



NASAL MUCOCILIARY CLEARANCE TIME IN TYPE 2 DIABETES MELLITUS: A CASE CONTROL STUDY

Physiology

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ABSTRACT

Diabetes mellitus (DM) is a common metabolic disorder resulting in chronic rise in blood glucose level leading to derangements in multiple organ systems. The diabetics are highly susceptible to repetitive respiratory infections that can lead to serious morbidity and mortality. The nasal mucociliary clearance (NMC) time was determined in patients of type 2 DM between the age group of 40-55 years of either sex having diabetes for more than 3 years on treatment (n=30) and in normal healthy age and sex matched controls (n=30). The NMC time was assessed by Saccharine method of Anderson et al. The NMC time was significantly prolonged in type 2 diabetes mellitus (16.51±2.44 mins) as compared to control (9.96±2.24 mins).

KEYWORDS

Type 2 diabetes mellitus, Nasal mucociliary clearance time, Saccharine.

Introduction

Diabetes mellitus (DM) is a group of common metabolic disorders resulting in chronic rise in blood glucose level leading to various derangements in multiple organ systems in the body. It is classified on the basis of pathogenic process leading to increased blood glucose level. The two broad categories of diabetes mellitus are type 1, which is the result of total or near total absence of insulin in the body and type 2 diabetes mellitus which results from a variable degree of insulin resistance. Although type 2 DM more typically appears with increasing age and it is now being diagnosed more frequently in younger population particularly in obese children and adults. Further, due to insulin resistance in adipocytes, lipolysis and free fatty acids are increased which cause increased formation of very low density lipoproteins (LDL) and triglycerides by hepatic cells. These dysregulated metabolic effects are associated with various secondary changes in multiple organs in the body.¹ The primary pathophysiological effects in DM is due to its micro-vascular and macro-vascular damaging effects which are associated with dysfunctions of various organs like eye, nerves, heart, blood vessels and failure of certain organs like kidneys, lungs etc.² The pulmonary complications are due to thickening of the alveolar walls, alveolar capillaries, and pulmonary arterioles and thus causing pulmonary dysfunction.³ In postmortem studies, epithelial and capillary basal laminae of alveoli are significantly thicker in diabetes as compared to age matched controls.⁴

There are three different clearance mechanisms which operate in our pulmonary system to remove the inhaled and deposited foreign particles as well as cellular debris to maintain the airways clean and sterile. These clearance mechanisms are mucociliary clearance, coughing reflex and alveolar clearance.⁵ Nasal mucociliary clearance is a primary defence mechanism of respiratory tract which transports the nasal mucus of having a thickness about 10-15 μ m covering the respiratory tract towards the nasopharynx. It does so by beating of cilia at frequency of 7-16 Hz optimally at body temperature of 37°C.^{6,7} Thus, the primary function of nasal mucociliary clearance is to protect from the damaging effects of substances or particles inhaled in the respiratory tract.⁸ Impaired mucociliary clearance has been associated with frequent respiratory infections.⁹ To our knowledge not much studies have been done to assess nasal mucociliary clearance time in type 2 diabetes mellitus patients.

Material and methods

The present study was conducted in the department of physiology in collaboration with department of medicine, Pt BD Sharma PGIMS, Rohtak in thirty patients of confirmed type 2 DM between the age group of 40-55 years (Group I) who were on treatment for 3 years at least and thirty normal healthy age and sex matched subjects as

controls (Group II). A written consent for nasal mucociliary clearance was taken after explaining the method of study. For measuring the nasal mucociliary clearance the saccharin particles, stop watch, pointed forceps and nasal speculum were used. A complete and thorough ear, nose and throat examination was performed and patients of deviated nasal septum, nasal polyp, allergic rhinitis and sinusitis, patients with history of any medications particularly antihistaminic and antihypertensive (beta blockers), respiratory and nasal symptoms within preceding 2 weeks and those with tobacco or gutka addictions were excluded from the study. The nasal mucociliary clearance was assessed by Saccharine method of Anderson et al.¹⁰ Using a Thudichum's nasal speculum and a forcep a particle of one millimetre (mm) diameter of saccharine was placed over the floor of the nose just behind the anterior end of the inferior turbinate of sitting subject with head tilted 10 degree to avoid falling of saccharine particles in nasopharynx and the time was noted. The subjects were instructed to swallow once every 30 seconds and when he/she could taste the sweetness of the saccharine that time was noted by the examiner. The test was carried out in both nostrils separately to minimise the effect of nasal cycle on nasal mucociliary clearance and the average of the two was taken as nasal mucociliary clearance time in minutes. All subjects were tested in similar environmental conditions and were instructed not to inhale and exhale forcefully, sniff, eat or drink and avoid coughing and sneezing during this time. If coughing or sneezing occurred then the test was repeated. A single examiner performed the test in all patients and controls to avoid inter observer variability. The nature of the particle was not informed to the subjects and controls to ensure the reliability of this method.

The observations were statistically analyzed and calculated using student's 't' test (unpaired t-test) in SPSS version 20. The results were expressed as mean±standard deviation (mean±SD). A p-value of less than or equal to 0.05 was taken as statistically significant.

OBSERVATION AND RESULTS

It was observed that the mean nasal mucociliary clearance time in males and females in controls was 9.96±2.33 minutes (range-7.63 to 12.29 minutes) & 9.94±2.16 minutes (range-7.78 to 12.10 minutes), respectively and the difference between the mean values of NMC time was found statistically insignificant (Table 1, Fig 1).

Table 1: Mean nasal mucociliary clearance time in male and female controls between age group 40-55 years.

Parameter	Male (Mean±SD)	Female (Mean±SD)	P value
Nasal Mucociliary Clearance Time (minutes)	9.96±2.33	9.94±2.16	0.97

p value ≤ 0.05 is taken as significant

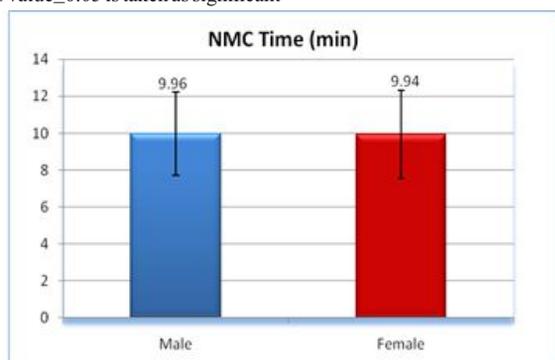


Fig 1: Mean nasal mucociliary clearance time in male and female controls between age group 40-55 years.

Further, it was observed that the mean nasal mucociliary clearance time in males and females in type 2 diabetes mellitus subjects was 16.56 ± 2.14 minutes (range-14.42 to 18.70 minutes) & 16.47 ± 2.78 minutes (range-13.69 to 19.25 minutes), respectively (Table 2, Fig 2). The difference between the mean values in males and females was found statistically insignificant.

Table 2: Mean nasal mucociliary clearance time in male and female patients of type 2 diabetes mellitus between age group 40-55 years.

Parameter	Male (Mean±SD)	Female (Mean±SD)	P value
Nasal Mucociliary Clearance Time (minutes)	16.56±2.14	16.47±2.78	0.91

p value ≤ 0.05 is taken as significant

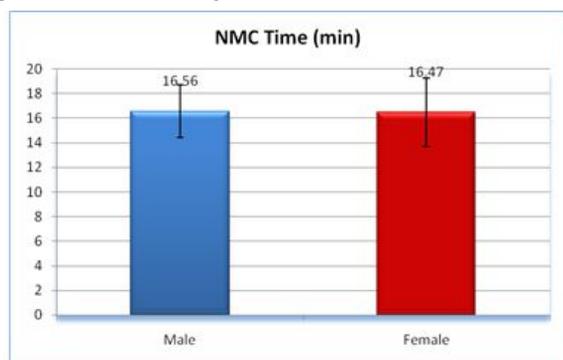


Fig 2: Mean nasal mucociliary clearance time in male and female patients of type 2 diabetes mellitus between age group 40-55 years.

It was observed that the mean nasal mucociliary time was increased in males and females in type 2 DM subjects as compared to males and females in controls (Table 3, Fig 3). The difference between the mean values of NMC time of male and female in controls and type 2 DM subjects was statistically insignificant.

Table 3: Mean Nasal Mucociliary clearance time in male and female in controls and patients of type 2 diabetes mellitus between age group 40-55 years.

Parameter	Case (Group I)		P value	Control (Group II)		P value
	Male	Female		Male	Female	
Nasal Mucociliary Clearance Time (minutes)	16.56 ± 2.14	16.47 ± 2.78	0.91	9.96 ± 2.33	9.94 ± 2.16	0.97

p value ≤ 0.05 is taken as significant

*p value ≤ 0.001 = highly significant

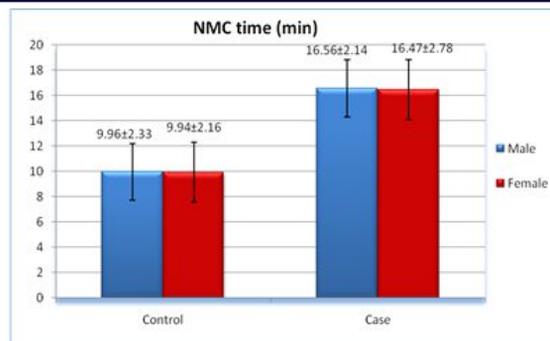


Fig 3: Mean nasal mucociliary clearance time in male and female in controls and type 2 DM patients between age group 40-55 years.

It was also observed that the mean nasal mucociliary clearance time in type 2 DM subjects was 16.51 ± 2.44 minutes (range-14.07 to 18.95 minutes) while in matched controls it was 9.96 ± 2.24 minutes (range-7.72 to 12.20 minutes) (Table 4, Fig 4). The study conducted showed that the mean nasal mucociliary clearance time was significantly prolonged (p value ≤ 0.001) in type 2 diabetes mellitus patients as compared to age and sex matched controls.

Table 4: Mean nasal mucociliary clearance time in patients of type 2 diabetes mellitus between age group 40-55 years and age and sex matched controls.

Parameter	Case (Group I) (Mean±SD)	Control (Group II) (Mean±SD)	p value
Nasal Mucociliary Clearance Time (minutes)	16.51±2.44	9.96±2.24	≤0.001*

p value ≤ 0.05 is taken as significant

*p value ≤ 0.001 = highly significant

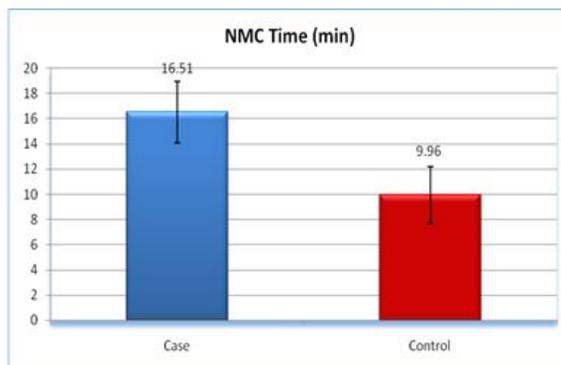


Fig 4: Mean nasal mucociliary clearance time in patients of type 2 diabetes mellitus between age group 40-55 years and age and sex matched controls.

Discussion

In a study conducted by Sachdeva et al, the nasal mucociliary clearance was determined in 50 diabetes mellitus patients of either sex aged between 16-85 years (both type 1 and type 2 DM) and was matched with 50 healthy non smokers and non alcoholic controls. The NMC time was ascertained by the procedure recommended by Anderson et al. It was seen that the mean NMC time was 7.49 ± 1.06 minutes (range 5.6-9.5) in controls and in diabetes mellitus patients of both type 1 and 2, the mean NMC time was 18.02 ± 5.08 minutes (range 9-30). Further, when the NMC time was categorically analysed in these patients it was seen that type 2 diabetes mellitus patients had mean value of 15.16 ± 3.67 minutes (range 9-20.7).¹¹ Likewise, consistent with this study it was seen in our study that the nasal mucociliary clearance time in healthy controls was 9.96 ± 2.24 minutes (range 7.72- 12.20). Furthermore, in type 2 DM subjects the mean NMC time was 16.51 ± 2.44 minutes (range 14.07-18.95). Thus, the nasal mucociliary clearance time was significantly prolonged (p value ≤ 0.001) in type 2

diabetes mellitus patients as compared to age and sex matched controls (Table 4, Fig 4).

In a study conducted by de Oliveria-Maul et al, of 252 subjects, 37 subjects between the age group 14-90 years had diabetes only and 84 subjects between the age group 25-82 years had both diabetes mellitus and hypertension. The healthy controls selected for the comparison were 79 in number and were in age group of 18-94 years. The nasal mucociliary clearance was determined in all subjects using the saccharine transit time. The saccharine transit time was measured in minutes with time ≤ 12 minutes as normal. It was found that aging, diabetes mellitus and hypertension were independently associated with decreased nasal mucociliary clearance. It was also found that gender does not affect saccharine transit time (STT) and there is 2% prolongation of STT for every 1 year increase in age. However, diabetes mellitus is associated with 2.6 times higher risk of increased STT. Furthermore, it was found that aging is associated with increased STT but more so when it is present with diabetes mellitus.¹² Similar findings were also observed in our study that gender does not affect saccharine transit time. It was demonstrated that the mean NMC clearance time was more or less same in both male and female controls as it was 9.96 ± 2.33 minutes (range-7.63-12.29) and 9.94 ± 2.16 minutes (range 7.78-12.10), respectively (Table 1, Fig 1). Further in type 2 DM patients the mean NMC time were 16.56 ± 2.14 minutes (range 14.42-18.70) in males and 16.47 ± 2.78 minutes (range-13.69-19.25) in females (Table 2, Fig 2).

Similarly in another study conducted by Selimoglu et al, in 32 non smoking diabetes mellitus patients, 15 males and 17 females aged between 7- 65 years (mean 35 years) when compared with 10 nondiabetic controls aged between 12-57 years (mean 33 years). The NMC time was determined using saccharine transit time. It was found that non diabetic controls had significantly faster mean nasal mucociliary clearance (7.19 mm/min) compared to the diabetics (5.17 mm/min). It was consistent with our studies that diabetics have more NMC time compared to their healthy controls; however, the limitation of this study was its small number of control subjects.¹³ In a study conducted by Yue, it was reported that diabetes mellitus patients without history of nasal disease had nasal problems including mucociliary function complicated by diabetes mellitus. In these diabetic subjects, mean value of nasal mucociliary clearance was considerably decreased and was more often associated with dry noses but with increased pH values both of which were higher than those seen in non diabetic individuals ($p \leq 0.05$).¹⁴

In a study conducted by Yadav et al, the nasal mucociliary clearance was assessed in 240 normal subjects using the saccharine transit time. Out of 240 healthy subjects, 120 were males and 120 were females. These normal subjects were divided in six groups each comprising of one decade starting from 11 to 20 years. The mean nasal mucociliary clearance time demonstrated was from 7.34-14.48 minutes in males and 7.36-15.³⁸ minutes in females in different age groups. Furthermore it was also seen that the mean NMC time in males in age group from 41-50 years and 51-60 years were 8.42 minutes and 11.58 minutes, respectively. Similarly, the mean NMC time in females in age group 41-50 years and 51-60 years were 9.54 minutes and 11.48 minutes, respectively. Thus it was evident from this study that the NMC time showed an insignificant difference between two genders.¹⁵ In consistent with this study in our research also the mean NMC in healthy males between 40-55 years was 9.96 minutes and in females it was 9.94 minutes (Table 1, Fig 1).

The nasal and tracheal mucosal lining share a common mucociliary structure and manifest similar response to noxious stimuli. The nose has been identified as a useful structure to assess inflammatory events and other pathophysiological mechanisms in lower respiratory tracts.¹⁶⁻¹⁷ Further, alteration in nasal and bronchial mucociliary clearance are correlated.¹⁸ Nasal mucociliary clearance is considered as mirror image of bronchial mucociliary clearance and thus a biomarker of nasal mucosal function.¹⁹ It is reported that the normal value of nasal mucociliary clearance in healthy subjects as 5.9 minutes in Haryana. However, it was studied in younger children that have better nasal mucociliary clearance mechanisms.²⁰ Similarly, the mean

value of NMC time at Chandigarh, Calcutta and Nagpur are reported to be 5.06, 4.4 and 7.1 minutes respectively in healthy subjects.²¹⁻²³ Further, the wide variation of NMC time is demonstrated from western countries ranging from 3.3-35 minutes in adults.²⁴⁻²⁵ Furthermore, it has been seen that there can be considerable variation in value at different places even in India depending on habit, climate, habitat and difference in facial configuration.²⁶

Diabetic neuropathy may be responsible for the slower rate of nasal mucociliary clearance in diabetes patients. Furthermore, the constituents of mucus and its differential control suggest that mucus transport may be modified by changes in constituents of mucus or by the amount of mucus secreted. Thus, delayed nasal mucociliary clearance time in diabetes mellitus patients may be due to decrease in ATPase activity. Regulation of water content by controlling pH and its ionic composition may also alter the activity of the mucociliary escalator. Respiratory airway mucus is a complex mixture of glycoproteins, proteoglycans, lipids, lesser amount of proteins and sometimes deoxyribonucleic acid (DNA). About 80% of molecular weight of glycoproteins is made up of oligosaccharides which surround the polypeptide core and protect it from protein degradation. The nasal mucociliary barrier is the first hurdle in the tracheo-bronchial system and the potentially noxious particles must invade it in order to establish itself in nasal mucosa.⁸ The concentration of bactericidal nasal nitric oxide (NO) is low in insulin dependent diabetes mellitus.²⁷ Likewise diabetics have a prolonged resistance measured by rhinomanometry (RMM). This increase is more evident before than after decongestion which indicates a chronic state of increased congestion. Chronic congestion is also influenced by mucociliary clearance which is reduced in diabetics due to alkalinised pH values of nasal secretions. Insulin dependent diabetes mellitus and as such diabetes lasting for more than ten years of duration result in further more deterioration of mucociliary clearance.^{11,13,28}

Conclusion

Even though type 2 diabetes mellitus patients did not have any respiratory symptoms, the above findings of our study do reveal underlying subclinical pathological changes of respiratory tract defense mechanisms. As the disease progression of diabetes increases it may lead to full blown and frequent respiratory tract infections. Thus it could be concluded that prolonged nasal mucociliary clearance time may be one of the earliest and easily measurable non metabolic derangements in diabetes mellitus and type 2 DM subjects may undergo periodic nasal mucociliary clearance function screening along with other pulmonary function assessments. However, additional research needs to be done encompassing other parameters like effect of duration and level of hyperglycemia, effect of ageing on NMC clearance time etc.

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