ORIGINAL ARTICLE

METFORMIN MODULATES SERUM CA 19-9 AND ITS RELATED FACTORS MORE EFFECTIVELY THAN GLIBENCLAMIDE IN DIABETIC PATIENTS

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ABSTRACT

Objective: CA 19-9 is a marker that shows the relapse of tumors. Raised CA 19-9 in diabetes mellitus cases and the effect of hypoglycemic agents on the marker prompted us to compare the effect of metformin and glibenclamide on CA 19-9 levels in patients with diabetes mellitus.

Material & Methods: It is a randomized control trial (RCT). Normal control (group A1) included 40 staff members from KTH/KMC. A total number of 79 patients with type 2 diabetes mellitus were randomized into two groups; group A2 (n=39) who took metformin (500 mg/day) and group A3 (n=40) received glibenclamide (2.5 mg/day). The study was conducted for 6 months and variables including fasting blood glucose, blood lipids, plasma sialic acid, HbA1-c, insulin and C-peptide, CA 19-9, and insulin resistance were measured initially and at week 10.

Results: At the endpoint, there were reductions in FBG and HbA1C levels among metformin and glibenclamide groups compared to baseline ($p<0.003$, $p<0.001$, and $p<0.05$, $p\leq0.05$ respectively). The metformin group also showed a significant reduction in CA 19-9 level from baseline ($p\leq0.05$) and the same was the case for PSA ($p<0.04$) but the effect of glibenclamide on CA 19-9 was negligible and PSA slightly increased (deteriorated) from baseline. Between groups comparison at the endpoint showed a significantly high level of PSA in the glibenclamide group than in the metformin group ($p\leq0.05$). Insulin, HOMA-IR, and C-peptide levels improved in both groups from baseline. The favorable effects of metformin on blood lipids and body weight were more than glibenclamide. Correlation studies revealed a significantly positive correlation ($p\leq0.05$) of CA 19-9 with FBG, HbA1-c, PSA, insulin, and triglyceride levels in the metformin group, and FBG, HbA1-c, PSA, and total cholesterol in glibenclamide group.

Conclusions: From these findings, we suggest greater beneficial effects of metformin on CA 19-9 and other related factors than glibenclamide.

Keywords: CA 19-9, Diabetes mellitus, Glibenclamide, Metformin.

This article may be cited as: Waqas M , Idrees M , Qayyum S, Ihtesham M, Shafi M, Rahman IU. Metformin modulates serum CA 19-9 and its related factors more effectively than glibenclamide in diabetic patients. J Med Sci 2022 July;30(3):212-215

INTRODUCTION

CA 19-9 is a tumor-associated carbohydrate antigen, the serum level of which is elevated among patients with cancer of the ovaries, pancreas, colon and rectum, upper gastrointestinal tract, and liver. It is a tetrasaccharide most commonly attached to O-glycans on the cell surface. Although it is clinically used as a tumor marker of the gastrointestinal tract, its diagnostic sensitivity and specificity are highest for pancreatic cancer. Increased levels are also found in cholecystitis and pulmonary sequestration as well as impaired renal and hepatic functions[1-4].

Literature shows that the levels of CA 19-9 are increased in patients with type 2 diabetes mellitus because of non-tumor factors such as uncontrolled hyperglycemia, lipidemia, and impaired function of pancreatic β-cells. Recently it has been observed that CA 19-9 is correlated with the duration and severity of diabetes as well as the presence of diabetic complications and that the serum concentration is affected by insulin treatment[5,6]. However, the effect of the treatment algorithm on serum CA 19-9 is not properly defined in the literature.

Hence this study was arrangedtoo determine changes in CA 19-9 concentrations and its related factors among type 2 diabetics who are using metformin or glibenclamide.

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Date Received: 24-08-2022
Date Revised: 06-09-2022
Date Accepted: 22-09-2022

MATERIALS AND METHODS

Of the 203 subjects in Khyber Teaching Hospital (KTH), Peshawar for medical checkups between July 2020 and December 2020, 112 were diagnosed as having type 2 diabetes mellitus without diabetic complications. Seventy-nine met the eligibility criteria and were randomized into the metformin group (n=39) and the glibenclamide group (n=40) (Table1).

Inclusion criteria: Newly diagnosed cases of type 2 Diabetes mellitus with fasting blood glucose of above 126 mg/dl, aged 30-60 years, and having normal renal and liver profiles.

Exclusion criteria: Patients already using glucose-lowering medicine or chemotherapy, those having cancers, diabetic complications (microvascular/macrovascular), gall bladder/thyroidal/GI diseases, genital diseases, pancreatitis, fatty liver, or any other condition causing elevation of CA 19-9.

This randomized controlled parallel-group trial was carried out for 24 weeks. Thirty-three subjects did not meet the inclusion criteria so they were excluded. Seventy-nine participants were randomized into 2 groups; group A2 were given metformin 500 mg/day (26 males/13 females), group A3 received glibenclamide 2.5mg/day (29 males/11 females). Forty healthy subjects (28 males/12 females) from the staff of KTH/KMC, Peshawar served as normal control (group A1).

Fasting (venous) blood specimen was obtained after 12-14 hours of overnight fasting. Different biochemical parameters including fasting blood glucose (FBG), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) concentrations were determined with OPTIZEN autoanalyzer (2120) using commercially available kits. HbA1c was detected by the Fast ion-exchange resin separation method. Insulin and C-peptide (CP) were determined using the biochemical immune analyzer. CA 19-9 levels were determined by radioimmunoassay. Serum/plasma sialic acid assay (SSA)/(PSA) was performed by using the Warren method. A white blood cell (WBC) count was performed using a hematology analyzer. For insulin resistance, a homeostasis model assessment was used and calculated as Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) = Insulin (μLU/ml) X FBG (mmol/L)/22.5.

Quantitative variables were analyzed using mean and standard deviation, while qualitative variables with frequency and percentages. SPSS 21.0 was used to compile results. P-value < 0.05 was taken as significant. Clinical characteristics of normal controls and diabetic patients were compared using the Independent sample t-test. Mann-Whitney test and Kruskal Wallis test were applied considering the data was not normally distributed among the study groups.

RESULTS

Table 1 and Table 2 show the characteristics of study groups and changes in metabolic variables in diabetic subjects after treatment with metformin or glibenclamide respectively. Table 3 shows the correlation of CA 19-9 with metabolic variables after controlling for age, sex, and BMI. There was positive correlation with HbA1-c ($r=0.171$, $P<0.05$), PSA ($r=0.163$, $P\leq0.05$), insulin ($r=0.151$, $P\leq0.005$) and TG ($r= 0.351$, $\leq P<0.04$) among patients on metformin monotherapy and HbA1-c ($r=0.129$, $P\leq0.05$), PSA (0.155, $P\leq0.05$) and TC ($r=0.389$, $P<0.05$) among patients on glibenclamide monotherapy.

Data are mean ±SD Group A1= Normal control; Group A2= Metformin treated; Group A3= Glibenclamide treated[¤] $p\leq0.05$ vs. Normal control

DISCUSSION

Research shows elevated CA 19-9 concentration in patients of Type II diabetes mellitus than normal control subjects. The exact mechanism remains unclear but several factors are believed to be responsible for this elevation such as hyperglycemia, hyperlipidemia, impaired β-cell function and so forth[5, 7-9]. There is impaired catabolism of CA 19-9 due to the hyper glycation of proteins responsible for its catabolism[6]. A positive association between blood glucose and CA-19-9 and a decline in its concentration with diabetes treatment has been reported previously[10]. Recently, Tu et al[11] have shown that low CA 19-9 is associated with alleviation of insulin resistance in obese patients who are diabetic. Based on these observations, we conducted a study to observe and compare the level of CA 19-9 in newly diagnosed diabetics following metformin and/or glibenclamide monotherapy. The patients on metformin monotherapy manifested a significantly low level of CA 19-9 along with PSA from baseline whereas the patients on glibenclamide monotherapy failed to show significant improvement either in CA19-9 or PSA concentrations, rather the PSA level further deteriorated in glibenclamide group. These findings are well supported by our previous study showing a significantly positive effect of metformin on PSA in type 2 diabetics[12]. We also found a significantly positive correlation of CA 19-9 with HbA1-c, PSA, TC, and HDL-c in diabetic patients and this is in agreement with the previous reports[11]. Based on these findings, we suggest that hyperglycemia and hyperlipidemia induced hyper sialylation is believed to be responsible for increased synthesis of CA 19-9 in diabetics, and a decrease in the process of sialylation by metformin may contribute to a reduction in serum CA 19-9 concentration.

CA 19-9 is released by the pancreas and its level in the body is elevated in many cancerous conditions but has a high sensitivity (70-90%) and specificity (68-91%) for

Table 1: Baseline features of normal control, diabetic patients on metformin and diabetic patients on glibenclamide.

Variables	Group A1	Group A2	Group A3
N	40	39	40
Age	49.50±6.30	51.10±7.80	50±6.10
Sex (M/F)	28/12	26/13	29/11
BMI (Kg/m2)	21.60±0.90	25.70±1.15¤	25.20±0.80¤
Smoking (Cig/day)	35	28	22
Time since diagnosis of diabetes (y)	-	2.1±0.50	2.7±0.10
FBG (mmol/L)	5.09±0.35	9.11±2.60¤	9.24±2.14¤
HbA1-c (%)	6.05±0.70	8.50±0.90¤	8.30±0.95¤
CA 19-9 (U/L)	8.11 (4.77-13.8)	10.58±1.05¤	10.45±1.30¤
SSA/PSA (mmol/L)	2.01±0.10	2.40±0.26¤	2.39±0.19¤
Insulin (μLU/ml)	17.88±4.01	10.95±8.01¤	11.50±16.30¤
HOMA-IR	4.11±1.10	4.97±8.20¤	4.56±11.45¤
CP (ng/ml)	2.59±0.81	1.89±0.95¤	2.01±1.05¤
TC (mmol/L)	4.21±0.78	5.50±1.45¤	4.90±0.95
HDL-c (mmol/L)	1.40±0.25	1.07±0.30	1.22±0.41
LDL-c (mmol/L)	2.44±0.35	2.69±0.68¤	2.54±0.70
TG (mmol/L)	0.78±0.60	2.10±0.45	1.82±0.70

Data are mean ±SD

Group A1= Normal control; Group A2= Metformin treated; Group A3= Glibenclamide treated¤p≤0.05 vs. Normal control

Table 2: Changes in various biochemical/metabolic variables of diabetic patients on metformin and/or glibenclamide monotherapy

Variables	Group A1	Group A2
BMI (Kg/m2)	25.35±0.55 (−0.35)	25.50±0.80 (+0.30)
FBG (mmol/L)	5.90±1.35 (−3.21) *	6.05±1.10 (−3.19) *
HbA1-c (%)	7.60±0.60 (−0.90) *	7.45±0.80 (−0.85) *
CA 19-9 (U/L)	9.11±1.40 (−1.46) *	9.77±1.85 (−0.68)
SSA/PSA (mmol/L)	2.15±0.13 (−0.25) *	2.42±0.21 (+0.03) †
Insulin (μLU/ml)	13.20±6.50 (+2.25)	13±7.90(+1.50)
HOMA-IR	4.60±8.50 (−0.37)	4.30±10.70 (−0.26)
CP (ng/ml)	2.15±0.66 (+0.26)	2.12±0.80 (+0.11)
TC (mmol/L)	4.55±0.74 (−0.95) *	4.91±0.70 (+0.01)
HDL-c (mmol/L)	1.24±0.45 (+0.17)	1.10±0.60 (−0.12)
LDL-c (mmol/L)	2.50±0.30 (−0.19)	2.61±0.55 (+0.07)
TG (mmol/L)	1.35±0.50 (−0.65) *	1.95±0.90 (+0.13) †

Data are mean ±SD Group A2= Metformin treated; Group A3= Glibenclamide treated

() Change from baseline

*P≤0.05 Baseline vs. Post-treatment

†P≤0.05 Group A2 vs. Group A3

Table 3: Partial correlation of CA 19-9 with metabolic variables in diabetic subjects on metformin or glibenclamide monotherapy after controlling for age, sex, and BMI

Variables	Group A2		Group A3	
	r	p	r	p
FBG (mmol/L)	0.151	<0.002	0.130	<0.001
HbA1-c (%)	0.171	<0.05	0.129	≤0.05
SSA (mmol/L)	0.163	≤0.05	0.155	≤0.05
Insulin (μLU/ml)	0.151	≤0.05	0.146	<0.06
HOMA-IR	0.209	<0.16	0.195	0.13
CP (ng/ml)	0.110	<0.21	0.108	<0.14
TC (mmol/L)	0.271	<0.11	0.389	<0.05
HDL-c (mmol/L)	-0.264	0.14	0.100	0.31
LDL-c (mmol/L)	0.31	<0.06	0.409	<0.23
TG (mmol/L)	0.351	≤0.05	0.293	<0.09

pancreatic cancer[3,13,14]. Sialic acid is an acetylated form of neuraminic acid. Its level in the blood rises in cancer and diabetic patients and is a reputable tumor marker as well as a cardiovascular risk factor[15, 16]. Studies indicate that sialic acid regulates vessel wall permeability. Raised levels of sialic acid are present in the vascular endothelium and type 2 diabetes-associated extensive microvascular damage may be responsible for its shedding into the circulation. The result is an increase in vascular permeability and high SSA concentrations[17, 18]. Our findings are further strengthened by the fact that the use of metformin is as-

sociated with longevity in diabetic patients who have pancreatic carcinoma. [19].

CONCLUSION

These findings suggest that metformin modulates CA 19-9 and its related factors more effectively than glibenclamide suggesting the former to be a preferred choice in the prevention of diabetic complications than the latter. Further multicentre studies are required on a large scale to validate the data regarding the effects of metformin in modulating CA19-9 and eventually preventing diabetic complications.

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CONFLICT OF INTEREST: Authors declare no conflict of interest

GRANT SUPPORT AND FINANCIAL DISCLOSURE: NIL

AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

Waqas M:	Conception, literature search and overall supervision
Idrees M:	Writing up
Qayyum S:	Data collection
Ihtesham M:	Statistical analysis
Shafi M:	Bibliography
Rahman IU:	Data collection

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.