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The effect of body mass index and glycated hemoglobin levels on oxygen saturation in Type 2 diabetics

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***Abstract*---**A high Body mass index (BMI) has multi-organ effects and influences cardiovascular and respiratory function in several direct and indirect ways. The present study examined the effect of obesity and HbA1c levels on oxygen saturation (SpO_2) in Type 2 diabetics. 102 subjects (82 F, 20 M), all with confirmed diabetes, were included in the study. Their body-mass indices (BMI's) were calculated from obtained anthropometric data on height and weight. HbA1c (%) was estimated using a latex agglutination inhibition assay and SpO2 (%) levels measured using pulse oximeter provided by the EDAN elite V6 series patient monitor. Boxplots displaying the five number summary were used in descriptive statistics. Pearson correlation and student's T-test were used for statistical analysis. BMI showed a highly significant negative correlation with SpO2 ($r = -0.47$; $p < 0.00001$). BMI was positively correlated with age ($r=0.22$; $p =0.028$). However, no correlations were found between HbA1c on the one hand, and age, BMI and SpO_2 on the other. Conclusions: HbA1c levels appear to be unaffected by age, BMI, SPO_2. Variations of values between males and females about HbA1c and SpO_2 are also insignificant. Higher BMI has been known to exert both metabolic as well as mechanical influences on respiratory and cardiovascular systems and is significantly associated with lower SpO_2 levels indicating an underlying

oxygenation-ventilation compromise. However, higher HbA1c levels were not associated with any changes in oxygen saturation levels, indicating that glycation of the hemoprotein may have negligible effects on its oxygen-carrying capacity.

***Keywords*---**Obesity, Body mass index, HbA1c, oxygen saturation, Type 2 diabetes, hypoxia-inducible factors.

Introduction

Diabetes mellitus is characterized by a spectrum of derangements which result in elevated blood sugar levels. These may arise from defects in insulin sensitivity of tissues, also termed as insulin resistance and/or defects in the synthesis or secretion of insulin. The World Health Organization states that more than 422 million people worldwide had diabetes in 2014. However, the most significant increase is expected to occur in the emerging economies of South Asia, the Near East, and countries in Africa, where the cases may increase by around 50% by 2030.[1]

Diabetes mellitus is associated with multiple complications affecting various organ systems. The end result is tissue damage by different direct and indirect mechanisms owing to the fluctuations in blood glucose levels. Persistently elevated blood sugar levels may exert an injurious effect by various mechanisms. [2] Obesity is a prevalent co-morbidity seen in individuals with type 2 diabetes (T2DM). It may worsen diabetic complications. [2] The prevalence of diabetes has been increasing but not the disease-specific death rate.[3]

Hemoglobin is a protein that oxygenates body tissues and carries carbon dioxide for disposal to the lungs, among other functions.[4] A ketoamine reaction occurs between glucose and the N-terminal valine of both β-chains of the hemoglobin molecule resulting in the production of glycated hemoglobin. The primary form of glycated hemoglobin is hemoglobinA1c (HbA1c). As a result of persistent elevation in plasma glucose, nonenzymatic glycation of hemoglobin increases. This alteration in hemoglobin reflects the glycaemic history of the patient over the last 2–3 months which corresponds to the average life span of erythrocytes.[5,6] It has been theorized that glycation may influence the shape and concomitantly alter the function of hemoglobin. This may potentially cause changes to the hemoglobin-oxygenaffinity. High HbA1c levels have been implicated in increased blood viscosity, the glycosylation process reducing RBC flexibility and provoking aggregation. Glycosylation may also hinder Nitric-oxide mediated blood vessel relaxation. Oxygen-dissociation velocities maybe affected. All these factors may culminate into potential diminutions in oxygen delivery to tissues triggering adaptive vasodilatory responses.[4,6,7]

HbA1c is a useful biomarker of long-term glycemic control and has a bearing on the lipid profile. Studies have reported significant associations between the glycemic marker and dyslipidemia. Poorer glycemic control is associated with significantly elevated triglycerides, low-density lipoprotein (LDL) levels and diminished levels of the 'healthy' high-density lipoproteins (HDL).[7]

Very few studies have assessed the association of body mass index (BMI) with the saturation of peripheral oxygen (SpO_2), which is the measure of percentage of hemoglobin saturated with oxygen[8]. The successive SARS-CoV-2 waves causing widespread cases of cardiopulmonary compromise have increased the demand for non-invasive SpO_2 monitors. These 'pulse oximeters' provide a quick, convenient and feasible method to obtain instant information as to the oxygenation-ventilation status of the patient. Diabetes is associated with alterations in levels of HbA1c levels and has a strong interrelationship with increased BMI. Thus, this information can be further explored for establishing a relationship between tissue hypoxia and obesity in diabetic patients. This may help in understanding the high morbidity and mortalities seen in this group of individuals who contracted SARS-CoV-2 infection. The present study aims for evaluating the effect of increased BMI and HbA1c levels on SpO2 levels in diabetic patients.

Materials and Methodology

Sample selection

The institutional ethical committee approved our study protocol. A total of 102 subjects (82 Females and 20 Males) with age 18-75yrs were included into the study. The subjects included in the study were patients diagnosed with Type 2 DM with a medical history of more than 1 year. Previous medical records were accessed to confirm diagnosis of Type 2 DM including data on Oral Glucose Tolerance Test (OGTT) and HbA1c levels. Patients were under oral hypoglycemic medication for more than 1 year. Smokers, patients with respiratory disorder (such as asthma, COPD, etc), and patients on any injectable form of insulin were excluded from the study.

Anthropometry

Weight was measured using a digital scale with sensitivity of 0.1 kg. Height was measured to the nearest 0.1 cm using a wall mounted scale. BMI was calculated as weight in kilograms divided by the square of height in meters (m^2). HbA1c (%) was estimated via a latex agglutination inhibition assay and SpO2 (%) levels measured using pulse oximeter.

Latex Agglutination Inhibition Assay (biochemical analysis)

The concentrations of both HbA1c and Total Hemoglobin were determined. HbA1c/Total Hemoglobin ratio was used in deriving the % HbA1c. Whole blood taken from the patient was mixed with a denaturant in a 1:41 dilution, followed by incubation for five minutes at room temperature. Addition of denaturant resulted in erythrocyte lysis and enzymatic hydrolysis of hemoglobin. Hemoglobin derivatives got transformed into alkaline hematin. Subsequent reactions resulted in a green-colored product, which was measured at a wavelength of 600nm. HbA1c measurement utilizes a latex agglutination inhibition assay. Addition of an agglutinator caused agglutination of latex coated with HbA1c specific mouse monoclonal antibodies. Agglutination occurs in absence of HbA1c and increases absorbance. In the presence of HbA1c, agglutination is inhibited and absorbance decreases. The increase in absorbance is measured at a wavelength of 700 nm.

Dynamic Range

The dynamic range of the Beckmann Coulter™ Kit for Total Hemoglobin is 7 – 23 g/dL which corresponds to 4.4 – 14.3 mmol/L. The dynamic range for Beckmann Coulter™ HbA1c extends from 2.6% -14.5%.

Precision

Precision estimates of the assay were as per CLSI recommendations. The within run precision was ≤ 3% CV while the total precision is ≤ 4% CV.[9]

Monitoring of pulse oxygen saturation

SpO2 was estimated with a pulse oximetry probe of the EDAN elite V6 series patient monitor. The probe was applied on the fingertip and the measurement of transdermal light absorption was used in deriving the oxygen saturation through suitable algorithms. The probe was applied for a suitable time period and saturation values were recorded only after obtaining a stable reading.

Statistical analysis

The SPSS version 20 software was used for all analyses. Comparison studies utilised the Student's T-test while the relationships between variables were assessed using Pearson's correlation coefficient. For two-tailed assessments, a p value <0.05 was considered statistically significant.

Results

Average age of the females was 58.6±11.31 years while that of males was 58.8±12.49 years. Average BMI of females was significantly higher (29.15±5.38 kg/m^2) compared to males (25.05±4.25 kg/m^2). SpO_2 (%) of females and males was 94.585±2.62 and 95.25±2.59 respectively. HbA1c (%) levels in females and males averaged 8.22±1.89 and 8.16±1.99, respectively [Table 1].

Table 1: Descriptive statistics of the various recorded parameters

Variable	Gender	Total Count	Percent	Mean	SE Mean	StDev	Minimum	Maximum
Age	Female	82	80.3922	58.60	1.25	11.31	23.00	85.00
	Male	20	19.6078	58.80	2.79	12.49	47.00	95.00
BMI Kg/m2	Female	82	80.3922	29.151	0.594	5.379	17.200	48.200
	Male	20	19.6078	25.053	0.950	4.249	19.400	34.800
SPO2%	Female	82	80.3922	94.585	0.290	2.624	87.000	99.000
	Male	20	19.6078	95.250	0.580	2.593	89.000	99.000
HBA1C%	Female	82	80.3922	8.219	0.208	1.887	6.000	14.900
	Male	20	19.6078	8.160	0.445	1.991	6.000	13.600

Boxplots were used in explanatory analysis of the data and elucidated numerical data distributions. They also displayed skewness. Data quartiles (or percentiles) and averages were displayed. The plots displayed the five-number summary viz. the minimum score, first (lower) quartile, median, third (upper) quartile, and maximum score of the recorded parameters viz. HB1AC%, SpO2, BMI, and age of the respondents for each of the male and female patient group. [Figure 1,2,3,4]

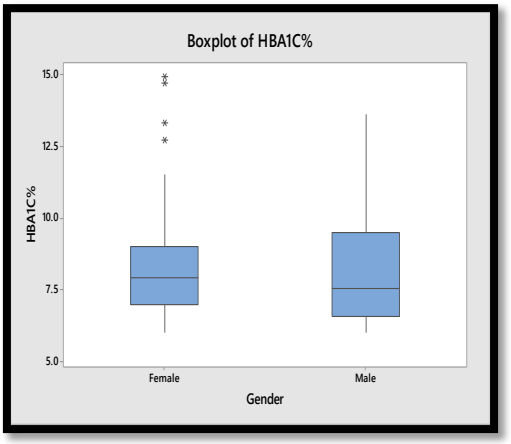

Figure 1

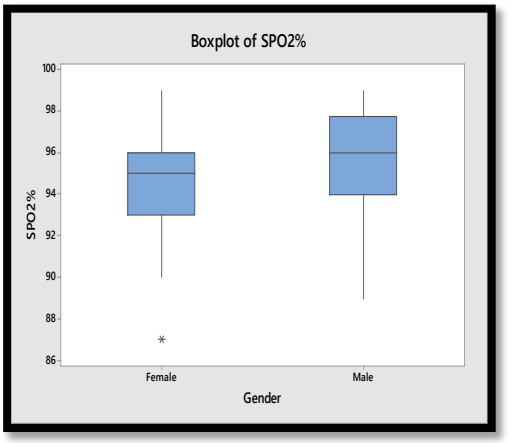

Figure 2

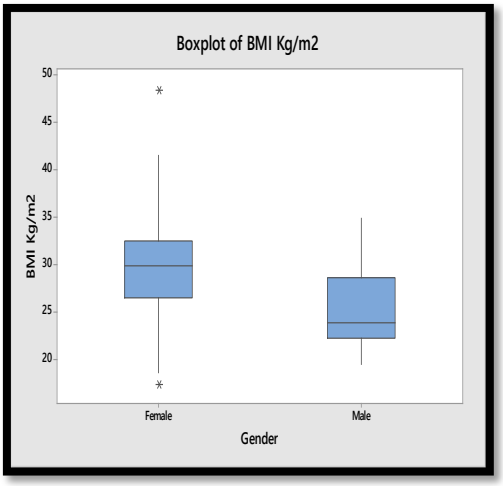

Figure 3

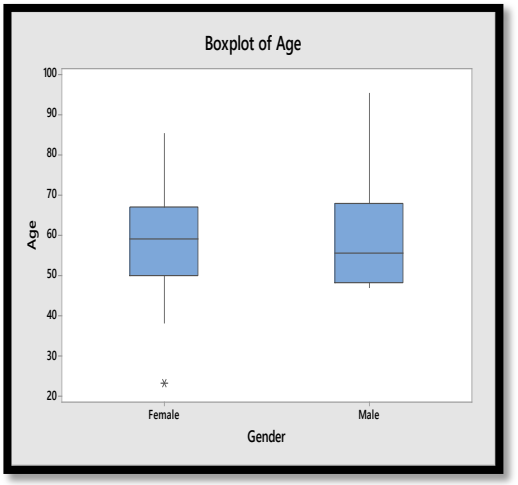

Figure 4

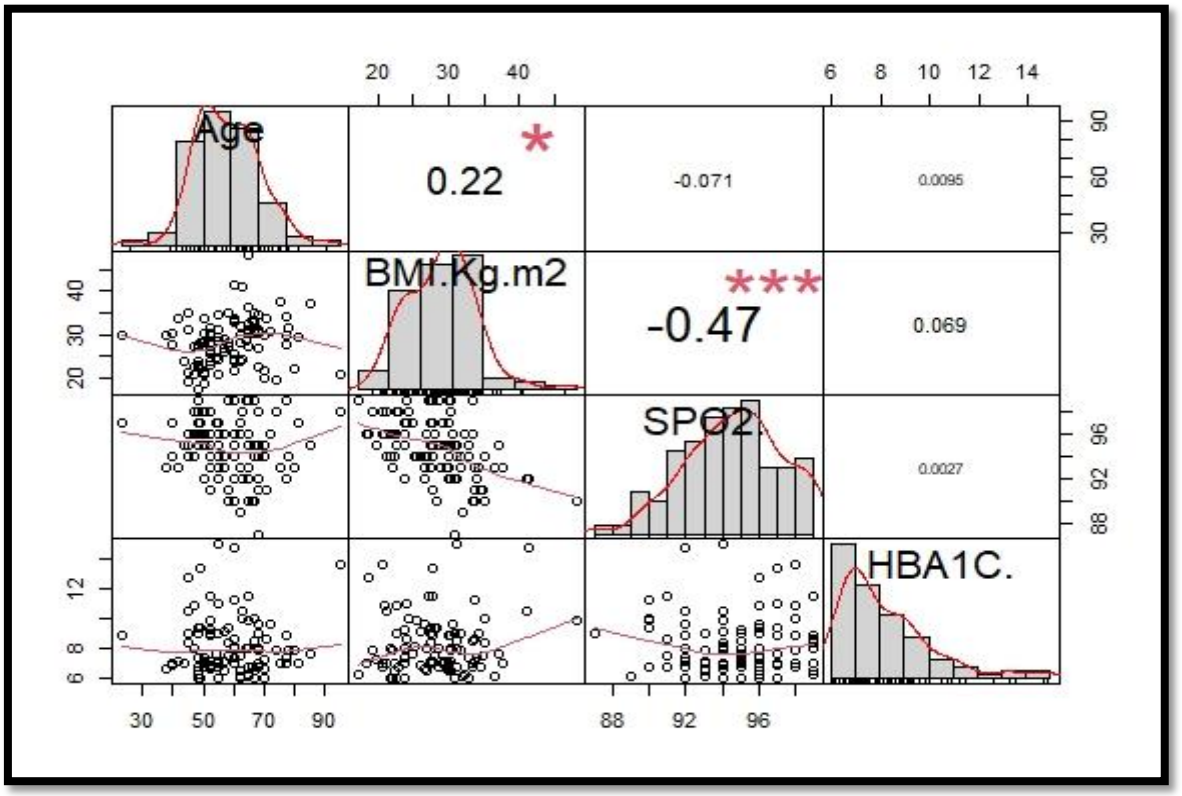

Figure 5: The correlation matrix for the various parameters is depicted. The coefficients with asterisk indicate a highly significant correlation

BMI showed a highly significant negative correlation with SpO2 ($r = -0.47$; $p < 0.00001$) BMI was positively correlated with age ($r= 0.22$; $p =0.028$). However, no correlations were found between HbA1c on the one hand, and age, BMI and SpO_2 on the other. [Figure5].

Discussion

Diabetes and obesity are major noncommunicable diseases of the modern era and pose serious effects on cardiopulmonary physiology.[2, 10] In the present study, we assessed the association between obesity and hypoxemia in diabetic patients. Our results reported that the value of BMI is inversely proportional to value of SpO_2. Similar results were derived by Garg et al. in their study.[4] Hypoxemia denotes a condition in which hemoglobin has a less than normal oxygen saturation. Jin Pu et al. observed that a possible accumulation of advanced glycation end products in chronic diabetics may interfere with measurements and actually lead to under-diagnosis of hypoxemia in such patients.[7] It has been observed that overweight and obese subjects may have compromised cardiovascular function. Although some increase in cardiac output and circulating blood volume has been seen, the resting oxygen consumption may also be increased. Thus, the overall blood flow may be insufficient in relation to the body weight. Overweight individuals may have hypertrophied adipocytes without a proportionate increase in blood supply

and oxygenation.[11] Some studies have shown decreased perioperative and adipose tissue oxygenation in obese and diabetic patients. Apparently, obese individuals had compromised oxygenation of adipose tissue and this was associated with insulin resistance. [12] In overweight and obese patients without evidence of cardiopulmonary disease, it has been observed that BMI has a negative correlation with oxygen levels. A possible putative factor for this could be the reduced expiratory reserve volumes secondary to increased adiposity in the trunk regions.[10]

A review of various studies performed by Levy et al proposed that insulin resistance and hyperglycemia, acting via induction of oxidative stress, concomitant inflammation, and damage caused by AGE cross-linking, can induce microvascular abnormality. Impaired microvascular perfusion is common among patients with hypertension, diabetes and obesity thus they are at a higher risk for moderate or severe infection-related morbidity.[13-16] In this study, a positive correlation was found between BMI and age (0.028) which holds parallels the results proposed by a study performed on a rural Bangladeshi population.[17]

Glycation of hemoglobin may potentially modify its properties. Changes to affinity for oxygen may alter the oxygen dissociation curve. A potential increase in affinity for oxygen has been hypothesized which may affect oxygen delivery to tissues.[4] The measurement of glycated hemoglobin in the form of HbAlc has become a prominent tool in assessing the glycemic control of diabetic patients. It has less measurement error than fasting blood glucose.[4,18, 19] Studies report proportionately increased cardiovascular risk in diabetics with high HbA1c levels.[20,21] However, no correlation was found between HbA1c and SpO_2 in the present study indicating that glycation of hemoglobin maybe a relatively benign process.

The cardiovascular system is substantially influenced by obesity. There can be a paradoxically reduced cardiac output, which may be secondary to increased peripheral resistance. Left ventricular hypertrophy and compromised left ventricular systolic function are some of the vicious adaptations triggered by obesity. All these changes influence oxygenation of tissues.[22] Cardiovascular disease is responsible for an overwhelming majority of deaths in diabetics.[23]

The role of Hypoxia-inducible factors

Hypoxia-inducible factors (HIFs) are essential regulators of the mammalian response to hypoxia with both positive and negative roles. These are transcription factors whose activation has emerged as a significant pathological event in the development of metabolic diseases triggered or worsened by obesity. Hypoxia incites changes to adipocyte insulin signaling pathways through these factors. If oxygen and iron are sufficient, HIF-1α undergoes proteolysis. If either of the two are insufficient, HIF-1α escapes proteolysis and is able to dimerise with HIF-1β. The dimer consequently binds to hypoxia response elements (HREs) and triggers events to counter hypoxia. It has been observed that HIF-1α is essential for normal glucose tolerance. Diabetes promotes HIF protein destabilization and reduces HIF-1α activity. Obesity adaptively increases HIF-1α by maintaining a relative hypoxia. However, this results in fibrotic changes in fat tissues. [24,25]

HIFs have negative roles as well. Hypoxia has been seen to occur in severe SARS-CoV-2 pneumonia and respiratory distress. There is growing evidence that hypoxia modulated HIF activation may result in a pro-inflammatory state.[26] HIFs have also been released in patients with high BMI due to cyclic hypoxia secondary to obstructive sleep apnea (OSA). The latter is identified explicitly by episodic upper airway obstruction causing fluctuations in oxygenation. SpO2 levels may drop to as as low as 50% of normal in OSA sufferers.[26, 27, 28] In obese patients who have contracted SARS-CoV-2 infection, there is a twin-effect of lung-damage induced systemic hypoxia and cyclic hypoxia. This may result in an 'over-stimulation' of HIF activity and subsequent overactivation of inflammatory mediators. The cytokine storm seen in this group of patients may be secondary to the above events and may help in explaining the poorer disease course observed.[26] Disease severity has a direct correlation to body mass indices, with higher BMI significantly predictive of the same.[29, 30, 31] A higher BMI may have deleterious effects on both innate and adaptive immune responses. It has been established that overweight and obese subjects are in a state of chronic, mild inflammation. Host response to pathogens may thus be severely compromised in these individuals, explaining the poorer prognoses observed.[32] Thus, one can assume that both overactivation as well as underactivation of the immune system may be seen in the overweight and obese individuals. Consequently, a high BMI predisposes to increased risk of hospitalization, ICU admission or even death.

Conclusion

BMI has shown a rising trend, especially during the forced sedentary lifestyle during the current COVID-19 pandemic and is a major healthcare concern. Raised BMI levels have been seen to be independent associated risk factors for increased morbidity and mortality. We observed in this study that in diabetic patients, higher BMI was significantly associated with compromised oxygen saturation levels. This could be due to the both mechanical and metabolic effects of obesity on the respiratory and cardiovascular system possibly affecting microvascular perfusion. Interestingly, the poorer prognoses observed in obese patients in the current COVID-19 pandemic could also be explained through plausible pathways involving hypoxia inducible factors. HIFs activated through hypoxia in overweight subjects may result in both exaggerated as well as dulled immune responses. However, HbA1c levels did not influence SpO_2 indicating that glycation, although deleterious in several tissues, may not negatively influence the oxygen carrying capacity of hemoglobin.

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