# Reduced Lung Function and Progression to Prediabetes: A Prospective Study

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## 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





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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 prediabeticphase (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 ≥ 126 mg/dl or 2-hOGTT ≥ 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.



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## 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 (±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 ± 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 ± 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

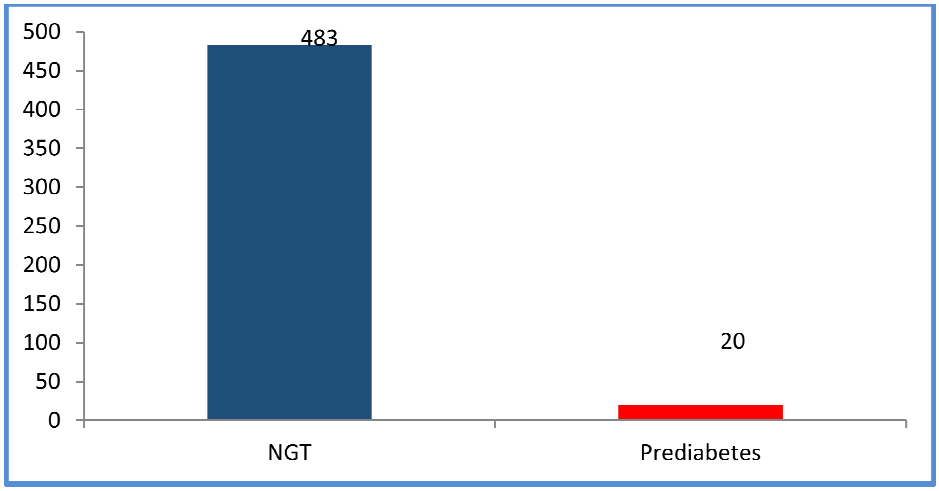


**Figure 1. Group distribution of study subjects into NGT and prediabetes according to number**

**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





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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- ƙB, 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 ± SD | *P*-value |
|---|---|---|---|
| **NGT** | 483 | 111.20 ( ± 11.30) | < 0.001 |
| **Prediabetes** | 20 | 86.25 (± 5.84) | |

NGT = normal glucose tolerance

**Table 4. Comparison of $FEV_1$ (% predicted) between study groups**

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

NGT = normal glucose tolerance

**Table 5. Comparison of $FEV_1$ /FVC (% Predicted) between study groups**

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

NGT = normal glucose tolerance





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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

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