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ORIGINAL ARTICLE

CA 19-9 is Associated with Poor Glycemic Control in Diabetic Patients: Role of Insulin Resistance

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SUMMARY

Background: **CA19-9 is considered a tumor marker. Reports have suggested higher CA19-9 levels in diabetic patients even with no malignancy. Our aim was to reveal the relation of CA19-9 with glycemic control in diabetic and non-diabetic subjects. For the first time we considered diabetes as an outcome based on a cut-off where the association of CA19-9 with diabetes is considerable.**

Methods: **The study was carried out at an outpatient metabolism clinic. A total of 422 consecutive participants were enrolled. Subjects with prior diagnosis of any cancer, renal, endocrine, or hepatic problems were not included. Age, gender, and medications as well as weight, height, and BMI were recorded. Creatinine, fasting plasma glucose (FPG), post-prandial plasma glucose (PPPG), fasting plasma insulin, HbA_{1c}, C-peptide, HOMA-IR, and CA 19-9 were measured.**

Results: **In all, 266 (63.03%) subjects had recently been diagnosed with diabetes. CA19-9 was significantly higher in the diabetic group (16.73 ± 13.83 vs. 11.93 ± 11.42, $p < 0.001$). BMI, waist circumference, FPG, and HbA_{1c} were higher in quartiles with greater CA19-9 levels. Number of diabetic subjects in each quartile had a stepwise increase (48%, 56%, 72%, and 77%, $p < 0.01$). FPG, PPPG, HbA_{1c}, and HOMA-IR were directly correlated with CA19-9 levels independent of age, gender, and BMI. We presume the 10.83 U/mL value for CA19-9 to be the optimal cut-off in indicating diabetes status (sensitivity: 0.63, specificity: 0.55).**

Conclusions: **Otherwise normal diabetic subjects have greater CA19-9 values. CA19-9 should be interpreted with regard to diabetes status. We suggest that CA19-9 levels above 10.83 U/mL in the absence of other pathologies are in favor of glycemic impairments. CA19-9 values greater than 34.30 U/mL may accompany an 84% frequency of diabetic subjects especially in settings such as referral metabolism clinics. CA19-9 values of less than 6.46 U/mL are likely to rule out the presence of diabetes, especially while testing in general population.**

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KEY WORDS

CA19-9, diabetes, tumor markers, glucose metabolism, insulin resistance

INTRODUCTION

CA19-9 is a high molecular weight glycolipid. Formed by altered glycosylation, it is considered a cancer marker [1]. CA19-9 is mainly derived from pancreatic and billiary structures [2]. However, other normal tissues including colonic, salivary, and endometrium synthesize it as well [2]. As a tumor marker, it was first introduced using monoclonal antibodies against serum of patients with colorectal cancer [3]. Since then, it has been widely used as a marker in a variety of gastrointestinal, hepatobilliary and even urothelial cancers [4-7]. Among all, pancreatic cancer is more emphasized [8]. Apart from malignancies, CA19-9 levels are also associated with certain benign conditions including bronchioalveolar pathologies, cirrhosis, pancreaticobilliary disorders and

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even heavy tea consumption [6,9-14].
Pancreatic cancer and chronic pancreatitis related diabetes are reported to be accompanied by elevated CA19-9 levels [15]. In these cases, the association of CA19-9 with the presenting diabetes is clarified [11,15]. However, studies indicate that the CA19-9 association with diabetes is not limited to the above mentioned conditions. Previous reports have suggested higher CA19-9 levels in diabetic patients with no malignancy [9,13], but with deprived metabolic compensation and poor glycemic control [16,17]. On the other hand diabetes is of growing importance due to its prevalence and the health impact it imposes [18]. Diabetes and its underlying factors such as obesity are associated with increased risk of a variety of malignancies [19,20]. Specifically, diabetes is correlated with increased risk of pancreatic cancer [21]. Therefore, investigating the elevation of CA19-9 and the corresponding diabetic status is crucial to determine a more precise interpretation.
Debates still persist on whether diabetes and its predictors are also accompanied with a presence of high levels of CA19-9 [22-24], especially in normal ranges of CA19-9 where less investigation has been performed. Moreover, the possible contributors and the extent of their associations with elevated CA 19-9 levels have not been elucidated yet.
Our aim was to comprehensively reveal the relation of CA19-9 with diabetes. Further, to determine the independently associated variables among related factors. Finally, for the first time, we considered diabetes as an outcome to determine the percentile values for CA19-9 and derive a cut-off where the association of CA19-9 with diabetes is considerable.

MATERIALS AND METHODS

Participants

The study was carried out at an outpatient metabolism clinic of the Vali-Asr hospital, affiliated with Tehran University of Medical Sciences (TUMS) from March 2010 to March 2012. A total of 422 consecutive participants were enrolled in the study. Subjects were referred for routine general examination rather than a specific complaint. Subjects with prior diagnosis of any cancer, renal, thyroid, adrenal, or hepatic problems as well as those taking insulin, anti-hypertensive drugs, and lipid modifying agents were not included in this study. Diabetic participants had recently identified diabetes and were under treatment with life style modification plus metformin, glibenclamide or both concurrently. None had signs of long-term complications in general examination. All were tested and none had microalbuminuria. Those with a diagnosis of type 1 diabetes and pancreatitis were excluded from the study. All participants completed a written informed consent before entering the study. The study protocol was approved by the research ethics committee of TUMS according to the Declaration of Helsinki.

Data collection

Characteristic data such as age, gender and medication were obtained by detailed history taking. Current smoking was defined as smoking within the year preceding the test. Each subject's weight and height was measured in light clothing without shoes. After a normal expiration and in standing position, waist circumference was measured halfway between the lowest rib and iliac crest, rounded to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Diabetes mellitus was diagnosed according to the criteria of American Diabetes Association [25].

Laboratory investigation

Venous blood samples were drawn subsequent to a 12 hour overnight fast. Fasting plasma glucose (FPG) was measured by glucose oxidase method (intra- and inter-assay coefficient variation of 2.1% and 2.6%). Plasma glucose was measured again, exactly 2 hours after 75 g oral glucose administration (Post Prandial Plasma Glucose, PPPG). Insulin was determined by radioimmunoassay, by an antibody with no cross-reactivity for pro-insulin and C-peptide (Immunotech, Prague, Czech Republic). The intra- and inter-assay coefficients of variation were lower than 4.3% and 3.4%, respectively.
C-peptide was also measured by radioimmunoassay (Immunotech, Prague, Czech Republic) and creatinine by the Jaffe method (Parsazmun, Karaj, Iran). Hemoglobin A_{1c} (HbA_{1c}) was assessed using the high performance liquid chromatography (HPLC; DS5 Pink kit; Drew, Marseille, France). The homeostasis model assessment of insulin resistance index (HOMA-IR) was evaluated using the equation: (fasting plasma glucose (mg/dL) x fasting insulin (U/L)/405) [26]. CA19-9 was measured using an electrochemiluminescent method (Roche, Basel, Switzerland).

Statistical analysis

The SPSS 16 package for windows (Chicago, IL, USA) was used for analysis. The normality of each variable distribution was determined by the Kolmogorov-Smirnov test. Variables were described as mean ± standard deviation. We used Student's *t*-test for continuous variables to declare the differences in each parameter between the diabetic and non-diabetic group.
Afterward, CA19-9 values were regarded as the outcome. The determinant variables were described based on CA19-9 quartiles. One-way ANOVA was used for the comparison of each variable and Bonferroni post hoc test revealed the multiple comparisons of either two quartiles. The association of CA19-9 with glycemic related variables was evaluated by linear regression after adjusting for age, sex, and BMI, using the Enter approach and with regard to diabetes status. Finally, a receiver operating characteristics (ROC) curve was graphed testing CA19-9 for the diabetes status as the state variable. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios (PLR, NLR) were calcu-

Table 1. Principal characteristics of the study population with respect to their diabetes status.

	Subjects without Diabetes (n = 156)	Subjects with Diabetes (n = 266)
Gender (male; %)	25 ± 3.5	45 ± 3.1 [c]
Age (years)	48.19 ± 10.06	55.12 ± 9.54 [c]
Current smoking (%)	8.97 ± 2.29	13.16 ± 2.08
BMI	28.06 ± 4.57	29.42 ± 4.53 [b]
Waist circumference (cm)	91.42 ± 12.11	98.06 ± 11.26 [c]
Creatinine (mg/dL)	0.95 ± 0.18	0.97 ± 0.19
Fasting plasma glucose (mg/dL)	95.60 ± 11.35	151.42 ± 45.70 [c]
2 hour Post-prandial plasma glucose (mg/dL)	109.16 ± 28.91	206.84 ± 79.11 [c]
Fasting plasma insulin (U/L)	9.65 ± 5.62	9.95 ± 9.48
HbA_{1c} (%)	5.64 ± 0.78	7.29 ± 1.54 [c]
C-peptide (ng/mL)	2.35 ± 1.36	2.50 ± 1.06
HOMA-IR (units)	2.39 ± 2.36	3.51 ± 2.18 [c]
CA 19-9 (U/mL)	11.93 ± 11.42	16.73 ± 13.83 [c]

Data are presented as mean ± standard deviation (SD), [a] - $p < 0.05$, [b] - $p < 0.01$, [c] - $p < 0.001$.

Table 2. Principal characteristics of the study group with respect to their CA19-9 quartiles.

	CA19-9 ≤ 6.09 (n=105)	6.09 < CA19-9 ≤ 11.60 (n = 106)	11.60 < CA19-9 ≤ 21.05 (n = 106)	21.05 < CA19-9 (n = 105)	ANOVA significance
Gender (male; %)	27 (18 - 35)	41 (31 - 50)	42 (33 - 52)	40 (30 - 50)	NS
Age (years)	51.9 (50.0 - 53.9)	51.8 (49.6 - 54.0)	54.6 (52.8 - 56.3)	51.9 (49.9 - 54.0)	NS
Current smoking (%)	8.6 (3.1 - 14.0)	13.2 (6.7 - 19.8)	10.4 (4.5 - 16.3)	14.3 (7.5 - 21.1)	NS
BMI	28.8 (27.9 - 29.7)	28.0 (27.1 - 28.9)	28.5 (27.8 - 29.3)	30.3 (29.4 - 31.3) [d, e]	< 0.05
Waist circumference (cm)	93.7 (91.5 - 95.8)	91.5 (88.9 - 94.0)	96.6 (94.6 - 98.5) [c]	100.7 (98.5 - 103.0) [b, d]	< 0.01
Creatinine (mg/dL)	0.96 (0.93 - 1.01)	0.96 (0.93 - 1.00)	0.99 (0.96 - 1.02)	0.97 (0.94 - 1.01)	NS
Fasting plasma glucose (mg/dL)	114.5 (108.4 - 120.6)	118.7 (112.8 - 124.6)	136.4 (127.8 - 144.9) [b, c]	153.6 (142.0 - 165.1) [b, d, e]	< 0.01
2 hour Post-prandial plasma glucose (mg/dL)	154.8 (138.7 - 170.9)	160.9 (146.3 - 175.4)	192.6 (177.6 - 207.6) [a]	220.0 (200.4 - 239.7) [b, d]	< 0.01
Fasting plasma insulin (U/L)	8.29 (7.38 - 9.20)	8.50 (7.55 - 9.44)	10.4 (9.08 - 11.72)	11.84 (9.79 - 13.89) [b, d]	< 0.01
HbA_{1c} (%)	6.07 (5.87 - 6.27)	6.20 (5.97 - 6.43)	6.94 (6.64 - 7.23) [b, d]	7.56 (7.21 - 7.91) [b, d, e]	< 0.01
C-peptide (ng/mL)	2.19 (1.91 - 2.48)	2.278 (1.88 - 2.68)	2.44 (2.18 - 2.70)	2.70 (2.34 - 3.07)	NS
HOMA-IR (units)	2.33 (2.06 - 2.61)	2.47 (2.17 - 2.77)	3.48 (2.99 - 3.97) [b, d]	4.11 (3.54 - 4.67) [b, d]	< 0.01
Diabetes (%)	48 (38 - 57)	56 (46 - 65)	72 (63 - 80) [b]	77 (69 - 85) [b, c]	< 0.01

Data are presented as mean (confidence interval - CI), [a] - $p < 0.05$, [b] - $p < 0.01$ versus group 1, [c] - $p < 0.05$, [d] - $p < 0.01$ versus group 2, [e] - $p < 0.05$, [f] - $p < 0.01$ versus group 3, NS - not significant, multiple comparisons were tested using Bonferroni post hoc test.

Table 3. The β coefficients of glycemic related variables on CA 19-9 after adjusting for age, gender, and BMI.

	β	95% confidence interval
Fasting plasma glucose	0.079	0.051 - 0.107 [c]
2-hour Post-prandial plasma glucose	0.040	0.022 - 0.058 [c]
Fasting plasma insulin	0.183	-0.016 - 0.383
HbA_{1c}	2.934	2.119 - 3.750 [c]
C-peptide	0.797	-1.373 - 2.966
HOMA-IR	1.253	0.646 - 1.860 [c]

[a] - $p < 0.05$, [b] - $p < 0.01$, [c] - $p < 0.001$.

Table 4. The multivariate adjusted β coefficients of glycemic variables on CA 19-9.

	β	95 % confidence interval
Fasting plasma glucose	0.011	-0.038 - 0.060
2-hour Post-prandial plasma glucose	0.008	-0.021 - 0.038
HbA_{1c}	1.949	0.787 - 3.112 [b]
HOMA-IR	0.677	0.064 - 1.290 [a]

[a] - $p < 0.05$, [b] - $p < 0.01$, [c] - $p < 0.001$.

lated. The cut-off point of CA19-9 for optimum sensitivity and specificity of indicating diabetes status was derived calculating the shortest distance on the curve [27]. Two more separate cut-offs were derived. First, the cut-off with maximal PPV and PLR and, second, the cut-off with best NPV and NLR [28]. Statistical level of significance was considered as a p-value < 0.05.

RESULTS

A total of 422 patients entered the study, and 266 (63.03%) subjects were diagnosed as having diabetes. Considering the CA19-9 levels in our study group, 16 (3.79%) subjects had values greater than 37 U/mL. They were referred for oncologist consultion and were assured not to have an additional underlying disease (except for their diabetes status). The median value of CA19-9 was 11.60 U/mL, the 97.5th percentile was 40.00 U/mL. The median and 97.5th percentile of CA19-9 for diabetic and non-diabetic subjects was 14.00 U/mL and 41.07 U/mL, and 8.80 U/mL and 39.95 U/mL, respectively.

Subjects with diabetes were significantly older (55.12 ± 9.54 vs. 48.19 ± 10.06 years, $p < 0.001$), consisted of more men (45% vs. 25%, $p < 0.001$), had higher BMI (29.42 ± 4.53 vs. 28.06 ± 4.57 kg/m^2, $p < 0.01$) and waist circumferences (98.6 ± 11.26 vs. 91.42 ± 12.11 cm, $p < 0.001$). Diabetic subjects had higher FPG, PPPG, HbA_{1c}, and HOMA-IR levels (all had $p < 0.001$). CA19-9 was significantly higher in the diabetic group (16.73 ± 13.83 vs. 11.93 ± 11.42, $p < 0.001$). The frequency of smokers did not differ significantly among diabetic and non-diabetic subjects and was not included in the analysis afterward. Table 1 describes the principle characteristics of the study population with regard to their diabetic status.

When comparing study variables in different CA19-9 quartiles, age, gender, and creatinine level showed no significant difference (Table 2). BMI and waist circumference were higher in quartiles with greater CA19-9 levels ($p < 0.05$ and $p < 0.01$, respectively). Among glycemic related variables, only C-peptide was not significantly different among four quartiles. FPG and HbA_{1c} levels were greater, in either quartile when compared to the lower quartile in a stepwise manner. Number of diabetic subjects in each quartile had a stepwise increase (48%, 56%, 72%, and 77%, respectively, $p < 0.01$).

Linear regression revealed that FPG, PPPG, HbA_{1c}, and HOMA-IR were directly correlated with CA19-9 levels even when adjusted for age, gender, and BMI (all had $p < 0.001$, Table 3). Having the four above mentioned variables in a multivariate regression model, HbA_{1c} and HOMA-IR still had significant direct correlation with CA19-9 levels (Table 4). When the same model was repeated with respect to diabetes status, only subjects with diabetes had the significant correlation ($b = 1.905$, $p < 0.05$ for HbA_{1c} and $b = 0.844$, $p < 0.01$ for HOMA-IR).

Table 5. ROC curve statistics of CA 19-9 levels indicating diabetic status.

CA 19-9	Sen	1 - Spe	DOC	PPV	NPV	PLR	NLR
6.46 [a]	0.80	0.60	0.63	0.69	0.78	1.34	0.49
6.85	0.79	0.59	0.63	0.70	0.77	1.34	0.51
7.82	0.76	0.53	0.58	0.71	0.77	1.42	0.52
8.85	0.71	0.50	0.58	0.71	0.75	1.43	0.57
9.99	0.64	0.45	0.58	0.71	0.72	1.41	0.66
10.83 [b]	0.63	0.38	0.53	0.74	0.74	1.63	0.60
11.85	0.58	0.35	0.54	0.74	0.73	1.67	0.64
12.75	0.54	0.29	0.54	0.76	0.72	1.84	0.65
13.87	0.50	0.28	0.57	0.75	0.71	1.79	0.69
14.80	0.46	0.27	0.60	0.74	0.70	1.70	0.74
34.30 [c]	0.08	0.03	0.92	0.84	0.64	3.08	0.95

[a] - Cut-off for best NPV and NLR, [b] - Best overall cut-off having least distance on curve, [c] - Cut-off for best PPV and PLR, Sen - Sensitivity, Spe - Specificity, DOC - Distance On Curve equaling Square root of (1 - Sen)^ 2 + (1 - Spe)^ 2, PPV - Positive Predictive Value, NPV - Negative Predictive Value, PLR - Positive Likelihood Ratio, NPR - Negative Likelihood Ratio.

Finally, we derived a ROC curve for having diabetes with CA19-9 as the test variable (area under curve = 0.638, $p < 0.001$). Table 6 shows sensitivity and 1-specificity for selected values of CA19-9. We presume the 10.83 U/mL value as the optimal cut off point, maximizing both sensitivity and specificity in indicating diabetes status (0.63 and 0.55, respectively). As the optimal cut-off to maximize PPV and PLR, we presume that CA19-9 values greater than 34.30 U/mL have a PPV of 84% in detecting diabetes. This accounts for a PLR of around 3. Finally, as the optimal cut-off for having best NPV and NLR, a CA19-9 value of less than 6.46 U/mL is chosen. This accounts for a NPV and NLR of 78% and 0.49, respectively.

DISCUSSION

Apart from malignancies [4,5,8], CA19-9 levels are associated with a number of benign [9,10,13] and even non-pathologic conditions [14,29]. Our result correlates CA19-9 level with glycemic status even in normal ranges of CA19-9 and even in asymptomatic healthy-appearing individuals.

In concordance to a number of reports, we found that subjects with diabetes have higher values of serum CA19-9 [30-32]. All previous studies had their evaluation in a smaller number of patients. A previous study declared that there is no correlation between diabetes and CA19-9 levels. They concluded that CA19-9 elevation should be evaluated in the same manner of a non diabetic subject. However, the mentioned study only had 28 samples with non-insulin dependent diabetes, which makes their results vulnerable to bias [24]. As we admit, recent reports revealed that CA19-9 is directly associated with diabetes [31] and HbA_{1c} [33]. In comparison, our result is not limited to an age-group [33] since normal aging can affect CA19-9 levels as well [29]. Moreover, we assume that the association of CA19-9 with diabetes is independent of gender and BMI. This goes further than the earlier studies [31,32]. Only one study has reported CA19-9 to be associated with HbA_{1c} in a multivariate model and only in diabetic patients [30]. The study included micro-vascular complications in the modeling. We showed that HbA_{1c} - Ca19-9 correlation is saved even when extracting the effects of FPG and PPPG. Among diabetic and non-diabetic patients, having a lower HbA_{1c} value is accompanied by having lower CA19.9 levels. Glycemic control can lower the HbA_{1c} levels, as a marker of long-term control in diabetic patients [34]. We propose that CA19-9 elevation can be reversible by means of glycemic control [35]. None of the abovementioned studies evaluated the possible role of HOMA-IR in relation to CA19-9. Here, for the first time, we introduce the possible role of insulin resistance in CA19-9 elevation. Direct association of CA19-9 with HbA_{1c} and HOMA-IR was persistent in the diabetic group unlike non-diabetic subjects. This is in favor of considering a generalized metabolic status - in terms of insulin resistance - in determining CA19-9.

Recently identified diabetic patients with high levels of CA19-9 might benefit from pancreatic cancer screening [15,16], especially if the CA19-9 elevation is not accompanied by a proper elevation of HbA_{1c}. We found HbA_{1c} to contribute to a great portion of CA19-9's variance. Other reports had indicated higher cut off values to be investigated for malignancies in diabetic patients [30,31]. Yet they did not discuss the changes in ranges of CA19-9 that are considered to be normal.

Previously, a 97.5th percentile cut-off of 57.14 U/mL was derived for CA19-9 in diabetic patients [30]. Our actual 97.5th percentile was 40.00 U/mL (41.07 U/mL for diabetic and 39.95 U/mL for non-diabetic subjects). Earlier studies proposed that elevated CA19-9 would benefit from being evaluated for HbA_{1c} and FPG [16, 31]. For the first time we defined a cut-off value for CA19-9 in otherwise healthy-appearing subjects (> 10.83 U/mL), which is lower than what is investigated for other benign or malignant conditions [2]. Values above the cut-off are likely to be a warning of poor glycemic control. As a result, even in asymptomatic patients with elevated CA19-9 levels, screening for glycemic status might be indicated.

In fact, our 10.83 U/mL cut-off for CA19-9 which optimizes the distance on curve, has limited sensitivity and specificity which may restrict its clinical use. However, the PPV and NPV for the selected cut-off were both 74%. This is far more appropriate, knowing that the actual accuracy of CA19-9 in detection of malignancies is not much different [8]. When we introduced a single cut off, we optimized both the sensitivity and the specificity simultaneously. However, having optimization for each of them separately leads to more applicable results. We derived two separate cut-offs to simplify the interpretation of a CA19-9 value. The first cut off optimizes NPV (and NLR, as they move together) and the second optimizes PPV (and PLR, as they move together as well) [28]. A CA19-9 value greater than 34.30 U/mL (less than conventional CA19-9 cut-offs for malignant conditions) has a PPV of 84% in detecting diabetes. Such persons would be three times more likely to be diabetic, which can be a significant finding within the setting of endocrinology and metabolism clinics. Interestingly, our results show that a random elevated CA19-9 level is much more likely to result from a benign metabolic condition. This supports the use of CA19-9 as a screening marker of malignancy [2]. On the other side, a CA19-9 value of less than 6.46 U/mL has a NPV and NLR of 78% and 0.49, respectively. However, an important point lays here. Both NPV and NLR are measures which depend on the prevalence of the outcome. In a general population setting, the prevalence of diabetes is far less than metabolism clinics (as our setting). Thus, the lower cut-off of around 6.46 U/mL has clinical implications in the general population, and potentially, as a screening measure. Considering Iran, with a prevalence of diabetes which is around 10% [36-38], simple calculation suggests a NPV of around 95% for detecting diabetes [28]. Someone with a random CA19-9 value below the cut-off of 6.46 U/mL is far less likely to have underlying diabetes, when coming from the general population. Our study does not reveal the time-frame status of changes in CA19-9 levels with respect to glycemic status. Further prospective studies can do so. Regarding some miscellaneous conditions which have been reported to elevate CA19-9 levels, we should clarify some points. First, most of the reported life style related conditions are limited to case reports rather than established findings and account for extreme elevations of CA19-9 [14]. Second, in the statistical section, we tried our best to adjust the results and control for the possible confounding factors including age, gender, and BMI. Third, most of these reported conditions include rare cases and are results of extreme unusual behaviors (consuming 2 L of tea beverage per day) [13,14,29]. We shall mention that unusual life style related conditions, which may contribute to modest elevations of CA19-9, are regarded as a probable limitation of our study. Upcoming studies can also elucidate the role of insulin resistance and metabolic syndrome in elevation of CA19-9. This might be a generalized pathophysiology beyond metabolic control, glycemic status, pancreatic function, and CA19-9 levels.

CONCLUSION

First, we determined that otherwise normal diabetic subjects have greater CA19-9 values. Second, we suggest that CA19-9 levels above 10.83 U/mL in the absence of other pathologies are in favor of glycemic impairments. CA19-9 values greater than 34.30 U/mL may accompany an 84% frequency of diabetic subjects especially in settings such as metabolism clinics. CA19-9 values of less than 6.46 U/mL are likely to rule out the presence of diabetes, especially while testing in the general population. Third, we propose possible underlying pathophysiological links between elevations of CA19-9, abnormal glycosylation, glucose metabolism, insulin resistance, and pancreatic dysfunctions.

Declaration of Interest:
The authors declare no conflicts of interests. The study has received no grant or equipment or drug.

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