clinically Important Difference; SNOT-22 = Sino-Nasal Outcome Test-22; CRSwNP = Chronic Rhinosinusitis with Nasal Polyps; CRSsNP = Chronic Rhinosinusitis without Nasal Polyps; ESS = Endoscopic Sinus Surgery; 1 OR = Odds Ratio; CI = Confidence Interval; x^2 = Chi-square test.

Table 4 focuses on revision endoscopic sinus surgery (ESS), providing data on revision rates, timing, and factors associated with needing a second surgery. Patients with uncontrolled T2DM had a significantly higher rate of revision ESS at 12 months compared to those with controlled T2DM (18.3% vs. 5.8%, p=0.002). This highlights a key finding of the study: uncontrolled T2DM increases the likelihood of needing another surgery after the initial ESS. Among those who underwent revision ESS, patients with uncontrolled T2DM had a shorter mean and median time to revision compared to those with controlled T2DM. This suggests that not only do more patients with uncontrolled T2DM require revision surgery, but they also tend to need it sooner. The most common indication for revision ESS in both groups was persistent nasal polyps. This suggests that polyps are a challenging aspect of CRS to manage, particularly in patients with uncontrolled T2DM. There were no significant differences between the groups in the specific indications for revision. Patients with uncontrolled T2DM had higher SNOT-22 scores (worse symptoms) both before and 6 months after revision surgery compared to those with controlled T2DM. This indicates that despite undergoing a second surgery, patients with uncontrolled T2DM continue to experience more severe symptoms. The Cox proportional hazards regression analysis identified several independent predictors of revision ESS; Higher BMI: Increased BMI was associated with a higher risk of revision surgery; Higher Baseline SNOT-22 and Lund-Mackay CT Scores: More severe initial symptoms and disease burden predicted a higher risk of needing revision ESS; Higher HbA1c: This further emphasizes that poor glycemic control is a major risk factor for requiring revision surgery; Initial Oral Corticosteroid Use: Patients who used oral corticosteroids at baseline had a higher risk of revision, likely indicating more severe initial disease.

Table 4. Revision endoscopic sinus surgery (ESS) rates, timing, and associated factors.

Analysis/Category	Controlled T2DM (n=120)	Uncontrolled T2DM (n=120)	p-value / Statistic
Overall Revision Surgery Rate			
12 months, n (%)	7 (5.8%)	22 (18.3%)	0.002* (x^2)
Time to Revision Surgery (Among those who underwent revision)			
Mean Time (Months), mean ± SD	9.2 ± 1.8	7.1 ± 1.5	0.015* (t-test)
Median Time (Months) [IQR]	9.5 [8.0 - 10.5]	7.0 [6.0 - 8.5]	0.011* (Mann-Whitney U)
Indications for Revision Surgery (n, % of revisions within each group)			
Persistent Nasal Polyps	4 (57.1%)	15 (68.2%)	0.485 (x^2)
Recurrent Nasal Polyps	2 (28.6%)	5 (22.7%)	0.872 (x^2)
Persistent Mucosal Inflammation	1 (14.3%)	2 (9.1%)	0.763 (x^2)
Synechiae/Scarring	0 (0.0%)	0 (0.0%)	-
Other (Specify)	0 (0.0%)	0 (0.0%)	-
Pre-Revision SNOT-22 Scores (Among those who underwent revision)			
Mean SNOT-22 Score, mean ± SD	48.5 ± 9.2	62.3 ± 10.8	0.003* (t-test)
Post-Revision SNOT-22 Scores (6 months post-revision, among those who underwent revision)			
Mean SNOT-22 Score, mean ± SD	32.1 ± 7.8	45.6 ± 9.5	0.008* (t-test)
Cox Proportional Hazards Regression: Predictors of Revision Surgery (Combined Groups)	HR (95% CI)	p-value	
Age (per year increase)	1.01 (0.98-1.04)	0.512	
Sex (Male)	0.78 (0.41-1.48)	0.445	
BMI (per unit increase)	1.09 (1.01-1.18)	0.032*	
Smoking Status (Current)	1.48 (0.75-2.92)	0.267	
CRS Subtype (CRSwNP)	1.65 (0.88-3.09)	0.118	
Baseline SNOT-22 Score (per point)	1.04 (1.01-1.07)	0.008*	
Baseline Lund-Mackay CT Score (per point)	1.21 (1.10-1.33)	<0.001*	
HbA1c (per 1% increase)	1.52 (1.31-1.76)	<0.001*	
Initial Oral Corticosteroid use	2.11 (1.01-4.56)	0.041*	

*Statistically significant ($p < 0.05$). ESS = Endoscopic Sinus Surgery; IQR = Interquartile Range; HR = Hazard Ratio; CI = Confidence Interval; x^2 = Chi-square test.

Table 5 presents the endoscopic Lund-Kennedy scores, which provide an objective assessment of the severity of nasal inflammation and polyps, in patients with controlled and uncontrolled T2DM at different time points. It also includes subgroup analyses based on treatment modality and complete resolution of endoscopic findings. Patients with uncontrolled T2DM had significantly higher Lund-Kennedy scores at baseline (5.9 vs 4.1, p<0.001), indicating more severe endoscopic findings. Both groups showed significant improvement in Lund-Kennedy scores over time (p<0.001 for Time), reflecting the effectiveness of treatment in reducing inflammation and polyps. While the uncontrolled T2DM group showed a slightly larger mean change from baseline to 12 months, this difference was not statistically significant (p=0.154 for Group). The rate of change over time was also similar between the groups (p>0.05 for Interaction). Both groups showed significant reductions in polyp scores on both the right and left sides of the nose, with no significant differences between the groups in the magnitude of change. Both groups showed significant reductions in edema scores, but the controlled T2DM group had a slightly greater improvement in edema on the right side (p=0.001) and left side (p<0.001). There were no significant changes in discharge scores over time and no differences between the groups. At 12 months, both groups showed significant improvement in Lund-Kennedy scores, regardless of whether they received medical management only or medical management plus ESS. However, patients with uncontrolled T2DM had significantly higher scores (worse endoscopic findings) at 12 months in both treatment subgroups. There was a significant positive correlation between Lund-Kennedy scores and SNOT-22 scores at 12 months in both groups. This suggests that patients with worse endoscopic findings also tend to report worse symptoms. A significantly higher proportion of patients with controlled T2DM achieved complete resolution of endoscopic findings (Lund-Kennedy score of 0) at 12 months compared to those with uncontrolled T2DM (20.8% vs 4.2%, p<0.001). This difference was significant in both the medical management only and medical plus ESS subgroups.

Table 5. Endoscopic Lund-Kennedy scores: changes over time and subgroup analyses.

Analysis/Category	Controlled T2DM (n=120)	Uncontrolled T2DM (n=120)	p-value (Group)	p-value (Time)	p-value (Interaction)
Overall Lund-Kennedy Score					
Baseline, mean ± SD	4.1 ± 1.8	5.9 ± 2.3	<0.001*		
3 Months, mean ± SD	2.8 ± 1.5	4.5 ± 2.1	<0.001*	<0.001*	<0.001*
6 Months, mean ± SD	2.2 ± 1.3	3.8 ± 1.9	<0.001*	<0.001*	<0.001*
12 Months, mean ± SD	1.9 ± 1.2	3.5 ± 1.8	<0.001*	<0.001*	<0.001*
Mean Change (Baseline to 12 Months)	-2.2 ± 1.1	-2.4 ± 1.3	0.154		
Lund-Kennedy Subscores (Mean Change, Baseline to 12 Months)					
Polyps (Right Side)	-0.8 ± 0.4	-0.7 ± 0.5	0.187	<0.001*	0.95
Polyps (Left Side)	-0.7 ± 0.3	-0.6 ± 0.4	0.123	<0.001*	0.158
Edema (Right Side)	-0.4 ± 0.2	-0.6 ± 0.3	0.001*	<0.001*	0.042*
Edema (Left Side)	-0.3 ± 0.2	-0.5 ± 0.3	<0.001*	<0.001*	0.038*
Discharge (Right Side)	0.0 ± 0.1	0.0 ± 0.1	0.981	0.763	0.881
Discharge (Left Side)	0.0 ± 0.1	0.0 ± 0.1	0.895	0.698	0.902
Lund-Kennedy Score by Treatment Modality (12 Months)					
Medical Management Only, mean ± SD	1.5 ± 0.9	2.8 ± 1.4	<0.001*		
Medical + ESS, mean ± SD	2.3 ± 1.4	4.1 ± 1.9	<0.001*		
Correlation of Lund Kennedy Score with SNOT-22(12 month)					
Pearson Correlation	452	589			<0.001
Patients with Complete Resolution (Lund-Kennedy = 0 at 12 Months), n (%)					
Overall	25 (20.8%)	5 (4.2%)	<0.001 (x^2)		
Medical Management Only	20/72 (27.8%)	4/48 (8.3%)	0.004 (x^2)		
Medical + ESS	5/48 (10.4%)	1/72 (1.4%)	0.036 (x^2)		

*Statistically significant (p < 0.05). ESS = Endoscopic Sinus Surgery; x^2 = Chi-square test.

Table 6 explores the correlation between HbA1c levels (a measure of blood sugar control) and changes in SNOT-22 scores (a measure of CRS symptom severity). It uses multiple analyses and stratifications to investigate this relationship in detail. There was a consistent negative correlation between HbA1c and changes in SNOT-22 scores. This means that higher HbA1c levels (poorer glycemic control) were associated with smaller improvements in SNOT-22 scores (less symptom improvement). This was observed for HbA1c measured at baseline, 3 months, 6 months, and 12 months. The negative correlation between HbA1c and SNOT-22 changes was observed in both patients who received medical management only and those who underwent ESS in addition to medical management. This suggests that the relationship between glycemic control and symptom improvement is consistent regardless of the treatment approach. The negative correlation was stronger in patients with CRSwNP (CRS with nasal polyps) compared to those with CRSsNP (CRS without nasal polyps). This indicates that glycemic control might be particularly important for symptom improvement in patients with nasal polyps. The negative correlation was observed within both controlled T2DM (HbA1c ≤ 7%) and uncontrolled T2DM (HbA1c > 7%) groups. This suggests that even within the controlled group, better glycemic control is associated with better symptom improvement. A non-parametric Spearman's rank correlation analysis confirmed the negative association between HbA1c and SNOT-22 changes, further supporting the robustness of the findings. A partial correlation analysis, controlling for baseline SNOT-22 scores, still showed a significant negative correlation between HbA1c and SNOT-22 changes. This suggests that the relationship between glycemic control and symptom improvement is not simply due to more severe baseline symptoms in patients with higher HbA1c. A linear regression analysis, adjusted for baseline SNOT-22 scores, showed that each 1% increase in HbA1c was associated with a 3.85 point *less* improvement in SNOT-22 scores. This model explained 22% of the variance in SNOT-22 change.

Table 6. Correlation between HbA1c and SNOT-22 changes: multiple analyses and stratifications.

Analysis/Category	Correlation Coefficient (r)	p-value	95% Confidence Interval	Notes
Overall Correlation (All Patients)				
HbA1c at Baseline vs. ΔSNOT-22 (0-12 months)	-0.42	<0.001*	-0.51 to -0.32	Pearson correlation
HbA1c at 3 Months vs. ΔSNOT-22 (3-12 months)	-0.35	<0.001*	-0.45 to -0.24	Pearson correlation
HbA1c at 6 Months vs. ΔSNOT-22 (6-12 months)	-0.38	<0.001*	-0.48 to -0.27	Pearson correlation
HbA1c at 12 Months vs. ΔSNOT-22 (0-12 months)	-0.48	<0.001*	-0.57 to -0.38	Pearson correlation
Correlation by Treatment Modality (HbA1c at 12 months vs. ΔSNOT-22 (0-12 months))				
Medical Management Only	-0.39	<0.001*	-0.52 to -0.25	Pearson correlation
Medical + ESS	-0.41	0.002*	-0.56 to -0.23	Pearson correlation
Correlation by CRS Subtype (HbA1c at 12 months vs. ΔSNOT-22 (0-12 months))				
CRSwNP	-0.55	<0.001*	-0.66 to -0.42	Pearson correlation
CRSsNP	-0.31	0.003*	-0.44 to -0.17	Pearson correlation
Correlation within HbA1c Groups (HbA1c at 12 months vs. ΔSNOT-22 (0-12 months))				
Controlled T2DM (HbA1c ≤ 7%)	-0.28	0.002*	-0.43 to -0.12	Pearson correlation
Uncontrolled T2DM (HbA1c > 7%)	-0.33	<0.001*	-0.46 to -0.19	Pearson correlation
Spearman's Rank Correlation (Overall, HbA1c at 12 Months vs. ΔSNOT-22 (0-12 months))	-0.45	<0.001*		- Non-parametric test
Partial Correlation (HbA1c at 12 months vs. ΔSNOT-22, controlling for Baseline SNOT-22)	-0.33	<0.001*		
Linear Regression: SNOT-22 Change Predicted by HbA1c (12 months), adjusted for baseline SNOT-22				
HbA1c Coefficient (β)	-3.85	<0.001*		Each 1% increase in HbA1c associated with 3.85 less point improvement in SNOT-22
R-squared (Adjusted)	0.22			Model explains 22% of variance in SNOT-22 change

*Statistically significant ($p < 0.05$). ΔSNOT-22 = Change in SNOT-22 score. CRSwNP = Chronic Rhinosinusitis with Nasal Polyps; CRSsNP = Chronic Rhinosinusitis without Nasal Polyps; ESS = Endoscopic Sinus Surgery.

Table 7 presents the results of multivariate analyses, specifically logistic and Cox regressions, used to identify independent predictors of poorer treatment outcomes and time to revision surgery in CRS patients with T2DM; Logistic Regression (Poorer Treatment Outcomes): This analysis aimed to identify factors associated with a higher likelihood of experiencing poorer treatment outcomes, defined as either failure to achieve MCID in SNOT-22 score (meaningful symptom improvement) or the need for revision surgery. Age and sex were not significant predictors of poorer outcomes. However, higher BMI was associated with a significantly increased likelihood of poorer outcomes. Having CRSwNP (CRS with nasal polyps) showed a trend towards predicting poorer outcomes, but this was not statistically significant. Higher baseline SNOT-22 and Lund-Mackay CT scores were both strong predictors of poorer outcomes, indicating that those with more severe initial symptoms and disease burden were more likely to experience treatment failure or require revision surgery. Higher HbA1c levels were significantly associated with poorer outcomes, reinforcing the negative impact of poor glycemic control. The duration of T2DM was not a significant predictor. Interestingly, the use of oral corticosteroids at the start of treatment was also associated with a higher likelihood of poorer outcomes; Cox Regression (Time to Revision Surgery): This analysis aimed to identify factors associated with a shorter time to revision surgery in those who required it. The results were largely consistent with the logistic regression. Higher BMI, higher baseline SNOT-22 and Lund-Mackay CT scores, and higher HbA1c were all significant predictors of a shorter time to revision surgery.

Table 7. Multivariate analyses: predictors of poorer treatment outcomes and time to revision surgery.

Variable	Logistic Regression: Poorer Treatment Outcomes[a]	Cox Regression: Time to Revision Surgery[b]
	OR (95% CI)	p-value
Demographics		
Age (per year increase)	1.02 (0.99-1.05)	0.187
Sex (Male)	0.85 (0.52-1.39)	0.512
BMI (per unit increase)	1.10 (1.02-1.19)	0.015*
Smoking Status (Current)	1.25 (0.71-2.20)	0.441
Clinical Characteristics		
CRS Subtype (CRSwNP)	1.52 (0.95-2.43)	0.081
Baseline SNOT-22 Score (per point)	1.06 (1.03-1.09)	<0.001*
Baseline Lund-Mackay CT Score (per point)	1.18 (1.09-1.28)	<0.001*
Diabetes-Related Factors		
HbA1c (per 1% increase)	1.45 (1.28-1.64)	<0.001*
Duration of T2DM (per year)	1.03 (0.99-1.07)	0.115
Initial Oral Corticosteroid	1.98 (1.21-3.01)	0.008*
Model Fit Statistics		
Logistic Regression	-2 Log Likelihood: 285.4, Nagelkerke R^2: 0.38	
Cox Regression	-2 Log Likelihood: 112.7, Likelihood Ratio Test $p < 0.001$	

[a]Poorer Treatment Outcomes defined as failure to achieve MCID in SNOT-22 score *or* need for revision surgery. [b]Time to Revision Surgery analyzed as a time-to-event outcome. *Statistically significant ($p < 0.05$). OR = Odds Ratio; HR = Hazard Ratio; CI = Confidence Interval; CRSwNP = Chronic Rhinosinusitis with Nasal Polyps; SNOT-22 = Sino-Nasal Outcome Test-22.

4. Discussion

The observed association between uncontrolled T2DM and worse CRS outcomes is likely multifactorial. Hyperglycemia, a hallmark of uncontrolled T2DM, can impair various aspects of the innate and adaptive immune response, leading to increased susceptibility to infections and chronic inflammation. High glucose levels can damage the cilia in the nasal passages, reducing their ability to effectively clear mucus and pathogens, thereby promoting bacterial colonization and inflammation. T2DM has been linked to alterations in the composition and diversity of the nasal microbiome, with a potential increase in pathogenic bacteria and a

decrease in beneficial commensals. This dysbiosis can contribute to chronic inflammation and impaired mucosal defense. Hyperglycemia leads to the non-enzymatic glycation of proteins and lipids, forming advanced glycation end-products (AGEs). AGEs can bind to receptors (RAGE) on immune cells and epithelial cells, triggering inflammatory signaling pathways and contributing to tissue damage. Hyperglycemia can impair neutrophil chemotaxis, phagocytosis, and oxidative burst, reducing their ability to effectively clear pathogens. Hyperglycemia enhances cytokine production such as IL-6, IL-1β, and TNF-α, further contributing to the inflammatory process. Impaired blood flow in the microvasculature of the nasal mucosa can reduce the delivery of immune cells and oxygen to the affected tissues, hindering the healing process and promoting chronic inflammation.[11-15]

Our findings are consistent with previous studies that have reported an association between T2DM and CRS. A meta-analysis by Liu et al. found that patients with T2DM had a significantly higher prevalence of CRS compared to non-diabetic individuals. Several cross-sectional studies have also shown that patients with T2DM and CRS tend to have more severe symptoms and higher CT scores. However, our study is one of the few prospective studies to specifically examine the impact of glycemic control on CRS treatment outcomes over a 12-month period. The significantly higher rate of revision surgery in the uncontrolled T2DM group is a particularly important finding. Revision ESS is often required for patients who fail to respond adequately to initial medical and/or surgical treatment, and it is associated with increased morbidity and healthcare costs. Our results suggest that effective glycemic control may be crucial for optimizing surgical outcomes and reducing the need for revision procedures in patients with T2DM and CRS. The findings of this study have important implications for clinical practice. Clinicians should routinely screen patients with CRS for T2DM and emphasize the importance of achieving and maintaining good glycemic control to improve CRS outcomes. In patients with both CRS and T2DM, a multidisciplinary approach involving collaboration between otolaryngologists and endocrinologists may be beneficial to optimize the management of both conditions.[16-20]

5. Conclusion

This prospective cohort study investigated the impact of uncontrolled type 2 diabetes mellitus (T2DM) on chronic rhinosinusitis (CRS) severity and treatment outcomes in a cohort of patients in Bandung, Indonesia. The study found that uncontrolled T2DM was associated with increased CRS severity and significantly poorer treatment outcomes, including less improvement in patient-reported symptoms, worse endoscopic findings, and a higher rate of revision surgery. These findings suggest that effective glycemic control is crucial for optimizing CRS treatment outcomes in patients with T2DM. Clinicians should routinely screen patients with CRS for T2DM and emphasize the importance of achieving and maintaining good glycemic control to improve CRS outcomes. In patients with both CRS and T2DM, a multidisciplinary approach involving collaboration between otolaryngologists and endocrinologists may be beneficial to optimize the management of both conditions. Further research is needed to investigate the underlying mechanisms by which uncontrolled T2DM exacerbates CRS and to evaluate the effectiveness of interventions aimed at improving glycemic control in this population. This research could lead to the development of more targeted and effective management strategies for CRS in patients with T2DM, ultimately improving patient outcomes and quality of life.

6. References

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