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Original Article

Effect of varying levels of Glycemia on CA-19.9

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ABSTRACT

***Objective*:** To compare differences in CA-19.9 levels among participants with and without Type 2 diabetes mellitus and to correlate increasing glycemia levels and HbA1c with CA-19.9

***Study Design*:** Comparative cross-sectional study

***Place and Duration of Study*:** Department of Chemical Pathology, Combined Military Hospital, Multan Pakistan, from Feb to Aug 2022.

***Methodology*:** One hundred thirty-one patients with diabetes and without diabetes were enrolled. CA-19.9, fasting plasma glucose, HbA1c, amylase, lipase, and anthropometric parameters were assessed. Patients with diabetes were divided into three groups based on FPG and HbA1c levels to investigate the relationship between CA-19.9 and glycemic status.

***Results*:** There was no significant difference among CA-19.9 of Controls and patients with diabetes (19.45±14.89 versus 15.83±13.98, p=0.155). FPG and HbA1c showed a moderate positive correlation to CA-19.9 (r = 0.283, p= 0.001 and r= = 0.305, p<0.001 respectively). Inter-group comparison (post-hoc analysis) showed a significant rise of CA-19.9 with increasing HbA1c in groups with HbA1c 5.61-7.0% Vs >7.0% (p=0.020), HbA1c <5.6 %Vs >7.0%(p=0.037) and with increasing FPG in groups with FPG 5.6-7.0 mmol/L Vs >7.0 mmol/L (p=0.005).

***Conclusion*:** The glycemic status of patients with diabetes can influence their serum CA-19.9 levels, and glycemic control should be considered while interpreting these levels in such patients. T2DM patients with poor glycemic control have a higher CA of 19.9 than those with better control.

Keywords: CA-19.9, Fasting plasma glucose, HbA1c, Type-2 Diabetes Mellitus

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INTRODUCTION

Carbohydrate Antigen 19.9 (CA-19.9) is a tumour -associated antigen which is used not only in the diagnosis of pancreatic cancer but is also elevated in various gastrointestinal conditions, such as colorectal, ovarian, gastric, hepatocellular and cholangio-cellular carcinomas as well as in inflammatory conditions of the hepatobiliary system,[1] non-malignant conditions such as obstructive jaundice, cystic fibrosis and in Hashimoto thyroiditis.[2,3]

Type 2 diabetes mellitus (T2DM) is an expanding global health problem, where about 1 in 11 adults suffer from this disease (90% have T2DM).[4,5] Globally, the incidence of diabetes increased from 11.3 million in 1990 to 22.9 million in 2017, with a 102.9% increase. The current prevalence of this disease in our country is 11.77%. In addition to posing a high risk for both microvascular and macrovascular complications, this " lifestyle" disease has been claimed to be a risk factor for pancreatic cancer, which has one of the lowest survival rates of all cancers.[6,7] The association between diabetes and pancreatic cancer remains controversial, with a few studies finding a 2-fold increased risk of pancreatic cancer among diabetic patients of 5 years duration, and a significant positive correlation of CA-19.9 with FPG, to those documenting that cancer preceded and caused diabetes.[8,9] Several novel medications are in development, intending to halt the progressive pancreatic β-cell failure characteristic of T2DM. Despite an extensive search of the literature, no local study determining the association of the effects of glycemia on CA-19.9 levels in our population was found. Therefore, it is pertinent to evaluate CA-19.9 levels in Type 2 DM patients and define the normal cut-off of CA-19-9 for pancreatic dysfunction in such patients to eliminate unnecessary additional interventional approaches.[10]

Considering the paucity of local data comparing CA-19.9 levels in T2DM, conflicting data on the subject, and the possible confounding role of CA-19.9

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in using it as a tumour marker in diabetic subjects, we compared differences in CA-19.9 levels among participants with or without diabetes mellitus. In addition, we aimed to correlate glycemia and HbA1c levels with CA-19.9 levels in diabetic subjects. The main outcome measures in our study were the presence or absence of diabetes, HbA1c, fasting glycemia, body mass index (BMI) and waist-to-hip ratio (WHpR).

METHODOLOGY

The comparative cross-sectional study was conducted at the Department of Pathology, Combined Military Hospital, Multan Pakistan, from February to August 2022 after approval by IERB (ERB No.37/2022 dated 03-01-2022). The sample size was calculated using the WHO calculator with 16.9% prevalence of T2DM in Pakistan.[11]

Inclusion Criteria: Patients of either gender, aged 30 to 80 years with diabetes mellitus, reporting exact medical fasting at laboratory reception, were included.

Exclusion Criteria: Patients who had a previously known malignancy, hypertension, ischemic heart disease, autoimmune disorder, liver /renal dysfunction, pregnancy, acute or chronic ailments, inappropriate fasting or further unwillingness to participate were excluded.

The study subjects were initially briefed about the study and enrolled after getting their consent to participate. Finally, selected individuals were explained in detail the study requirements, including blood sampling requirements, investigations to be conducted, patient confidentiality, and purpose of use of data for publication. Finally, selected individuals were formally interviewed as per the formatted study questionnaire and signed a formal written consent in the language they understood. The interpreter's help was sorted as and when needed. After history, these patients were examined for blood pressure and various new and conventional anthropometric measurements, including weight, height and waist/hip circumference.[12] Blood pressure (BP) was measured using a standard mercury manometer with the participant sitting for 5 min before measurement; the average of two measurements was recorded.

Blood sampling was done for FPG, lipid parameters, HbA1c, quantitative CRP, AST, ALT, CA-19.9, amylase and lipase. Subjects (n=25) with hemolysed, chylous or icteric samples were requested to visit the lab for repetition, and those who could only visit at the end of March 2022 were also excluded from the study (n=10). Plasma glucose analysis was done by hexokinase method; enzymatic colourimetric methods measured lipid parameters while ALT, AST, Amylase and Lipase were analysed by UV method on a fully automated chemistry analyser (c501-Roche Diagnostics). HbA1c and CRP (quantitative) were also analysed on c501-Roche. CA-19.9 levels were measured using the electrochemiluminescence method (Cobas e411, Roche Diagnostics). Normal ranges for serum CA-19.9 level were 0 to 35 U/mL, and the levels above the higher range were considered elevated. We divided diabetic subjects into three groups based on HbA1c <5.6%, 5.6-7.0% and >7.0%. Similar groups were formulated for fasting plasma glucose <5.6 mmol/l, 5.6-7.0 mmol/L and >7.0 mmol/L.[13]

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Pearson's correlation test and ANOVA were applied to explore the inferential statistics. The General Linear Model was used to evaluate a rise in CA-19.9 (Dependent variable) with an increase in both HbA1c (Fixed factor) and age in years (Random factor).

RESULTS

Our study sample included 71(54.2%) participants without diabetes and 60(45.8%) known patients with T2DM. The mean age among patients with diabetes and controls was 42.55±9.81 years and 39.51±9.85 years, respectively. There were 40(30.5%) female and 91(69.5%) males. Table-I provides the differences between age, HbA1c, fasting plasma glucose (FPG), BMI and WHpR between patients who have been known diabetics and otherwise. BMI, FPG and HbA1c were significantly higher in the study group than in the controls. There was no significant difference among CA-19.9 levels of Control groups and patients with diabetes, although levels were slightly higher among the control group (19.45±14.89 Vs 15.83±13.98, p=0.155). Inter-group comparison (post-hoc analysis) of CA 19.9 levels showed a signifi-cant rise of CA 19.9 with increasing HbA1c in groups with HbA1c 5.61-7.0% Vs >7.0% (p=0.020) and HbA1c <5.6% Vs >7.0%(p=0.037) (Table-II). A similar signifi-cant rise in CA-19.9 was seen with increasing FPG in groups with FPG 5.6-7.0 mmol/L Vs >7.0 mmol/L (p=0.005) (Table-III). FPG and HbA1c showed a moderate positive correlation to-CA 19.9 levels (r=0.283, p= 0.001 and r=0.305, p<0.001 respectively) as depicted in Table-IV.

The General Linear Model (GLM) depicted that HbA1c levels were a contributor towards a rise in CA-19.9 (p=0.014) independent of the subject's age (p=0.602) (Figure).

Table-I: Differences of Age, HbA1c, Fasting Plasma Glucose (FPG), Body Mass Index, CA 19.9 (u/ml) between Patients with T2DM (n=60) and Controls (n=71)

Parameter	Presence or absence of Diabetes	Mean+SD	*p*-value
Age (years)	Controls	39.51+9.85	0.080
	Patients	42.55+9.81	
Systolic BP (mm of Hg)	Controls	117.50+8.98	0.165
	Patients	120.40+14.25	
Diastolic BP (mm of Hg)	Controls	78.80+7.04	0.316
	Patients	80.08+7.51	
Body Mass Index (BMI)	Controls	24.98+3.921	0.030
	Patients	26.51+4.04	
Fasting plasma glucose (mmol/L)	Controls	6.20+2.61	0.001
	Patients	8.37+4.40	
HbA1c (%)	Controls	6.76+2.55	0.029
	Patients	7.72+2.34	
CA-19.9 (u/ml)	Controls	19.45+14.89	0.155
	Patients	15.83+13.98	

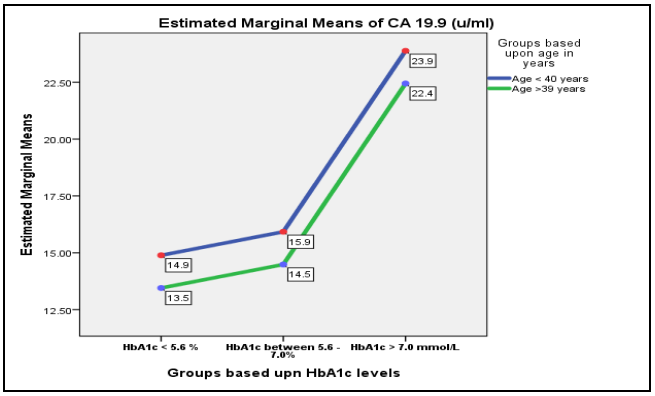

Figure: General Linear Model (GLM) depicting a rise in CA 19.9 (Dependent variable) with increase in both HbA1c, (Fixed factor) and age in years (Random factor) depicting age (p=0.602) and HbA1c (p=0.014) [Model significance=0.499]

DISCUSSION

While many studies have focused on factors affecting CA-19.9 levels, only a few have explored the relationship between type 2 DM and CA-19.9 and have obtained varied results.[14,15] Some have even proposed using a higher cut-off value of CA-19-9 in people with diabetes to differentiate benign and malignant pancreatic disease. Benhamou *et al*.[17]

Table-II: One Way ANOVA Output Among Study Groups Based Upon Increasing Level of HbA1c (n=131)

Parameters	HbA1c<5.6% (n=40)	HbA1c 5.61-7.0% (n=44)	HbA1c >7.0% (n=47)	*p*-Value
Age (years)	36.40±6.96	38.11±5.75	47.34±11.24	<0.001
Inter-Group Comparison Table (Post Hoc Analysis) for age				
Age (Years)	HbA1c<5.6 % vs HbA1c 5.61-7.0 %	HbA1c 5.61-7.0 % vs HbA1c > 7.0 %	HbA1c <5.6 % vs HbA1c > 7.0 %	
	p-value= 0.640	*p*-value<0.001	*p*-value<0.001	
Fasting plasma glucose (mmol/L)	4.85±0.64	5.78±1.35	10.52±4.30	<0.001
Inter-Group Comparison Table (Post Hoc Analysis) for Fasting Plasma Glucose				
	HbA1c<5.6% vs HbA1c 5.61-7.0 %	HbA1c 5.61-7.0% vs HbA1c > 7.0%	HbA1c <5.6% vs HbA1c>7.0%	
Fasting plasma glucose (mmol/L)	*p*-value=0.266	*p*-value<0.001	*p*-value<0.001	
Waist-to-hip ratio (cm)	0.91±0.09	0.94±0.07	1.02±0.56	0.327
Inter-Group Comparison Table (Post Hoc Analysis) for WHpR				
Waist-to-hip ratio (cm)	HbA1c<5.6% vs HbA1c 5.61-7.0%	HbA1c 5.61-7.0% vs HbA1c > 7.0%	HbA1c <5.6 % vs HbA1c > 7.0 %	
	p-value=0.911	*p*-value=0.323	*p*-value=0.547	
Body Mass Index	28.84±3.35	25.93±4.08	26.17±4.50	0.285
Inter-Group Comparison Table (Post Hoc Analysis) for BMI				
Body Mass Index	HbA1c<5.6% vs HbA1c 5.61-7.0%	HbA1c 5.61-7.0% vs HbA1c > 7.0%	HbA1c <5.6% vs HbA1c > 7.0%	
	p-value=0.440	*p*-value=0.289	*p*-value=0.960	
CA-19.9	14.93±13.06	15.40±13.45	22.81±15.60	0.011
Inter-Group Comparison Table (Post Hoc Analysis) for CA 19.9				
CA-19.9	HbA1c<5.6% vs HbA1c 5.61-7.0%	HbA1c 5.61-7.0% vs HbA1c > 7.0%	HbA1c <5.6% vs HbA1c > 7.0%	
	p-value=0.957	*p*-value=0.020	*p*-value=0.037	

Table-III: One way ANOVA Output Among Study Groups Based Upon Increasing Level of Fasting Plasma Glucose (FPG) in mmol/L (n=131)

Parameters	FPG<5.6 (n=65)	FPG 5.61-7.0 (n=20)	FPG > 7.0 (n=46)	*p*-Value
Age (years)	35.67±6.02	42.70±7.71	47.52±11.01	<0.001
Inter-Group Comparison Table (Post Hoc Analysis) for age				
Age (Years)	FPG<5.6 to FPG 5.61-7.0	FPG 5.61-7.0 to FPG >7.0	FPG<5.6 vs FPG >7.0	
	p-value= 0.004	*p*-value<0.001	*p*-value=0.082	
HbA1c (mmol/L)	5.64+0.84	6.56+1.18	9.69+2.50	<0.001
Inter-Group Comparison Table (Post Hoc Analysis) for Fasting Plasma Glucose				
	FPG<5.6 to FPG 5.61-7.0	FPG 5.61-7.0 to FPG >7.0	FPG<5.6 vs FPG >7.0	
HbA1c (%)	*p*-value= 0.079	*p*-value<0.001	*p*-value<0.001	
WHpR(cm)	0.92+0.08	0.94+0.06	1.02+0.56	0.305
Inter-Group Comparison table (Post Hoc Analysis) for WHpR				
WHpR(cm)	FPG<5.6 to FPG 5.61-7.0	FPG 5.61-7.0 to FPG >7.0	FPG<5.6 vs FPG >7.0	
	p-value=0.974	*p*-value= 0.282	*p*-value= 0.649	
BMI	24.89+3.83	26.89+3.75	26.27+4.31	0.071
Inter-Group Comparison Table (Post Hoc Analysis) for BMI				
BMI	FPG<5.6 to FPG 5.61-7.0	FPG 5.61-7.0 to FPG >7.0	FPG<5.6 vs FPG >7.0	
	p-value= 0.126	*p*-value= 0.174	*p*-value= 0.831	
CA 19.9	14.61+12.72	15.66+12.94	22.22+15.60	0.006
Inter-Group Comparison Table (Post Hoc analysis) for CA 19.9				
CA 19.9	FPG<5.6 to FPG 5.61-7.0	FPG 5.61-7.0 to FPG >7.0	FPG<5.6 vs FPG >7.0	
	p-value= 0.954	*p*-value= 0.005	*p*-value= 0.116	

Waist-to-hip ratio (WHpR), Body mass index (BMI)

Table- IV: Pearson's Correlation Between CA 19.9 with Fasting Plasma Glucose (FPG), HbA1c, BMI, WHpR and Age (n=131)

Parameters		CA 19.9 (u/ml)
Age (years)	Correlation Coefficient	0.165
	p-Value	0.059
	n	131
Waist to Hip Ratio (WHpR)	Correlation Coefficient	-0.105
	p-Value	0.231
	n	131
Body Mass Index (BMI)	Correlation Coefficient	0.043
	p-Value	0.625
	n	131
Fasting plasma glucose (mmol/L)	Correlation Coefficient	0.283**
	p-Value	0.001
	n	131
HbA1c (%)	Correlation Coefficient	0.305**
	p-Value	<0.001
	n	131

***indicates statistical significance*

investi-gated the relationship between the CA-19-9 and metabolic control of diabetes in 51 adult patients. They concluded that CA-19-9 in diabetic patients is raised in acute metabolic situations, which correlated very well with blood glucose concentration. It was suggested that glucose toxicity may play a role in high serum CA-19-9 levels in these patients. Our study did not demonstrate any significant difference in CA-19.9 levels of T2DM patients compared to controls (*p*=0.155), although levels were relatively lower in the former. One of the possible reasons for these findings could be that we did not assess levels in relation to microvascular complications in type 2DM. Gul *et al*.[18] had previously demonstrated that serum CA-19.9 level was related to microvascular complications in type 2 DM patients.

Similarly, Yu *et al*. investigated the relation of serum CA-19.9 levels to the clinical characteristics and chronic complications of patients newly diagnosed with T2DM.[19] Moreover, interestingly, research has demonstrated that almost 10% of the population who are Lewis genotype negative are unable to express CA-19.9, so this could be a cause of the discrepant finding. Lewis's blood group status was not determined and was beyond the scope of the current study.

We measured CA-19.9 levels only once at baseline, so a single baseline finding cannot be generalised for future follow-up levels as evidence suggests that although some researchers had found CA-19.9 levels to be significantly elevated in T2DM patients, those who did long-term follow-up found that in some patients with no plausible explanation for raised CA-19.9 levels, the levels normalised on follow-up.[20] However, Our study revealed a moderate positive correlation of CA-19.9 with both FPG and HbA1c.

LIMITATION OF STUDY

CA-19.9 was measured only once at baseline; hence, this study could not account for its within-individual variability. Despite the limitations, the authors firmly believe that this local study has generated sufficient evidence for planning long-term epidemiological studies that will serve as a gateway to develop appropriate cut-offs for CA19.9 levels in diabetic patients within our setup.

CONCLUSION

The glycemic status of diabetic patients can influence their CA-19.9 levels, and glycemic control should be considered while interpreting these levels in such patients.T2DM patients with poor glycemic control have higher CA-19.9 than those with better control.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AH & JH: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

IR & SHK: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

QA & SZ: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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