Correlation Between Glycated Haemoglobin (Hba1c) and VO$_2$ Max. In Type-2 Diabetic Subjects in Central India: A Cross Sectional Study

Dr.Prashant T.Tayade$^1$, Dr.Shrinivas S. Chitta$^{2*}$, Dr. Mamta V.Rode $^3$, Dr. Mrunal S. Phatak $^4$

$^1$(Ex.Assistant Professor, Department of Physiology, Govt.Medical College, Akola, India)
$^2$(Assistant Professor, Department of Physiology Govt.Medical College, Akola, India)
$^3$(Associate Professor, Department of Physiology Govt.Medical College, Nagpur, India)
$^4$(Professor & Head, Department of Physiology Indira Gandhi Govt.Medical College, Nagpur, India)

Abstract:

Background: India leads the World with largest number of Diabetic subjects. Diabetes mellitus is one of the fastest growing chronic disease in world and India the “Diabetes capital of the World” is home to estimated 46 million people and predicted to be 79.4 million by the year 2030.

Materials & Methods: VO$_2$max and HbA1c were studied in Total 100 subjects of age group 35-45 years. Study groups comprised of 50 known case of Type-2 diabetic subjects having Diabetes since ≥ 3 years whereas control group comprised of 50 healthy normal subjects not involved in any regular physical exercise. VO$_2$max evaluated by Astrand- Astrand Nomogram, Glycated Hemoglobin levels (HbA1c) measured by cation – exchange resin Method.

Results: The HbA1c was significantly higher in Type 2 Diabetic subjects as compared to controls 10 ± 0.73 gm% vs 8.41 ± 0.745 gm%, p value < 0.001. The VO$_2$max was significantly decreased in Type 2 Diabetic subjects as compared to controls 2.824 ± 0.208 vs 2.932 ± 0.213; p value 0.012. There was statistically significant linear inverse correlation between of HbA1c and VO$_2$max in Type-2 Diabetic subjects.

Conclusions: Low cardio-respiratory fitness exists in Diabetes mellitus subjects which lowers the Exercise performance and increases the morbidity. Long term glycemic status may influences Cardio-respiratory fitness, suggesting poor glycemic control leads to decreased Cardio-respiratory fitness. Better glycemic control improves Exercise performance or Aerobic Work capacity. Further studies are required for establishing the correlation of exercise training & glycemic status in type 2 diabetics and its impact on aerobic fitness (VO$_2$max).

Keywords: Aerobic Work capacity, HbA1c, Type-2 diabetic subjects, VO$_2$max.

I. Introduction

Diabetes mellitus has become a widespread disease now days. The prevalence of Diabetes is rapidly rising with an alarming rate all over the Globe. According to World health organization report 2016 around 422 million adult people were affected with Diabetes Worldwide in year 2014 with global prevalence rate in adult population increased almost by double from 4.7% in 1980 to 8.5% in 2014 (WHO. Global report of Diabetes 2016) India leads the World with largest number of Diabetic subjects. Diabetes mellitus is one of the fastest growing chronic disease in world and India the"Diabetes capital of the World" is home to estimated 46 million people and predicted to be 79.4 million by the year 2030. The maximum burden of Diabetes in the society is contributed by type-2 Diabetes mellitus accounting for about 90 percent cases of Diabetes. And most of the increase will be in Type-2 Diabetes that parallels the incidence of Obesity. Incidence of Type 2 DM has already reached epidemic proportions. With increasing age the incidence of Type-2 Diabetes is increasing. The percentage is more in young population. It is associated with sedentary life style habit. The mentioned causes are high degree of genetic predisposition and susceptibility to environmental conditions.

The VO$_2$ max or Maximal Oxygen Consumption is the amount of oxygen that can be actually consumed by a person, when he or she is working maximally hard irrespective of the requirement. VO$_2$max is dependent on the efficiency of respiratory, circulatory and skeletal muscle system working together. It determines the Maximum Aerobic work capacity. It is observed that in Type-1 diabetics there is no apparent limitations to the peak VO$_2$ of subject compared to normal. While, studies show that, in people who are at risk for Type-2 diabetes, are associated with low cardio-respiratory fitness, and decreased insulin sensitivity. The study done by Silmara AO Leite, on western population suggest an Inverse relation between the cardio-respiratory fitness and risk for development of Diabetes. This indicates serious effect of Diabetes on Individuals Exercise performance thus compromising ones quality of life.

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Exercise is one of the recommended strategies for Type-2 diabetes in promoting Glycemic control. Diabetes mellitus is a impairment in carbohydrate, fat and protein metabolism caused by decreased sensitivity of tissue to insulin or deficiency in insulin secretion itself. The prolonged hyperglycemia consequently leads to excessive Non-enzymatic Glycosylation of various body proteins like Hemoglobin, collagen and albumin. Measurement of Glycated hemoglobin (Hb1Ac) levels constitutes the Glycemic index. Glycation occurs over the life span of the red blood cell (90-120 days) \(^{(10)}\) HbA1c is reflected as an average of the blood glucose present over the past 3-4 months. \(^{(11)}\) An elevated Hb1Ac levels indicates poor control of blood glucose levels or poor Glycemic index. A lot of information was available in western literature, taking into consideration the western sedentary life style habits. But little information is available in Indian Diabetics.

So, the concise study was undertaken to observe the trends of Maximum Oxygen Consumption (VO2max), Lipid profile, Glycated Hemoglobin and Waist-Hip ratio in Indian Type-2 Diabetics and to compare them with normal healthy subjects.

II. Aims and objectives

1) To find out Maximal Oxygen consumption (VO₂max) in Type-2 Diabetic Patient (Study group) & Normal Healthy subjects.
2) To find out levels of Glycated Hemoglobin in Type-2 Diabetic Patient (Study group) & Normal Healthy subjects.
3) To Correlate Glycated Hemoglobin levels with Maximal Oxygen consumption (VO₂max) in Type-2 Diabetic patients (Study group).

III. Materials & methods

The present study was carried out in Department of Physiology, Medicine and Bio-chemistry departmental laboratory, Indira Gandhi Govt Medical College, Nagpur; in the age group 35-45 years in male populations. The controls were taken from normal population. Their age, height, weight, socioeconomic and environmental status was matching with that of the study group.

3.1 Selection of subjects:
VO₂max, Glycated Hemoglobin, to be studied in Total 100 subjects of age group 35-45 years.
All subjects with normal Hemoglobin levels range for age & sex.
All subjects were undergone fasting & post-meal blood sugar testing and Family History of Diabetes was evaluated. Clinical examination was done.

Divided in 2 groups:
i. Study groups comprised of 50 known case of Type-2 diabetic subjects having Diabetes since \(\geq 3\) years.
ii. Control group comprised of 50 healthy normal subjects not involved in any regular physical exercise.

3.2 Exclusion criteria
a. Age groups \(\leq 35\) years & \(\geq 45\) years
b. Obesity
c. TB, Asthma.
d. Hepatic and Renal impairment.
e. Endocrine disorders other than diabetes.
f. Diagnosed congenital or Ischemic Heart Diseases..
g. Smokers and Alcoholics.
h. Subject having Hemoglobin less than 13.3 gm%, \(^{(12)}\)

3.3 Procedure
After selection, the subjects from both the groups, control as well as Type-2 Diabetes group were then given appointment in the group of four and were asked to report in the department of physiology in the morning time for measurement of anthropometric parameters and blood investigations. All the subjects were informed and advised to observe 8-12 hours over night fasting before the investigations.

Before starting the study work, all participants were given detailed information about the project and every attempt was taken to solve their queries.
3.4 Evaluation of Maximum Oxygen Consumption or VO$_2$max by Astrand- Astrand Nomogram:-

Method:
Bench stepping test was conducted at the rate of 30 steps per minute for five minutes. (so that it will elicit heart rate of between 125 & 170 beats per minute). The height of step being 40 cms, (16 inches) for males. One minute pulse rate was recorded immediately after the exercise.
The Heart rate & Body Weight (in KG) data were applied to the Nomogram. This was done by connecting with a straight edge, the point of Pulse (heart) rate scale and the Body Weight scale (stepping) & VO$_2$max (Liters/min) is read from middle scale at the point of intersection. (13)

3.5 Estimation of Blood sugar : (14)
Fasting as well as postmeal blood sugar level was quantitatively estimated in the laboratory of department of biochemistry, using semi autoanalyser, TRANSASIA, ERBA, CHEM-5- PLUS.

3.6 Estimation of Glycated Hemoglobin levels (HbA1c) by cation – exchange resin (15)

3.6.1 Principle:
Venous blood is mixed with lysing reagent for the preparation of hemolysate. Elimination of the labile Schiff’s base is achieved during hemolysis. The hemolysate is then mixed with a weakly blinding cation – exchange resin. The non-glycosylated haemoglobin binds to the resin leaving GHb free in the supernatant. The GHb percentage is determined by measuring the absorbance of the GHb fraction and of the total Hb at 415 nm (405 -420 nm).

3.6.2 Specimen:
Venous blood is collected with EDTA / Heparin using aseptic techniques.

3.6.3 Calculations:
Results for the unknown samples are calculated as follows:

$$\text{GHb}\% = \frac{\text{Abs. of Glycohemoglobin (GHB)}}{\text{Abs. of Total Hemoglobin (THB)}} \times 4.61 \text{ (Assay factor)}$$

Kit used: Monozyme’s glycohemin kit.

Equipment: glycated hemoglobin (HbA1c) was estimated on TRANSASIA SEMI AUTO ANALYSER, ERBA CHEM-5 PLUS.

Normal Range: <6 %.

IV. Observation And Results

Table No.1 Age, Height, Weight, BSA & BMI in Type 2 diabetics (Study group) and controls:

<table>
<thead>
<tr>
<th></th>
<th>Type-2 Diabetics (n = 50)</th>
<th>Controls (n = 50)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>41.32 ± 3.26</td>
<td>40.48 ± 3.21</td>
<td>0.197</td>
</tr>
<tr>
<td>Height (meter)</td>
<td>1.625 ± 0.04</td>
<td>1.627 ± 0.035</td>
<td>0.794</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>67.18 ± 2.68</td>
<td>66.1 ± 2.92</td>
<td>0.057</td>
</tr>
<tr>
<td>BMI (Kg/m$^2$)</td>
<td>25.46 ± 1.2</td>
<td>24.98 ± 1.12</td>
<td>0.040*</td>
</tr>
<tr>
<td>BSA(m$^2$)</td>
<td>1.7 ± 0.049</td>
<td>1.69 ± 0.054</td>
<td>0.19</td>
</tr>
</tbody>
</table>

* = p< 0.05 =Statistically significant
** = p< 0.01 =Statistically Highly significant
*** = p< 0.001 =Statistically Very Highly significant

Table No. 1 shows the mean age, height, weight, BSA & BMI of Type 2 Diabetic subjects and controls with their standard deviation and P value. There was no statistical difference in the age, height, weight & BSA of Type 2 Diabetic subjects and controls. But the BMI was significantly higher in Type 2 Diabetic subjects as compared to controls.

Table No.2: Fasting Blood Sugar and Post Meal Blood Sugar in (mg %) Type 2 Diabetics (Study group) and controls:

<table>
<thead>
<tr>
<th></th>
<th>Type-2 DM</th>
<th>controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS (mg %)</td>
<td>148.78 ± 22.5</td>
<td>84.92 ± 7.94</td>
<td>&lt;0.001 ***</td>
</tr>
<tr>
<td>PMBS (mg %)</td>
<td>253.24 ± 23.38</td>
<td>119.84 ± 7.48</td>
<td>&lt;0.001 ***</td>
</tr>
</tbody>
</table>

*** = p< 0.001 = Statistically Very Highly significant
Table No.2 shows the mean Fasting Blood Sugar and mean Post Meal Blood Sugar in mg% of Type 2 Diabetic subjects and controls with their standard deviation and P value. The Fasting Blood Sugar and Post Meal Blood Sugar values were significantly higher in Type 2 Diabetic subjects as compared to controls.

<table>
<thead>
<tr>
<th>Glycated Hemoglobin (HbA1c) (%)</th>
<th>Type-2 Diabetics</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHb (%)</td>
<td>8.41 ± 0.74</td>
<td>5.10 ± 0.73</td>
<td>&lt; 0.001 ***</td>
</tr>
</tbody>
</table>

*** = p< 0.001 = Statistically Very Highly significant

Table No.3 shows the mean Glycated Hb (HbA1c) in percentage, of Type 2 Diabetic subjects and controls with their standard deviation and P value.

Table No.4 Comparison of Maximal Oxygen Consumption (VO\(_2\)_max) in Liters/min in Type-2 Diabetics and controls:

<table>
<thead>
<tr>
<th>VO(_2)_max in (L/min)</th>
<th>Type-2 Diabetics</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.82 ± 0.208</td>
<td>2.93 ± 0.213</td>
<td>0.012*</td>
<td></td>
</tr>
</tbody>
</table>

* = p< 0.05 = Statistically significant

Table No.4. Shows the mean VO\(_2\)_max in Liters per minute of Type 2 Diabetic subjects and controls with their standard deviation and P value. The VO\(_2\)_max was significantly decreased in Type 2 Diabetic subjects as compared to controls.

Table No.5 Showing correlation of Glycated Hemoglobin and Maximal Oxygen Consumption (VO\(_2\)_max) in Type-2 Diabetic group.

<table>
<thead>
<tr>
<th>VO(_2)_max (L/min)</th>
<th>r-value</th>
<th>Type-2 Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.3631</td>
<td></td>
</tr>
</tbody>
</table>

** = p< 0.01 = Statistically Highly significant

Table No.5 shows the finding of correlation of Glycated Hemoglobin and Maximal Oxygen Consumption (VO\(_2\)_max) in Type-2 Diabetic group. It is seen that there was statistically significant linear inverse correlation between of Glycated Hemoglobin and Maximal Oxygen Consumption (VO\(_2\)_max) in Type-2 Diabetic group.

V. Discussion

5.1 Glycated Hemoglobin (HbA1c):

The mean value of Glycated Hemoglobin (HbA1c) in Type 2 Diabetics was 8.41 ± 0.74 % while that in controls was 5.10 ± 0.73 %. The mean values of HbA1c are depicted in Table no. 3 and. It was observed that the cases had higher Glycated Hemoglobin levels than the controls.

This indicates that the Diabetics had poorly controlled diabetes mellitus. Higher the level of Glycated Hemoglobin, poorer is the control of blood sugar i.e. higher is the level of circulating glucose and as discussed earlier hyperglycemia leads to non-enzymatic glycation of intracellular and extra cellular proteins forming advanced glycation end products (AGEs). (16)

5.2 Maximal Oxygen Consumption (VO\(_2\)_max):

Maximal Oxygen Consumption (VO\(_2\)_max) is depicted in Table no.4. The mean Resting pulse rate, Post-Exercise pulse rate & VO\(_2\)_max level in Type 2 Diabetics were 76.9 ± 6.38 beats/min, 157.04 ± 7.8 beats/min, 2.82 ± 0.208 L/Min while that in controls were 76.11 ± 6.0 beats/min, 153.04 ± 7.74 beats/min, 2.93 ± 0.213 L/Min respectively. The difference of Resting pulse rate was nonsignificant, While, Post-Exercise pulse rate was significantly higher in Type-2 Diabetics than controls. VO\(_2\)_max was significantly decreased in Type-2 Diabetics as compared to controls. These findings are in congruence with the findings of Schneider H. et al (17), He J. et al (2001) (18), Regensteiner JG. et al. (2009) (19)

This could be explained by a higher Glycolytic to Oxidative enzyme ratio which is caused by increased activity of Glycolytic enzymes but also decreased maximum velocity of Oxidative enzymes i.e citrate synthase & Cytochrome-c oxidase contributes to Insulin resistance in subjects with Type-2 Diabetes. (20)

The underlying cause of insulin resistance, suggested is impairment in GLUT4 translocation due to either impairment in signal transduction or internal to the glucose transporter system (21). Also decrease in the enzymatic activity regulating storage and oxidation of glucose in skeletal muscle. (22) Muscle fiber type and composition found in studies (23) with diabetes such as changed skeletal muscle fiber type (23) as well as increased fat content, capillary basement membrane width in the skeletal muscle (24) may result in low work...
efficiency. The accumulation of Intramyocellular Triglycerides (IMCL) \(^{(25)}\) which correlates well with in Vivo Insulin Resistance. \(^{(26)}\) In particular the impairment in muscle fatty acid oxidation being the primary defect causing the IMTG (Intramyocellular Triglycerides) accumulation, developing muscle insulin resistance in patients with obesity, IRS, and type 2 diabetes. Oxidative capacity of the mitochondria is highly correlated with insulin sensitivity and VO\(_2\text{max}\). \(^{(27)}\) It is also suggested that though Mitochondrial function is normal in type 2 diabetes, the coupled and uncoupled respiration getting blunted in type 2 diabetic patients which attributes to a low mitochondrial content. \(^{(28)}\) Also the increased frequency of mitochondrial DNA deletions in skeletal muscle of Type-2 diabetes, & increased one particular deletion 4,977 bp was found to be significantly increased in muscle tissue of Type-2 DM or Impaired glucose tolerance. \(^{(29)}\) It is demonstrated that insulin induced Mitochondrial ATP production is also compromised in Type-2 Diabetes. \(^{(30)}\)

Peroxisome proliferator activated receptor γ coactivator-1 (PGC-1\(\alpha\))-responsive genes involved in oxidative phosphorylation are downregulated in human diabetes and their expression is high at sites where insulin-mediated glucose disposal is present. These sites are activated by PGC-1\(\alpha\) and is found to be correlated with total-body aerobic capacity. \(^{(31)}\)

5.3. Correlation between Glycated hemoglobin and Maximal Oxygen Consumption (VO\(_2\text{max}\)): The correlation between glycated hemoglobin and VO\(_2\text{max}\) was studied as shown in Table no. 5 and a statistical significant inverse correlation was found, with a correlation coefficient of -0.3631. This VO\(_2\text{max}\) may decrease as the percentage of glycated hemoglobin increases i.e. more is the blood sugar level (uncontrolled diabetes) less may be the VO\(_2\text{max}\). These findings are in agreement with the findings of Bavenhom PN, et al (2003) \(^{(32)}\), Vanninen E., et al (1991) \(^{(33)}\) who also reported significant inverse correlation between glycated hemoglobin and VO\(_2\text{max}\). Glucose transport stimulated by Insulin in skeletal muscle is down-regulated in the presence of hyperglycaemia from patients with NIDDM. This increased glucose flux as a consequence to hyperglycaemia may result in resistance to any further insulin-induced gain in GLUT4 (as occurred in non-diabetic subjects) at the plasma membrane level. Reduced insulin stimulated cellular glucose transport and type I muscle fibres percentage in skeletal muscle from morbidly obese control and morbidly obese NIDDM subjects has been found to be related. \(^{(35)}\) Factors leading to the development of the decreased glucose transport capacity mediated via insulin in skeletal muscle, are attributed to be included reduced blood flow \(^{(36)}\), elevated free fatty acids \(^{(37)}\). Is it found that in the hexosaminebiosynthetic pathway there was increased routing of glucose which could be a contributing factor to the development of the muscle insulin resistance in Type-2 diabetes. Also Defronzo RA.(1992) \(^{(38)}\), Reaven G. (1988) \(^{(39)}\) in middle aged Type-2 Diabetics, despite fasting Hyperinsulinemia, have increased basal hepatic glucose output, impaired glycaemia induced insulin release & increased resistance to Glucose disposal mediated by insulin actions. Similar results were also observed by Meneilly GS. et al.(1999) \(^{(40)}\). Thus poor glucose control (Hyperglycemia) may have influence on VO\(_2\text{max}\), i.e the Cardio-Respiratory fitness.

VI. Conclusion
a. Type 2 Diabetics had significantly higher Glycated hemoglobin levels as compared to healthy normal controls.
b. The Maximal oxygen consumption (VO\(_2\text{max}\)) was significantly lower in Type 2 Diabetics as compared to healthy normal controls.
c. A negative linear correlation was found between Glycated hemoglobin and Maximal Oxygen Consumption (VO\(_2\text{max}\)) in Type 2 Diabetics.
d. The significantly lower value of Maximal oxygen consumption (VO\(_2\text{max}\)) in Type 2 Diabetics suggests that the low cardio-respiratory fitness exist in these subjects. Thus, Diabetes mellitus lowers the Exercise performance and increases the morbidity.
e. The Negative correlation between Glycated hemoglobin and Maximal oxygen consumption (VO\(_2\text{max}\)) suggest that the long term glycemic status may influences Cardio-respiratory fitness, suggesting poor glycemic control leads to decreased Cardio-respiratory fitness. Better glycemic control improves Exercise performance or Aerobic Work capacity.

Hence it is suggested that further studies are required for establishing the correlation of exercise training & glycemic status in type 2 diabetics and its impact on aerobic fitness (VO\(_2\text{max}\)).

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Correlation Between Glycated Haemoglobin (HbA1c) And VO2 Max. In Type-2 Diabetic....


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