

Correlation of body mass index and waist/hip ratio with glycated hemoglobin in prediabetes

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ABSTRACT

Introduction:

Prediabetes (preDM) is a state of disordered glucose metabolism rather than a distinctive clinical entity representing an interim condition and a risk factor for the development of diabetes. Diagnosis of asymptomatic people to assess the risk for development of DM should be done in overweight or obese adults (BMI ≥ 25 kg/m²) of any age along with person having one or more additional risk factors like physical inactivity, first degree relative with DM, high risk race/ethnicity, hypertension etc.

Objectives:

To correlate glycated hemoglobin (HbA_{1c}) levels with body mass index (BMI) and waist hip ratio (WHR) in prediabetic patients.

Materials & methods:

The present case control study was performed at Pt. B. D. Sharma PGIMS, Rohtak includes thirty prediabetic

patients of age group 20-40 years diagnosed on the basis of HbA_{1c} (5.7-6.4%). Thirty healthy and age matched control were taken. After taking written consent, they were subjected to physical examination and anthropometric measurements as per protocol and findings were noted. Venous blood sample was withdrawn for estimation of HbA_{1c} levels.

Results:

The correlation coefficient between BMI (27.01 ± 2.91 kg/m²) and HbA_{1c} (5.94 ± 0.21%) is r = 0.583 with p value = 0.001 and between WHR (0.87 ± 0.38) & HbA_{1c} is r = 0.495 with p value = 0.005. Both BMI & WHR are positively correlated with HbA_{1c}.

Conclusion:

Obesity is a risk factor for glycation of hemoglobin & hence, it is an effective measure for prevention of prediabetes and diabetes.



INTRODUCTION

Prediabetes (preDM) is a stage of disordered glucose metabolism rather than a distinct clinical entity and a risk factor for the development of diabetes along with an increase in cardiovascular and microvascular complications. The transition from preDM to diabetes may take years but may also be rapid. It is estimated that most individuals (up to 70%) with preDM eventually develop diabetes. The incidence is highest in individuals with combined impaired fasting glucose (IFG) & impaired glucose tolerance (IGT) and similar in those with isolated IFG (i-IFG) or isolated IGT (i-IGT) [1].

BMI ≥ 25 kg/m² is a major risk factor for development of prediabetes along with other risk factors like physical inactivity, first degree relative with DM, high risk race/ethnicity, women who delivered a baby weighing 9 lb or diagnosed with gestational DM, hypertension (HTN), HDL cholesterol (HDL-C) level of 35 mg/dL and a triglyceride (TG) level of 250 mg/dL, women with polycystic ovarian syndrome (PCOS), etc [2].

Figure 1 Formation of HbA_{1c} [5]

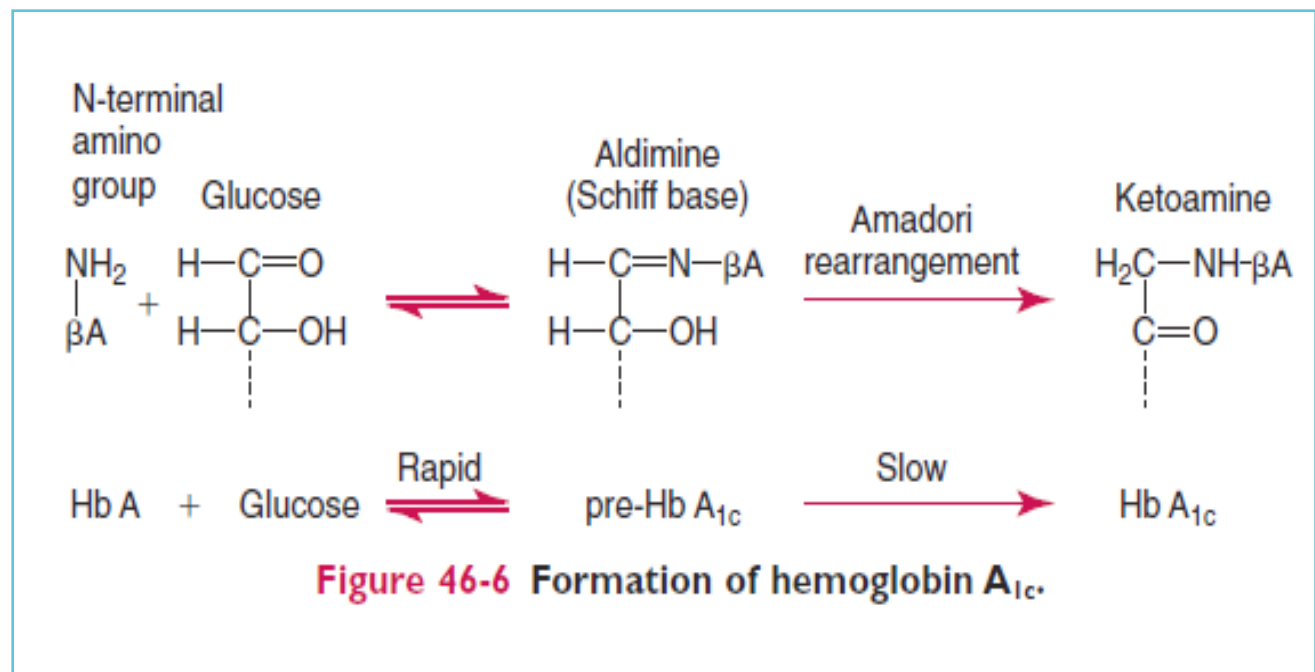


Figure 46-6 Formation of hemoglobin A_{1c}.

HbA_{1c} results from the nonenzymatic, irreversible concentration dependent covalent bonding of glucose to hemoglobin within the erythrocytes. Glycation occurs in a two step Maillard reaction. It involves the initial formation of a labile Schiff base which undergoes a subsequent Amadori rearrangement leading to formation of an Amadori product i.e., HbA_{1c}. Driven by the nucleophilic nature of the NH₂-terminal, amino group of hemoglobin condenses with glucose found in the erythrocyte. The cumulative amount of HbA_{1c} in an erythrocyte is directly proportional to the time dependant concentration of glucose within the erythrocyte [3,4] (Figure 1).

The concentration of HbA_{1c} correlates with the average blood glucose levels over the preceding three months. As a consequence of relationship between glycemia and HbA_{1c}, it is clear that there is a significant association between HbA_{1c} and various clinical outcomes. Moreover, HbA_{1c} is related to the risk of microvascular (in both type 1 and type 2 diabetes) as well as macrovascular (in type 1 diabetes) complications [6].

Thus, it is concluded that development of preDM is linked to environmental factors such as physical inactivity but the subsequent development of diabetes is affected by combination of genetic and environmental factors. Therefore efforts to prevent diabetes should be initiated prior to the development of preDM in order to obtain the maximum benefit [7].

MATERIALS & METHODS

The present study was conducted in the Department of Biochemistry, in collaboration with the Department of Medicine, Pt. B. D. Sharma PGIMS, Rohtak.

In the present study, 30 prediabetic patients diagnosed on the basis of HbA_{1c} levels were enrolled as cases. 30 healthy- and age-matched individuals were enrolled as controls.

Inclusion criteria

Patients of age group between 20-40 years satisfying the criteria of prediabetes based on HbA_{1c} were included in the study.

Criteria of prediabetes according to ADA is [8]

1. Impaired fasting glucose (IFG) with fasting plasma glucose levels of 100 to 125 mg/dL (5.6 to 6.9 mmol/L).
2. Impaired glucose tolerance (IGT) with plasma glucose levels of 140 to 199 mg/dL (7.8 to 11.0 mmol/L) 2-hour postprandial.
3. HbA_{1c} of 5.7 to 6.4%.

Exclusion criteria

- Patients with hemoglobin < 9 g/dL and any history suggestive of hemoglobinopathies.
- Patients with history suggestive of endocrine disorders like thyroid, adrenal and pituitary glands disorders.
- Patients with history suggestive of any drug intake affecting glucose metabolism.

Methodology

After getting written consent from the cases and controls, detailed history was taken and recorded in their respective proforma. They were subjected to physical examination and anthropometric measurements as per protocol and the findings were noted. Waist circumference (WC) was measured midway between the lowest point of rib cage and the superior border of iliac crest at the end of normal expiration with a stretch resistant measuring tape. Hip circumference (HC) was measured around the widest portion of the buttocks with the tape parallel to the floor. Waist hip circumference ratio (W/H Ratio) was calculated as WC in cm divided by HC in cm. Cut off values for WHR is 0.90 for men and 0.80 for women [9]. The weight and standing height of all study subjects were measured by using calibrated weighing scale and

stadiometer with a fixed vertical backboard and an adjustable head piece respectively. BMI can be calculated by the present weight in kg divided by height² in metre. BMI can be expressed in the units of kg/m² (Table 1).

Quetlet Index

$$\text{BMI} = \text{weight (kg)} / \text{height}^2 \text{ (in metre)}$$

SAMPLE COLLECTION

For estimation of HbA_{1c}, 2 mL of blood was collected in EDTA anticoagulant vacutainer. Samples were processed & analysed on the same day. HbA_{1c} was determined by turbidimetric inhibition immunoassay (TINIA) for hemolyzed whole blood. Glycohemoglobin (HbA_{1c}) in the sample reacts with anti HbA_{1c} antibody to form soluble

antigen antibody complexes. Since the specific HbA_{1c} antibody site is present only once on the HbA_{1c} molecule, complex formation does not take place. The polyhapten react with excess anti HbA_{1c} antibodies to form an insoluble antibody polyhapten complex that can be measured turbidimetrically. [11]

STATISTICAL ANALYSIS

Primary outcome were calculated by applying Unpaired 't' test and secondary outcome were obtained by using two-tailed Pearson correlation between variables of prediabetic cases and controls by using the statistical package (IBM SPSS 20). Data were considered to be significant if $p < 0.05$ and highly significant with $p < 0.001$.

Table 1 WHO classification of BMI grading [10]

BMI (kg/m ²)	Classification
< 18.5	Underweight
18.5-24.9	Normal Weight
25.0-29.9	Overweight
30.0-34.9	Class I Obesity
35.0-39.9	Class II Obesity
≥ 40.0	Class III Obesity

Table 2 Data of study group

S. no.	Data	Cases (n = 30) mean ± SD	Control (n = 30) mean ± SD	p value
1.	BMI (kg/m ²)	27.01 ± 2.91	24.16 ± 1.25	0.001
2.	WHR	0.87 ± 0.38	0.80 ± 0.38	0.001
3.	HbA _{1c} (%)	5.94 ± 0.21	5.24 ± 0.32	0.001

RESULTS & OBSERVATIONS

In the present study, out of 30 cases, 11 (37%) were normal, 13 (43%) were overweight and 6 (20%) were obese. Out of 30 controls, 20 (67%) were normal while 10 (33%) were overweight. 63% of cases had increased BMI that is much higher than 33% of controls having increased BMI (Table 2).

WHR showed statistical significant difference between cases (mean 0.87 ± 0.38) and controls (mean 0.80 ± 0.38) with p value = 0.001. Out of 30 cases, 27 (90%) had increase WHR while 3 (10%) had normal WHR. Out of 30 controls, 13 (43%) had increase WHR while 17 (57%) had normal WHR. So, 90% of cases had increase WHR in comparison to 43% of controls.

TWO-TAILED PEARSON'S CORRELATION BETWEEN PARAMETERS

In the present study, it was found that HbA_{1c} had positive correlation with BMI as well as WHR (Table 3, Figure 2A and 2B).

DISCUSSION

Development of preDM is linked to environmental factors such as physical inactivity but the subsequent development of diabetes is affected by combination of genetic and environmental factors [7]. Adverse environmental factors or disease can cause cells to fail to respond to insulin leading to insulin resistance (IR). Once IR develops, the body cells fail to respond to insulin and are unable to use it effectively leading

to development of IGT. When the condition develops further, apoptosis of islet cells occurs and glucose metabolism is disrupted leading to clinical DM [2].

In the present study, 63% of cases had increased BMI in comparison to 33% of controls having increased BMI. HbA_{1c} had significant positive correlation with BMI and WHR. Our observation is supported by study done by Li et al and Abtahi et al.

Li et al reported a positive correlation between HbA_{1c} and BMI in preDM. It is found that oxidative stress is a key determinant of glycation of hemoglobin leading to increase HbA_{1c} levels with elevated oxidative stress in nondiabetic subjects. Oxidative stress affects HbA_{1c} level through two ways. Firstly, the glycation of hemoglobin is a two step Maillard reaction involving the initial formation of a labile Schiff base and a subsequent Amadori rearrangement. Oxidative stress facilitates the autoxidation of glucose to dicarbonyl intermediates in an early step of the Maillard reaction and thus enhancing the glycation of proteins. Secondly, oxidative stress results in insulin resistance within adipose and skeletal muscle tissues and subsequent development of hyperglycemia which will further increase the oxidative stress [12].

Lipid peroxidation also affects glycation of hemoglobin independent of glucose concentration. Therefore, oxidative stress may partly explain the discordance between HbA_{1c} levels and blood glucose diagnosing diabetes and preDM.

Table 3 Correlation of HbA1c with different parameters

S. no.	Parameters	Correlation coefficient (r)	p value
1.	HbA _{1c} Vs BMI	0.583	0.001
2.	HbA _{1c} Vs WHR	0.495	0.005

Figure 2A Graph showing the correlation between HbA_{1c} and BMI

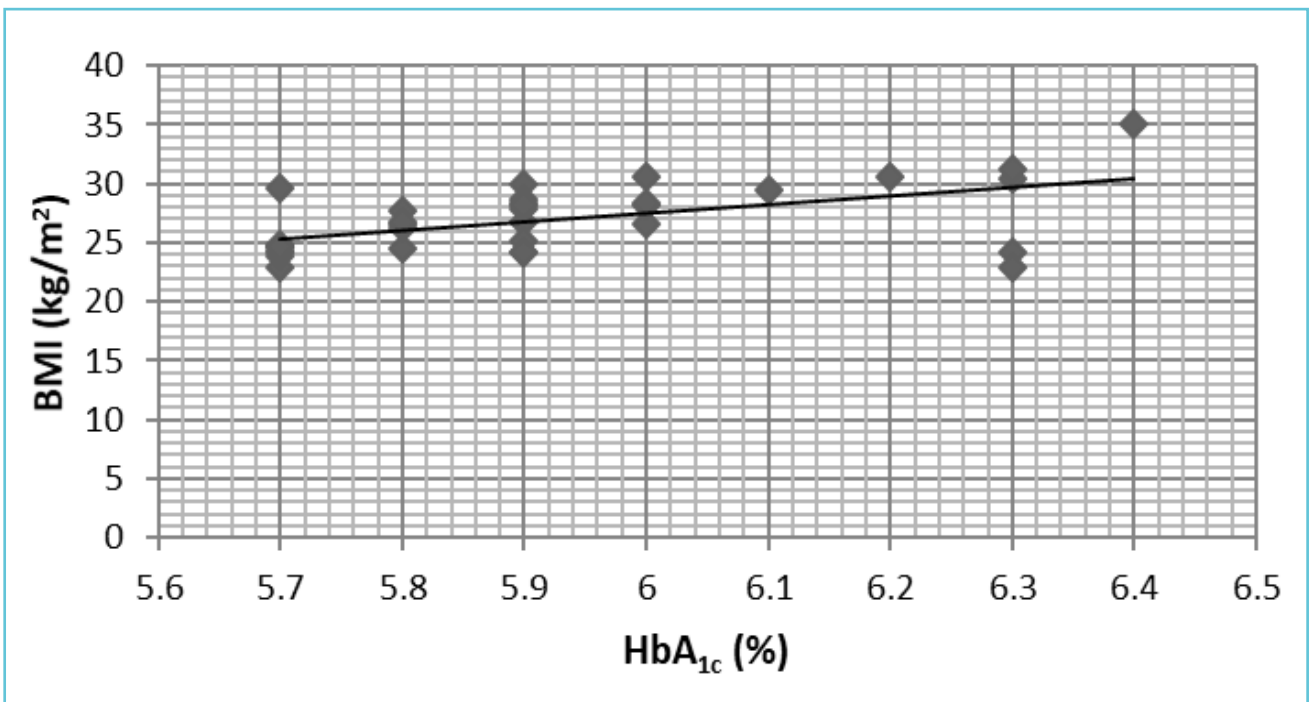
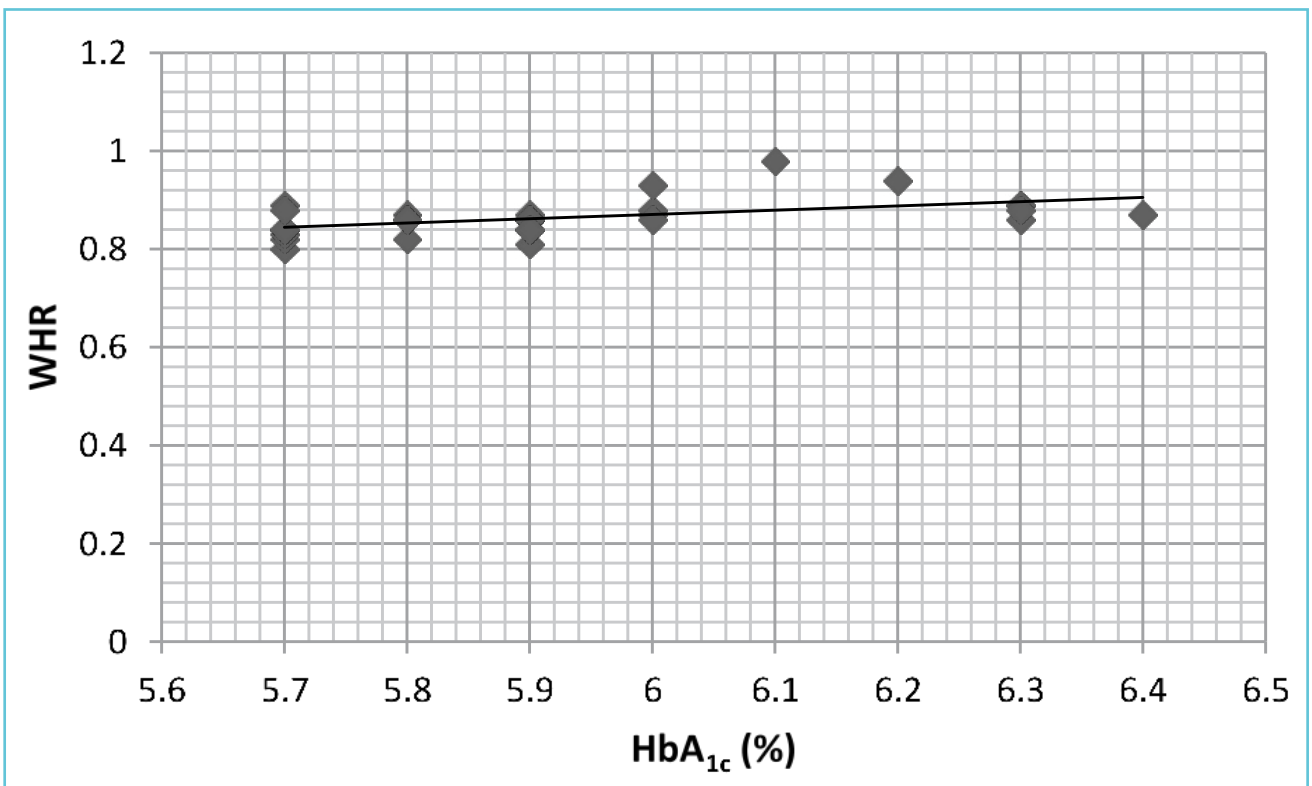


Figure 2B Graph showing the correlation between HbA_{1c} and WHR



Obesity has been reported as a strong independent predictor of systemic oxidative stress. Thus the association between BMI and HbA_{1c} is mediated by oxidative stress.

Obesity can induce systemic oxidative stress leading to increased glycation of hemoglobin independent of glucose levels. Thus HbA_{1c} concentration may be disproportionately elevated at a given glycemic level in obese subjects. So, HbA_{1c} cannot reflect the real concentration of glucose in obese subjects [13,14].

Abtahi et al observed that the prevalence of preDM was higher in obese person having higher range of waist circumference, WHR and BMI. Body weight is determined by many factors such as genetic, behavioral, cultural, socio-economic, physical inactivity, diet and psychosocial factors. Excess body weight is a risk factor for a variety of health hazards like DM, preDM and cardiovascular disease. It was concluded that people with lower BMI are less susceptible for development of DM & preDM and obese people have higher prevalence of abnormal blood glucose levels [15].

Various studies have shown that one to three quarters of subjects with IGT develop diabetes within a decade of discovery of IGT and annual progression rates from IGT to diabetes range from 1 to 10%. Thus by slowing the progression, the incidence of diabetes would be reduced and the onset of its complications would be prevented or delayed [16-19]. Early intervention is required to improve the progression of the complications and reduce the cost of disease in the long term. A sedentary lifestyle increases the risk for development of IR. Energy expenditure of 500 kcal/week decreases risk of developing type 2 DM by 6%. According to one study, vigorous exercise at least once a week reduces the risk of type 2 DM in women by 33% [2].

According to the Da Qing study exercise advice (with or without dietary advice) appears more

effective than dietary advice alone. Exercise increases insulin mediated glucose disposal in muscles. Although in humans low dietary fat content does not influence insulin mediated glucose disposal but hypocaloric diet leading to weight loss is associated with improved insulin mediated glucose disposal and reduction of glycemia. Thus, these interventions lead to reduce IR, slows the progression of glucose intolerance and arrests or delays β cell deterioration [20].

CONCLUSION

BMI and WHR has a role in glycation of hemoglobin and obesity is a preventable risk factor for the development of prediabetes and its further consequences.

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