Scholars Academic Journal of Biosciences (SAJB) **ISSN 2321-6883 (Online)**
Sch. Acad. J. Biosci., 2014; 2(8): 556-560 **ISSN 2347-9515 (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublishers.com **DOI:** 10.36347/sajb.2014.v02i08.017

Research Article

Glycosylated Hemoglobin Level and its Correlation with Pulmonary Function Test in Type II Diabetics

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Abstract: The risk of development and progression of chronic complications of diabetes is closely related to the degree of glycemic control as measured by glycosylated hemoglobin level. Glycosylation of tissue proteins occur when blood glucose level remain elevated for a prolonged duration. Due to this, there occur irreversible changes in the chemical structure of tissue proteins. Connective tissues in skin, muscles, respiratory system, vascular bed, kidney, peripheral nervous system, etc. are the major targets for glycosylation. Diabetic patients show reduced pulmonary function tests. Present study was undertaken to find out the correlation between glycosylated hemoglobin and pulmonary function test in type II diabetics. 42 Type II diabetics and 40 normal subjects were selected for the study. Anthropometric parameters, blood investigations and P.F.T. was performed on all subjects. Fasting and Post Meal blood glucose levels as well as HbA_1c % were significantly higher in Type II diabetics as compared to controls. All P.F.T. parameters excepting FEV_1 % were significantly reduced in Type II diabetics. A significant correlation was found between HbA_1c % and various P.F.T parameters like FVC, FEV_1, $FEF_{25-75\%}$, $FEF_{0.2-1.2L}$, PEFR and MVV. Also a negative correlation was found between HbA_1c % and all P.F.T parameters except $FEF_{25-75\%}$, and MVV. Decreased values of P.F.T parameters in Type II diabetics can be attributed to increased glycosylation of connective tissues and other proteins that leads to decrease in elasticity, flexibility, recoil, etc. of connective tissues producing stiff tissue and ultimately leading to a stiff lung i.e. restrictive lung pathology.
Keywords: Diabetes Mellitus, Glycosylation, Pulmonary Function Test

INTRODUCTION

Diabetes Mellitus is a heterogeneous metabolic disorder characterized by common features of chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism. Many organ systems are the targets in diabetes like cardiovascular system, eyes, kidney and nervous system. The possibility that the lung is also a target organ for diabetic complications was first suggested by Schuyler et al in 1976[1]. Since that time there have been many studies of pulmonary function in diabetic patients with conflicting results. Many have suggested plausible patho-physiological mechanisms also. Major consequences of hyperglycemia are excessive non enzymatic glycosylation of various body proteins including hemoglobin, albumin, collagen and elastin.

Glycosylated Hb (HbA_1c) is the result of simple chemical reaction between Hb and sugars after synthesis of Hb is complete. Koenig et al in 1976 and Bunn 1981 observed that HbA_1c conc. was proportional to fasting blood glucose conc. and glucose tolerance. Furthermore they showed that HbA_1c conc. fell when diabetic control was improved by treatment [2]. Measurement of HbA_1c is the standard method for assessing long term glycemic control. The HbA_1c has been shown to predict the risk for the development of many of the chronic complications in diabetes. HbA_1c is not for diagnosis of diabetes mellitus but only for monitoring the response to treatment.

The Landmark nine year DCCT completed in 1993 showed that the risk of development and progression of chronic complications of diabetes is closely related to the degree of glycemic control as measured byHbA_1c % [2].

Advanced glycosylation end products (AGE's) are formed as a result of non-enzymatic reactions between intracellular glucose derived dicarbonyl precursors (glyoxal, methyglyoxal, and 3 deoxyglucosone) with the amino group of both intracellular and extracellular proteins. On extracellular matrix components such as collagen or laminin, the formation of AGE's causes cross linking between polypeptides. Cross linking between collagen type I

molecules in large vessels, decreases their elasticity which may predispose these vessels to shear stress and endothelial injury.

Reduced elastic recoil of the lungs is one of the effects of diabetes on the respiratory system [3]. There is restrictive lung pathology in diabetes [4].

MATERIAL AND METHODS

The present study was carried out in the Diabetic Clinic of Indira Gandhi Govt. Medical College and Mayo Hospital, Nagpur. The approval of Institutional ethical committee was obtained. Written informed consent was obtained from all the subjects. All the subjects were males in the age group of 41 – 60 years. Study group included 42 Type II diabetics and for comparison, age and height matched 40 subjects were selected from staff members as control group.

Each group was supplemented by respiratory questionnaire [5] followed by thorough physical examination and investigations. All subjects from study group and control group were free from cardiac, respiratory and other such diseases which may impair pulmonary function. All were non-smokers with no history of smoking in the past. After selection, subjects from both groups were asked to report in Dept. of Physiology, I.G.G.M.C. Nagpur in the morning hours (10 A.M. – 12.30 P.M.) for measurement of anthropometric parameters, pulmonary function testing and blood investigations.

Standing height was measured by simply making the subject stand bare foot against a wall on which measuring scale is inscribed. Weight was done by KRUPS weighing machine in light weight garments without foot wears. BSA was calculated using Dubois chart [6]. BMI was calculated using formula[Weight in kg/(Height in meter)^2]. Fasting and post meal blood glucose level was measured using Glucose Oxidase Biosensor assay method by One Touch Horizon Glucose Meter. HbA_1c% was measured using cation exchange resin method (monozyme's glycohemin kit). Pulmonary function test was determined using MEDSPIROR – Recorder and Medicare system.

Necessary instructions were given to the subjects before performing P.F.T. They were asked to execute fast forcible expiration as much as possible at the end of deep full inspiration. Subjects were asked to perform the test till they become accustomed to the procedure. Then, three consecutive readings were obtained and the best was selected for the study. One single expiratory effort gives many readings, out of them FVC, FEV_1, FEV_1 %, $FEF_{25-75\%}$, $FEF_{0.2-1.2L}$, PEFR were selected for the study. After the rest of 15 minutes, the test to obtain Maximum Ventilation Volume was carried out. Subjects were asked to inhale and exhale as deep and as fast as possible for twelve seconds. The in-built calculation in the Medspiror gives MVV which was repeated for three consecutive times with a period of rest for ten minutes between each effort and best reading was selected for the study. Statistical analysis of observations was carried out. Mean and Standard Deviation were calculated and significance of difference was tested statistically by unpaired students 't test'[7]. Correlation coefficient (r) was calculated and tested for statistical significance [8]. Data is exhibited in the tables.

RESULTS

The results of pulmonary function test were compared between the study group (type II diabetes mellitus) and the control group. Values are expressed as Mean ± SD in the tables.

Table No. 1 shows that the anthropometric parameters are non-significant in type II diabetics as compared to controls.

Table No. 2 shows that fasting and post meal blood glucose level as well as HbA_1c% is significantly higher in Type II diabetics as compared to controls. Also all P.F.T. parameters excepting FEV_1 % are decreased significantly in Type II diabetics.

Table No. 3 shows a significant correlation between HbA_1c % and various P.F.T parameters like FVC, FEV_1, $FEF_{25-75\%}$, $FEF_{0.2-1.2\,L}$, PEFR and MVV. Also a negative correlation is found between HbA_1c % and all P.F.T parameters except $FEF_{25-75\%}$, and MVV.

Table 1: Showing comparison of anthropometric parameters in control group and type II diabetics.

Parameters	Control (n = 40)	Type II Diabetics (n = 42)
Age (yrs)	50.57 ± 5.81	50.73 ± 6.15*
Weight (kg)	61.32 ± 4.85	58.47 ± 8.18*
Height (meter)	1.63 ± 0.05	1.67 ± 0.08*
B.M.I. (kg/m^2)	23.06 ± 1.69	22.26 ± 2.35*
B.S.A. (m^2)	1.64 ± 0.08	1.60 ± 0.12*

Table 2: Showing comparison of blood parameters and P.F.T. parameters in control group and type II diabetics.

Parameters	Control	Type II Diabetics
Fasting (mg %)	93.87 ± 7.17	157.30 ±53.42***
Post Meal (mg %)	128.45 ± 7.01	250.59 ±90.71***
HbA_1c %	4.40 ± 1.04	8.30 ±1.78***
FVC (liter)	2.90 ± 0.22	2.43 ± 0.50***
FEV_1 (liter)	2.49 ± 0.22	2.31 ± 0.40**
FEV_1 %	85.74 ± 2.74	84.80 ± 3.96*
FEF 25-75 % (L/sec)	3.21 ± 0.40	2.69 ± 0.55***
FEF 0.2-1.2 L (L/sec)	5.96 ± 0.65	4.78 ± 1.16***
PEFR (L/sec)	7.21 ± 0.96	5.90 ± 1.10***
MVV (L/min)	110.87 ± 11.92	90.33 ± 20.00***

Table 3: Showing correlation of HbA_1c % with P.F.T. parameters in Type II Diabetics

P.F.T. Parameters	r value	t value
FVC	-0.025	-0158**
FEV_1	-0.070	-0.443**
FEV_1%	-0.210	1.360
$FEF_{25-75\%}$	0.039	0.251**
$FEF_{0.2-1.2L}$	-0.156	0.999**
PEFR	-0.129	-0.824**
MVV	0.133	0.848**

r = correlation coefficient, *p > 0.05 non-significant, **p < 0.05 significant, ***p < 0.001 highly significant

DISCUSSION

Fasting and post meal blood glucose level as well as HbA_1c % is found to be significantly higher in Type II diabetics [9] pointing to the fact that there is poor glycemic control. This may be because of irregular drug intake, inappropriate drugs, overeating, lack of diabetic life style discipline, etc. practiced by the patients [10].

HbA_1c % is an indicator of diabetes control. Higher the level of HbA_1c%, poor is the diabetes control i.e. there is a higher level of circulating glucose. If circulating glucose is constantly lingering at higher level for 3 months (as measured by HbA_1c %),it can lead to increased non-enzymatic glycosylation of tissue proteins. If respiratory system is a target of this affection, this will reflect in the P.F.T. parameters analyzed.

FVC and FEV_1 are significantly less in Type II diabetics. But FEV_1% is not significantly different in both cases and controls. This signifies that restrictive lung pathology occurs in diabetics. Similar findings were observed by other authors [11-13].

$FEF_{25-75\%}$ is an indicator of force of expiration of gases during middle 50% of forced expiration. In type II diabetics $FEF_{25-75\%}$ is significantly reduced compared to controls. Forced expiration is considered to be supported by muscular and recoil forces of respiratory system. The flow can be decreased even due to obstruction, but this is excluded as FEV_1% is normal. Thus decrease in recoiling forces of the lung is because of increased glycosylation of respiratory apparatus. Similar finding was observed in other study [14].

$FEF_{0.2-1.2\ L}$is the initial portion of forced expiratory maneuver. First 200 ml of the gas is from the dead space. Remaining 1 liter is exhaled from lung bronco-alveolar tree. This includes some gas from functional residual capacity, as normal tidal volume is 500 ml. This extraction of gas is due to compression forces that are built up by expiratory muscles. But due to glycosylation of connective tissues of the respiratory apparatus, compression forces that are built up by expiratory muscles might be reduced, resulting in a significantly reduced $FEF_{0.2-1.2\ L}$ in type II diabetics.

PEFR is gas exhaled in $1/10^{th}$ of a second during forced expiratory maneuver. At this time recoil forces of the lung and contractile forces of the musculature are functioning maximally and supporting the expiration to the maximal. But due to glycosylation of connective tissues of the respiratory apparatus, the muscular and recoil forces of the lung and the respiratory system for expiratory purpose might be decreased, leading to significantly decreased PEFR in type II diabetics [13,15].

MVV is the maneuver where maximum ventilator efforts are made. MVV in type II diabetics is significantly reduced indicating that muscular forces are weakened causing a decrease in lung compliance. This

again is due to glycosylation of connective tissues of respiratory apparatus [16, 17].

A significant correlation was found between HbA_1c % and various P.F.T parameters like FVC, FEV_1 [4,13,18], $FEF_{25-75\%}$, $FEF_{0.2-1.2\ L}$, PEFR [19] and MVV. Also a negative correlation was found between HbA_1c % and all P.F.T parameters except $FEF_{25-75\%}$, and MVV.

So in the present study, HbA_1c% is found to be significantly higher in type II diabetics as compared to controls which indicates uncontrolled blood sugar in last 3 months. This may be due to improper and irregular drug intake, drug resistance and many other factors which seem to be responsible for failure in lowering of blood sugar levels and has led to glycosylation of the various body tissue in general.

The message through the present work is that there is deterioration of lung function, there is production of restrictive lung, the obstructive element can be produced depending upon the exposure to infections, irritations, environmental pollutions etc. MVV supports the above finding that it has decreased due to restriction. The restrictive pathology is due to overall effect of glycosylation on the collagen and elastic framework of the respiratory apparatus. These tissues being present everywhere such as in skin, muscles, fascia, joints, lung parenchyma, pleura, there is overall damage to the whole respiratory apparatus. These micro damages produce less effective "negative-pressure-pump" and less compliant lung. Thus hypo effective pump and hypo compliant lung ultimately is exhibited as restrictive lung through the pulmonary function test.

Thus it confirms that diabetes mellitus if uncontrolled, produces restrictive respiratory pathology affecting both the pump as well as the lung.

But normally the diabetic patient may not appreciate the respiratory muscle weakness as during normal tidal respiration diaphragm is the widely used muscle and therefore tidal work load on non-diaphragmatic respiratory muscles being comparatively less, weakness of respiratory muscles is not much appreciated by the patient in routine life. This does not mean that respiratory muscles are not weakened. In diabetes the force building ability of respiratory musculature decreases. Magnitude of restriction will depend upon individual susceptibility and susceptibility of lungs as well as drug intake culture of the patient.

Therefore, it is strongly recommended to advice glycosylated hemoglobin and pulmonary function testing at regular intervals in diabetic patients to find out early deterioration of lungs in them.

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