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MONITORING OF CHRONIC SINUSITIS USING NASAL NITRIC OXIDE AS A MARKER OF SINUS HEALTH: A SYSTEMATIC REVIEW

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ABSTRACT

It was reported that, nasal nitric oxide (nNO) is continuously released in the paranasal sinuses which acts as antibacterial and antiviral agent and improves mucociliary clearance in sinuses environment. The levels of nasal nitric oxide (nNO) are significantly changed with inflammatory stimuli as well as with medical or surgical treatment for chronic sinusitis. The present systematic review is aimed at evaluating the role of nNO as biomarker for monitoring chronic sinusitis. A web-based search was conducted in MEDLINE with inclusion criteria of human studies in English language that aimed to evaluate the role of nNO as in monitoring chronic sinusitis. Study designs adoptedwereobservational studies or clinical trials with comparisons between patient with chronic sinusitis in study group and control group of patients with flu or healthy population. The outcome assessed was the level of nNO in both groups. Data were collected for characteristics of included study such as study design, sample size, mean age, type and location of sinusitis, and technique and procedures used to monitor nitric oxide. The search on the monitoring of chronic sinusitis using nasal Nitric oxide (nNO) as marker of sinus health resulted in 97 articles, of them 81 articles were irrelevant and six articles were reviews. The included studies in this review were 10 studies. Overall findings showed that significantly lower levels of Nasal NO were reported in the patients with chronic rhinosinusitis (CRS) (irrespective of nasal polyps or allergic rhinitis concomitance) compared to healthy volunteers. The lower levels of Nasal NO in chronic rhinosinusitis are related to the decreasing of NO metabolites. The nasal nitric oxide could be employed as a good biomarker for monitoring the sinus health. The lower levels of nasal NO are indicators to the incidence ofchronic sinus inflammation in patients with chronic rhinosinusitis (CRS) These lower levels of nasal nitric oxide increase significantly after sinus therapy or surgical treatment.

KEYWORDS: *Sinusitis, Nitric Oxide, Evaluation, Flu, Inflammation*

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INTRODUCTION

Chronic rhinosinusitis (CRS) is clinically described as chronic inflammation of the paranasal sinuses. Many individuals, especially in developed countries,have chronic rhinosinusitis [1]. Chronic rhinosinusitis may be infectious, allergic, seasonal or perennial and may be with or without nasal polyps [2]. Chronic rhinosinusitis can be associated with many health problems such as morbidity of patients and high health care costs [3]. Therefore, accurate diagnostic and rapid treatment for chronic rhinosinusitis must be done. Nitric oxide (NO) is an important signaling molecule produced by NO synthases (NOS) in the respiratory tract with maximum measured levels in the paranasal sinuses [4]. It was reported that, nasal nitric oxide (nNO) is continuously released in the paranasal sinuses which acts as antibacterial and antiviral agent and improve mucociliary clearance in sinuses environment [5]. The levels of nasal nitric oxide (nNO) are significantly changed with inflammatory stimuli [6] as well as with medical or surgical treatment for chronic sinusitis [7,8]. It was reported that, inflammatory stimuli induced NO synthesis (NOS) to produce large amounts of NO in the airway inflammatory diseases [6]. Conversely, Colantonio*et al*. [9] indicated that low concentrations of nNO have been measured in patients with chronic rhinosinusitis with nasal polyposis (CRSNP). Nasal NO levels significantly increased in patients with CRSNP after medical or surgical treatment [7,8] and this change in the level of nitric oxide could be measured easily in the nasal cavity and employed as sensitive and noninvasive markers for diagnosis of chronic sinusitis. The present systematic review is aimed at evaluating the role of nNO as biomarker for monitoring chronic sinusitis Figure 1.

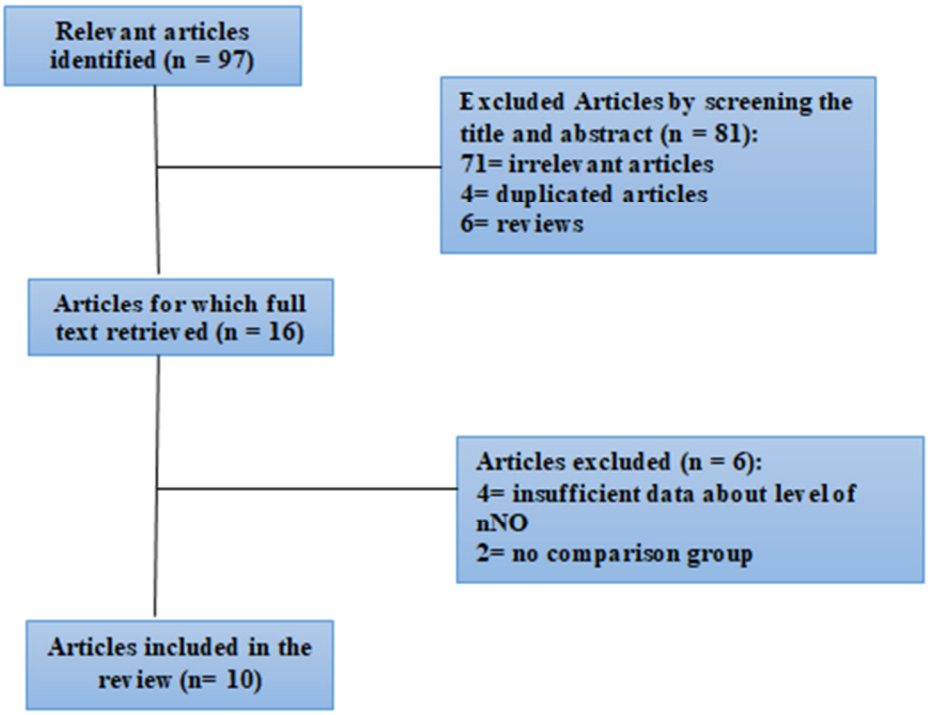

Figure 1
Flow diagram of the included studies in the systematic review

A web-based search was conducted in MEDLINE using search terms (Nitric Oxide) AND (Sinusitis OR Rhinosinusitis OR Sinus) AND (Assessment OR Evaluation OR Monitoring). The inclusion criteria which were applied represented by human studies in English language published before 1st of March 2018 which aimed to evaluate the role of nNO as in monitoring chronic sinusitis. Study designs were prospective observational studies or clinical trials with comparisons between patient with chronic sinusitis in study group and control group of patients with flu or healthy population. The outcome assessed was the level of nNO in both groups. Data were collected for characteristics of included study such as study design, sample size, mean age, type and location of sinusitis, and technique and procedures used to monitor nitric oxide. The extracted data were discussed in a qualitative synthesis of data and presented in Table 1.

Table 1
Summary of the findings of the included studies

Study	Study design	Sample size	Age of patients	Predisposing factor for sinusitis	Type of sinusitis	Technique and procedures used to monitor nitric oxide	Association between nitric oxide and sinus health
10	A prospective study	87	18–80 years old	Polyposis	Chronic rhinosinusitis with nasal polyps	The nNO measured by a hand-held electrochemical device (NIOX MINO; Aerocrine AB, Solna, Sweden) in accordance with the manufacturer's instructions and international guidelines[11,12]	Nasal NO was significantly decreased in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) compared to controls.
13	A prospective study	108	<18 years of age	Polyposis	Chronic rhinosinusitis with and without nasal polyps.	The nNO levels was measured by hand-held device. Using a handheld portable NIOX device	The nNO levels in chronic rhinosinusitis without nasal polyps' patients (CRSsNP) were significantly higher than those of chronic rhinosinusitis with nasal polyps' patients (CRSwNP), and both groups (CRSsNP) and (CRSwNP) exhibited lower levels of nNO compared to control subjects.
14	A prospective study	98	16 years or older	Asthma and polyposis	Chronic rhinosinusitis	The nNO levels were measured using a Sievers NOA280i chemiluminescence	Nasal NO levels were higher in rhinitis patients than

						analyser (GE Analytical Instruments, Boulder, Colorado, USA) at a constant expiratory flow rate of 50 mL/s according to the American Thoracic Society and European Respiratory Society recommendations	other upper airway disease (UAD) categories, irrespective of the asthma concomitance. Nasal NO levels were higher in asthmatics with rhinitis than those without UAD and those with CRS
15	A longitudinal study	78	Adult age	Polyposis	Chronic rhinosinusitis and nasal polyps	Disease severity was evaluated by means of endoscopic and Lund-Mackay radiological scores	The nasal NO (nNO) decreased in chronic rhinosinutis patients than that in control.
16	a clinical cohort study	69	<18 years of age	**Polyposis**	Chronicrhinosinutis with or without nasal **polyps**	Nasal nitric oxide (nNO) measurements were done with an electrochemical analyzer (NIOX MINO; Phadia AB/Aerocrine AB, Uppsala, Sweden) by following The American Thoracic Society/European Respiratory Society recommendations.	The nNO levels in patients with CRS increased and reached a plateau after sinus surgery for both groups CRSsNP and CRSwNP.
17	A prospective study	89	Patients <15 years old	**Polyposis**	Chronic rhinosinusitis with polyps and CRS with polyp and allergic rhinitis	Nasal Rhinosinusitis	NO concentration was measured using chemiluminescent analyzer, Sievers NO analyzer, NOA 280i (GE Analytical Instruments, Boulder, CO) according to American

							Thoracic Society/ European Respiratory Society recommendations
18	A prospective study	39	18 years or older	Common cold	Chronic rhinosinusitis	The nNO measurements were performed using the NIOX MINO_ Airway Inflammation Monitor (Aerocrine, Sweden), a hand-held electrochemicalNO analyzer, which measuresNOby electroluminescence	The measured levels of NO did not differ between healthy volunteers and common cold patients, but they were significantly lower in patients suffering from chronic rhinosinusitis.
19	A prospective study	187 patients	18–65 years	**Polyposis**	Chronic rhinosinusitis with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP) nasal polyps	Measurements of nNO was using a chemiluminescence NO analyzer (NIOX; Aerocrine AB, Solna, Sweden) calibrated with a certified NO calibration gas mixture according to European Respiratory Society/American Thoracic Society recommendations.	Levels of nNO were significantly lower in patients with CRSwNP compared with patients with CRSsNP and controls.
20	RCT	12	Mean age= 49 years old	Polyposis.	Chronic rhinosinusitis with nasal polyposis.	Nasal NO was measured at the same time of the day using a chemiluminescence analyzer (NIOX; Aerocrine AB, Stockholm, Sweden) under standard conditions using 3 techniques	Humming nasal NO increasesd after 2 weeks of oral steroid therapy for CRSNP.
21	A prospective study	39	age >18 years	**Polyposis**	Chronic rhinosinutis with or whithout nasal **polyps**	The nNO levels measured preoperatively and again at 1 month	Significant increase in nNO levels from baseline

						and 6 months postoperatively. nNO measurements were performed with a nasal NO analyzer (Eco Medics CLD 88sp NO Analyzer; Eco Physics Inc., Ann Arbor, MI).	to 1 month and 6 months postoperatively.

nNO= nasal nitric acid, CRSwNP= Chronic rhinosinusitis with nasal polyps, CRSsNP= Chronic rhinosinusitis without nasal polyps

The search on the monitoring of chronic sinusitis using nasal Nitric oxide (nNO) as marker of sinus health resulted in 97 articles, of them 81 articles were irrelevant and six articles were reviews. The included studies in this review were 10 studies [14-20, 22-24]. Overall sample size ranged between 12 to 187 patients. In general, all included studies in this review showed lower levels of Nasal NO measured in patients with chronic rhinosinusitis (CRS) either with nasal polyps (CRSwNP) or without nasal polyps (CRSsNP) or chronic rhinosinusitis (CRS) with polyps and allergic rhinitis when compared to control subjects. The report carried out by Frendø*et a*l.[10]revealed that, nNO levels were significantly decreased in chronic rhinosinusitis patients with nasal polyps (CRSwNP) compared to that measured in controls. The same results were recorded by Torretta*et al.*[15] and Jeong*et al.* [17]. In addition to that the study of Jeong, *et al.* [17] recorded significantly lower amounts of nNO in chronic rhinosinusitis (CRS) with polyps and allergic rhinitis than controls. Dabholkar, *et al.*[18] reported that there was no difference in levels of NO between healthy control and common cold patients, whereas nNO levels was significantly lower in patients with chronic rhinosinusitis. Bommarito, *et al.*[19] and Liu, *et al.* [13] postulated that nNO levels could be used as marker to distinguish between chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP). They found significantly lower levels of nNO in patients with CRSwNP compared to that in patients with CRSsNP and controls. Conversely, nNO concentrations increased significantly in patients with chronic rhinosinusitis (CRS) after endoscopic sinus surgery, this was reported by Fu, *et al.*[16] and Lee, *et al.* [21] studies. Fu, *et al.*[16] showed that nNO levels was higher in CRSsNP group than that in CRSwNP group. Their results revealed that, nNO levels were increased significantly in both groups, and this increasing in nNO levels was related to better quality of life for three months postoperative. At the same time, Lee, *et al.* [21] found a significant increase in nNO levels from baseline to one month and six months postoperatively. Furthermore, Vaidyanathan, *et al.*[20] detected increase in the levels of nNO after two weeks of oral steroid therapy in the CRSNP. They showed that in their results, nNO is more sensitive than exhalation and aspiration and is associated with improvements in some symptoms as size of polyp, and quality of life. In the study of Asano, *et al*[14] higher levels of nNO was measured in asthmatics with rhinitis patients more than those without upper airway infections and those with CRS. Higher concentrations of nNO reflect the presence of allergic rhinitis, irrespective of asthma concomitance.

DISCUSSION

Chronic rhinosinusitis has been regarded as a global health concern; which impacts directly the quality of life of patients and raises the economic and social burden [22,23]. The diagnosis of CRS is usually conducted by nasal endoscopy or by estimating the history of nasal symptoms. As well as sinus computed tomography (CT) is employed to diagnose the CRS [22]. But these clinical tools may not reflect the severity of inflammation in the nasal cavity or in sinuses [24]. Therefore, the recent studies focused on using some clinical biomarkers as alternative tools which could be used to detect the presence and the degree of inflammation in sinuses [25,26]. In this systematic review, the role of nasal nitric oxide as biomarker to monitor chronic rhinosinusitis (CRS) was evaluated. The lack of NO may play a role in the pathogenesis of this disease, so this change in nNO amount can be easily measured and provides a valuable non-invasive marker for chronic rhinosinusitis. Overall, significantly lower levels of Nasal NO were reported in the patients with chronic rhinosinusitis (CRS) (irrespective of nasal polyps or allergic

rhinitis concomitance) compared to healthy volunteers. The lower levels of Nasal NO in chronic rhinosinusitis are related to the decreasing of NO metabolites. Deroee, *et al*.(2009) reported that NO metabolite levels were decreased in nasal lavages of CRS patients. Also, Dabholkar, *et al.*[18] indicated that, the lack of nNO is attributed to the pathogenesis of chronic rhinosinusitis. Furthermore, Bommarito, *et al.*[19]and Liu, *et al.* [13]stated that nNO levels were significantly lower in patients with CRSwNP than that in patients with CRSsNP and controls, these significant differences in the nNO levels have been used to distinguish between chronic rhinosinusitis patient with nasal polyps (NP) and chronic rhinosinusitis patient without nasal polyps (NP). These results agree with that recorded in study of Fu, *et al.* [16] when the nNO levels reduced significantly in the patients with CRSwNP compared to that in patients with CRSsNP. On the other hand, after endoscopic sinus surgery or steroidal therapy a highly and significant increasing in the nNO levels were detected in the CRS patient compared to preoperative or pre-therapy stage, Fu, *et al.* [16]; Lee*, et al*[21] and Vaidyanathan, *et al*[20]. A significant increasing in the nNO levels was detected at the third and six month after surgery in the CRSwNP and CRSsNP groups respectively Fu, *et al.*[16]. Tabaee[27] showed that healing sinonasal tract, mucociliary function occurred three months after surgery of CRSwNP. It was reported that, nNO produced by the inducible nitric oxide synthases (iNOS) in sinus mucosa Fu, *et al.*[16]. Furthermore Lundberg, *et al*.demonstrated that, large amount of NO was continuously produced by inducible NO synthase (iNOS) in the healthy or non-inflamed paranasal sinus epithelium.

CONCLUSIONS

It is concluded that, nasal nitric oxide could be employed as a good biomarker for monitoring the sinus health. The lower levels of nasal NO are indicators to the incidence of chronic sinus inflammation in the chronic rhinosinusitis (CRS) patients. These lower levels of nNO increase significantly after sinus therapy or surgical treatment.

AUTHORS CONTRIBUTION STATEMENT

Khalil Kariri and Khalid Majrashi formulized the topic and wrote the proposal, while Ahmad Abdu Fagehi and Khalid Hakami, searched the literature and extracted the data. Ayman Hakami and NawarHamzi revised the articles and evaluated the eligibility. All authors contributed to the manuscript writing.

CONFLICTS OF INTEREST

Conflict of interest declared none.

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