

Reduced Lung Function and Progression to Prediabetes: A Prospective Study

Ovais Karnain Wadoo^{1*}, Ishtiaq Ahmad¹, Sheikh Imran Sayeed²

1. Senior Resident, Department of Physiology, Government Medical College, Srinagar, India.
2. Professor and Head, Department of Physiology, Government Medical college, Srinagar, India.

*Correspondence:

Ovais Karnain Wadoo, Senior Resident, Department of Physiology, Government Medical College, Srinagar, India.

Tel: (91) 700 634 5867

Email: drovaiskarnain@gmail.com

ORCID ID: (0000-0002-8167-9515)

Received: 15 August 2021

Accepted: 08 October 2021

Published in November 2021

Abstract

Objective: Prediabetes is a state that people have blood glucose levels higher than normal but still not in diabetes range. There is a close relationship between impaired lung function and diabetes mellitus (DM). Reduced lung function can be present before the clinical evidence of diabetes or insulin resistance.

Materials and Methods: The total number of subjects in this longitudinal study was 503 and compared with apparently healthy Kashmiri adults. All the subjects, at the time of their first visit, underwent Fasting Plasma Glucose (FPG) estimation, 2- hour oral glucose tolerance test (OGTT) and spirometry (FVC, FEV1 & FEV1/FVC). Those subjects who had normal glucose tolerance (NGT) were retested for glycemic status and spirometric values after a follow-up period of 2-18 (mean=10) months.

Results: Out of total 503 subjects on follow up 483 (96%) had NGT and 20 (4%) had prediabetes. Percent predicted forced vital capacity (FVC) and % predicted forced expiratory volume in 1st second (FEV1) were significantly lower (P -value< 0.001) while as % predicted FEV1/FVC was significantly higher (P -value< 0.001) in prediabetes as compared to NGT group.

Conclusion: Results of our study point out a predominantly restrictive pattern of lung dysfunction in the prediabetes group as compared to the NGT group.

Keywords: Lung function test, oral glucose tolerance test, Forced vital capacity, Spirometry

Introduction

Prediabetes is a state that people have blood glucose levels higher than normal but still not in diabetes range (1). It is a stage of intermediate hyperglycaemia between normal glucose tolerance (NGT) and type 2 diabetes mellitus (T2DM) (2). WHO divides prediabetes into impaired glucose tolerance

(IGT) and impaired fasting glucose (IFG) (3). Both IFG and IGT are the established risk factors for diabetes mellitus (DM) (4). Impaired IFG refers to a condition in which the fasting blood glucose is elevated above what is considered a normal level but still is not high enough to be classified as DM. It is

considered a prediabetes state, associated with insulin resistance and increased risk of cardiovascular pathology, although of lesser risk than IGT (5). IGT is a prediabetes state of dysglycemia that is associated with insulin resistance and increased risk of cardiovascular pathology. According to various researches on the natural history and pathogenesis of diabetes it has been learned that diabetes has a prolonged prediabetic phase (6). Prediabetes is asymptomatic and can often go undiagnosed for many years (7).

Microvascular and macrovascular damage and changes starts occurring during pre-diabetes and is linked with an increased risk of cardiovascular disease early in the passage to T2DM (8). Increased glucose levels damage endothelial cells and can lead to microvascular disease (9).

Pulmonary function tests are important investigations in the management of patients with suspected or earlier diagnosed respiratory disease. Spirometry is the recommended objective test performed to identify abnormalities in lung volumes and air flow (10). Spirometry is the most common of the pulmonary function tests (PFT's), measuring lung function especially the amount (volume) and/or speed (flow) of air that can be inhaled or exhaled.

Evidence from various researches suggested that there is a close relationship between impaired lung function and DM (11). Reduced lung function may be present before the clinical diagnosis of diabetes (12) or insulin resistance (13,14), suggesting that the lung may be involved in the pathogenesis of diabetes. The present study was undertaken to find the effect of progression to prediabetes on lung function in previously normal glucose tolerance test (NGTT) individuals.

Materials and Methods

This longitudinal study was done in the Postgraduate Department of Physiology Government Medical College Srinagar. The study group comprised healthy Kashmiri adults. The group consisted of both males and

females. The total number of subjects in the longitudinal study was 503. Subjects were selected only after their proper consent to participate as subjects in the study.

Inclusion criteria were healthy males and females of age 18 years and above. Exclusion criteria were age below 18 years, smokers. Previously diagnosed patients of type I and type II DM, pregnant females, those with diseases that can interfere with spirometry and blood sugar level results, those on drugs that affect blood glucose levels and pulmonary function.

The health status of the subjects was determined by history taking and thorough clinical examination. All the subjects, at the time of their first visit, underwent fasting plasma glucose (FPG) estimation, 2-hour oral glucose tolerance test (OGTT), and spirometry. Those subjects who had NGT were retested for glycemic status and spirometric values after a follow-up period of 2-18 (mean=10) months. Based on FPG and 2-hr. OGTT, subjects were classified into five categories according to blood sugar levels viz: NGT: FPG < 100 mg/dL and 2-h OGTT <140 mg/dL

Isolated IFG: FPG 100–125 mg/dl and 2-h OGTT < 140 mg/dl

Isolated IGT: FPG < 100 mg/dl and 2-h OGTT 140–199 mg/dl

Combined IFG/IGT: FPG 100–125 mg/dl and 2-hOGTT 140–199 mg/dl

Diabetes: FPG \geq 126 mg/dl or 2-hOGTT \geq 200 mg/dl

Isolated IFG, isolated IGT, and combined IFG & IGT were considered as subgroups of prediabetes.

Spirometry testing was done to determine forced vital capacity (FVC), forced expiratory volume in 1st second (FEV1), ratio of FEV1 and FVC (FEV1/FVC) and their percent predicted values i.e., % predicted FVC, % predicted FEV1, and % predicted FEV1/FVC. Pulmonary function was measured using RMS Helios 701 spirometer.

Statistical Analysis

Statistical analysis of the data was carried out by using Statistical Package for Social Sciences (SPSS Version 18.0 Japan Inc, Tokyo Japan). Data variables were expressed as Mean (\pm SD). *P*-value less than 0.05 (*P*-value < 0.05) was taken as statistically significant.

Ethical considerations

Ethical approval for this study was obtained from Institutional Ethical Committee Government Medical College Srinagar (GMC/IEC/2012).

Results

The total number of subjects in our study was 503. Out of total 503 subjects, 167 (33%) were males and 336 (67%) were females. Out of total 503 subjects on follow up 483 (96%) had

NGT and 20 (4%) had prediabetes.

Gender & Subgroup distribution of prediabetes into isolated IFG, isolated IGT, and combined IFG & IGT is shown in Table 1 and Table 2.

The Mean \pm SD FVC (% predicted) of prediabetes group was lower than that of NGT group and the difference was statistically significant as shown in Table 3.

The Mean \pm SD FEV1 /FVC (% predicted) of prediabetes group was higher than that of NGT group and the difference was statistically significant (*P*-value < 0.001) as shown in Table 5.

Discussion

Prediabetes is a global health problem. The prevalence of prediabetes is higher than diabetes prevalence. The person who develops prediabetes is going to become diabetic if he/she goes untreated in an appropriate

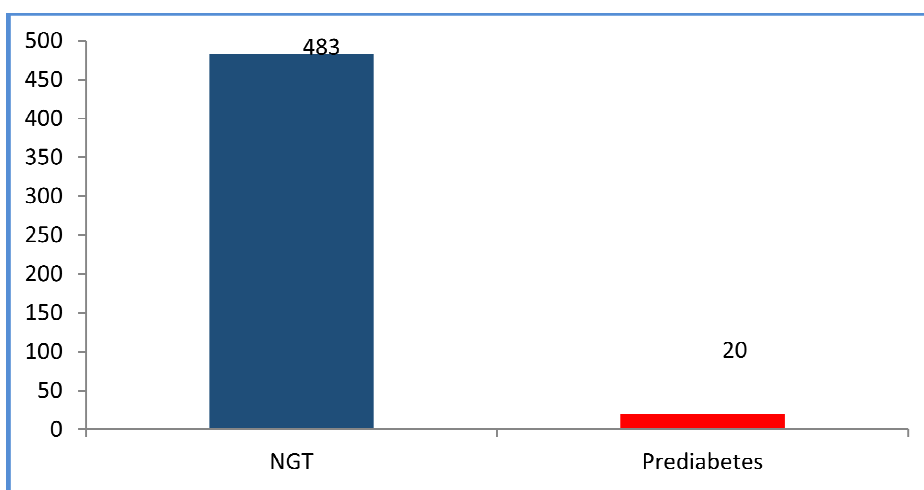


Figure 1. Group distribution of study subjects into NGT and prediabetes according to number

Table 1. Group distribution of study subjects according to Gender

Subject group	Male	Female
NGT	161	322
Prediabetes	6	14
Total	167	336

Table 2. Subgroup distributions of prediabetes according to number and percentage

Prediabetes group	Number of subjects	Percentage
Isolated IFG	8	40
Isolated IGT	7	35
IFG & IGT	5	25
Total	20	100

IFG= impaired fasting glucose; IGT= impaired glucose tolerance

manner (15). The lack of prediabetes guidelines/consensus and the screening on diabetes create the condition that makes prediabetes go unknown and unwatched (16). The chance of developing cardiovascular disease and diabetes is equal in individuals having IGT and IFG (17).

The natural history of diabetes includes an asymptomatic preclinical phase. Using IFG as a screening tool for screening population, detection of DM could be made 5-6 years earlier before the clinical diagnosis (18). Some studies (19,20) strongly recommended that IFG should be aggressively treated as a disease because it is an autonomous risk factor for T2DM and CVD. Gregory A. Nichols, et al, in 2007 observed the relation of diabetes with IFG and found that numerous newly identified IFG patients progressed to diabetes in less than three years (21).

The process by which impaired glycemic control may lead to a reduction in lung function is unresolved, However it has been advocated that the increased systemic inflammation associated with diabetes (22) may result in pulmonary inflammation (23) and consequently airway damage (24). On the other hand, a reduction in antioxidant defences resulting from increased oxidative activity linked with diabetes (25) can lead to a secondary reduction in the antioxidant defences of the lung and therefore can cause increased predisposition to environmental oxidative insults, resulting in ensuing loss of

lung function. In addition to an increase in intracellular oxidative stress, increased nuclear factor- κ B, and inflammatory mediator expression, long-term hyperglycemia can cause an increase in collagen molecule synthesis and cross-linking via the collection of advanced glycosylation end products, which may also negatively influence lung function (26).

The pathophysiology of pulmonary symptoms in DM is complex and multifactorial. The fundamental mechanisms for lung dysfunction in patients with DM include hyperglycemia, hyperinsulinemia, autonomic neuropathy, oxidative stress, micro/macro-angiopathy of alveolar capillaries and pulmonary arterioles, glycosylation of tissue proteins, collagen and elastin changes, alteration of connective tissue, surfactant dysfunction and malfunction of respiratory muscles. The histopathological changes in the lungs of diabetics are linked with the thickening of the alveolar epithelium and the pulmonary capillary basal lamina and also decreased recoiling of the lung (27). This is due to biochemical alteration of connective tissue constituents, especially collagen and elastin. There is increased cross-linkage formation between polypeptides of collagen which results in thickening, leading to restriction of lung volume and alveolar gas transport, reduced membrane diffusion capacity and pulmonary capillary blood volume (28,29).

In our study, 503 (167 males and 336 females)

Table 3. Comparison of FVC (% predicted) between study groups

Subject group	Number	Mean \pm SD	P-value
NGT	483	111.20 (\pm 11.30)	< 0.001
Prediabetes	20	86.25 (\pm 5.84)	

NGT = normal glucose tolerance

Table 4. Comparison of FEV₁ (% predicted) between study groups

Subject group	Number	Mean \pm SD	P-value
NGT	483	123.70 (\pm 13.50)	< 0.001
Prediabetes	20	104.85 (\pm 7.72)	

NGT = normal glucose tolerance

Table 5. Comparison of FEV₁/FVC (% Predicted) between study groups

Subject group	Number	Mean \pm SD	P-value
NGT	483	110.95 (\pm 8.67)	< 0.001
Prediabetes	20	121.05 (\pm 5.48)	

NGT = normal glucose tolerance

who had NGT on first visit were followed for 2-18 (mean=10) months. 483 (96%) had NGT, 20 (4%) had prediabetes and none had diabetes. The reason for poor outcome in terms of percentage for prediabetes and diabetes at follow-up was probably the less follow-up period.

Percent predicted FVC and % predicted FEV1 were significantly lower (P -value < 0.001) while as % predicted FEV1/FVC was significantly higher (P -value < 0.001) in prediabetics as compared to NGT group. These results of prospective study also point towards a predominantly restrictive pattern (low lung volume) of lung dysfunction in prediabetic group as compared to NGT group. Takashi et al (30) studied the relationship between prediabetes, DM, and lung function. In their prospective study, the results showed decreased lung volume (% FVC), but not airflow limitation (FEV1/FVC ratio). The decreases %FVC was significantly associated with the ensuing development of prediabetes with which our study results are in agreement. Yulan et al (31) studied 1237 asymptomatic

healthy people living in Saitama, Japan for a relationship between lung function and diabetes and prediabetes. Results of the study showed prediabetes was significantly related with low FVC, compared with NGT. The results of our study are consistent with the results of this study.

Conclusions

From our study, we conclude that restrictive lung disease (low lung volume) is significantly associated with prediabetes. This study contributes evidence for a prospective relationship between lung volume and the incidence of newly diagnosed prediabetes among subjects with normal glucose metabolism at baseline.

Acknowledgments

None

Conflict of Interest

None

References

- Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services.2020.
- American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes care*. 2014;37(Supplement 1):S81-90.
- World Health Organization. Global report on diabetes. Geneva: World Health Organization; 2016.
- Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England journal of medicine*. 2002;346(6):393-403.
- Nichols GA, Hillier TA, Brown JB. Progression from newly acquired impaired fasting glucose to type 2 diabetes. *Diabetes care*. 2007;30(2):228-33.
- Ramlo-Halsted BA, Edelman SV. The natural history of type 2 diabetes: implications for clinical practice. *Primary Care: Clinics in Office Practice*. 1999;26(4):771-90.
- American Diabetes Association. Screening for type 2 diabetes. *Diabetes*. 2004;27 Suppl 1: S11-4. <https://doi.org/10.2337/diacare.27.2007.S11>.
- Hsueh WA, Orloski L, Wyne K. Prediabetes: the importance of early identification and intervention. *Postgraduate medicine*. 2010;122(4):129-43.
- Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. *Journal of the American College of Cardiology*. 2012;59(7):635-43.
- National Institute for Health and Clinical Excellence. Management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). 2010.
- Goldman MD. Lung dysfunction in diabetes. *Diabetes care*. 2003;26(6):1915-8.
- Engstrom G, Janzon L. Risk of developing diabetes is inversely related to lung function: a population-based cohort study. *Diabetic medicine*. 2002;19(2):167-70.
- Lazarus R, Sparrow D, Weiss ST. Baseline ventilatory function predicts the development of higher levels of fasting insulin and fasting insulin resistance index: the Normative Aging Study. *European Respiratory Journal*. 1998;12(3):641-5.
- Engström G, Hedblad B, Nilsson P, Wollmer P, Berglund G, Janzon L. Lung function, insulin resistance and incidence of cardiovascular disease:

- a longitudinal cohort study. *Journal of internal medicine*. 2003;253(5):574-81.
15. Garber AJ, Handelsman Y, Einhorn D, Bergman DA, Bloomgarden ZT, Fonseca V, et al. Diagnosis and management of prediabetes in the continuum of hyperglycemia—when do the risks of diabetes begin? A consensus statement from the American College of Endocrinology and the American Association of Clinical Endocrinologists. *Endocrine practice*. 2008;14(7):933-46.
 16. Kenealy T, Elley CR, Arrol B. Screening for diabetes and prediabetes Commentary. *Lancet* 2007; 370(8): 1888-9. https://www.natap.org/2007/HIV/121407_01.htm.
 17. Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes care*. 2007;30(3):753-9.
 18. Harris R, Donahue K, Rathore SS, Frame P, Woolf SH, Lohr KN. Screening adults for type 2 diabetes: a review of the evidence for the US Preventive Services Task Force. *Annals of internal medicine*. 2003;138(3):215-29.
 19. Chang CJ, Wu CH, Yao WJ, Yang YC, Wu JS, Lu FH. Relationships of age, menopause and central obesity on cardiovascular disease risk factors in Chinese women. *International journal of obesity*. 2000;24(12):1699-704.
 20. Wen CP, Cheng TY, Tsai SP, Hsu HL, Wang SL. Increased mortality risks of pre-diabetes (impaired fasting glucose) in Taiwan. *Diabetes Care*. 2005;28(11):2756-61.
 21. Nichols GA, Hillier TA, Brown JB. Progression from newly acquired impaired fasting glucose to type 2 diabetes. *Diabetes care*. 2007;30(2):228-33.
 22. Arnalich F, Hernanz A, Lopez-Maderuelo D, Pena JM, Camacho J, Madero R, et al. Enhanced acute-phase response and oxidative stress in older adults with type II diabetes. *Hormone and Metabolic Research*. 2000;32(10):407-12.
 23. Walter RE, Beiser A, Givelber RJ, O'Connor GT, Gottlieb DJ. Association between glycemic state and lung function: the Framingham Heart Study. *American journal of respiratory and critical care medicine*. 2003;167(6):911-6.
 24. Cirillo DJ, Agrawal Y, Cassano PA. Lipids and pulmonary function in the third national health and nutrition examination survey. *American journal of epidemiology*. 2002;155(9):842-8.
 25. Gazis A, Page S, Cockcroft J. Vitamin E and cardiovascular protection in diabetes. *British Medical Journal*. 1997;314(7098):1845-6.
 26. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature*. 2001;414(6865):813-20.
 27. Kuziemski K, Specjalski K, Jassem E. Diabetic pulmonary microangiopathy—fact or fiction?. *Endokrynologia Polska*. 2011;62(2):171-6.
 28. Klein OL, Krishnan JA, Glick S, Smith LJ. Systematic review of the association between lung function and Type 2 diabetes mellitus. *Diabetic medicine*. 2010;27(9):977-87.
 29. Nandhini R, Safina SS, Saikumar P. Respiratory myopathy in type II diabetes mellitus. *Journal of Clinical and Diagnostic Research*. 2012;6(3):354-57.
 30. Yamane T, Yokoyama A, Kitahara Y, Miyamoto S, Haruta Y, Hattori N, et al. Cross-sectional and prospective study of the association between lung function and prediabetes. *BMJ open*. 2013;3(2):e002179.
 31. Li Y, Saito M, Tobimatsu S, Oshida H, Hori Y, Fuchigami H, et al. Prediabetes and impaired lung function in asymptomatic adults. *Diabetes research and clinical practice*. 2013;100(2):e51-4.