The Need for a New Cut-off Value for CA 19-9 in Patients with Type II Diabetes Mellitus

Tip II Diabetes Mellituslu Hastalarda CA 19-9 için Yeni Bir Cut-off Değeri İhtiyacı

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ABSTRACT

Aim: Pancreatic cancer (PC) is a disease with complex and poorly understood etiology. One of the common risk factors of PC is diabetes mellitus (DM). Increased carbohydrate antigen (CA) 19-9 levels can be used as a biomarker in diagnosis of PC. However, CA 19-9 levels have been reported to increase in some benign conditions as well. Increased levels of such PC-associated biomarkers due to benign conditions can lead to unnecessary interventional procedures. The aim of this study was to question the need for a new CA 19-9 cut-off value when diagnosing PC in patients with type II DM.

Material and Methods: This retrospective study evaluated a total of 449 patients. The patients were divided into two groups: the normal glucose regulation (NGR) group (n=292) and type II DM group (n=157). The mean glucose, HbA1c, CA 19-9, insulin, and homeostatic model assessment for insulin resistance (HOMA-IR) levels of the groups were compared. The correlation between CA 19-9 and glucose, HbA1c, insulin and HOMA-IR was evaluated.

Results: The type II DM group had significantly higher CA 19-9, glucose, HbA1c, insulin, as well as HOMA-IR levels compared to the NGR group (P=0.001 for CA 19-9 and P<0.001 in all other pairwise comparisons). There was a positive correlation between CA 19-9 and HbA1c as well as HOMA-IR (r=0.132, P=0.005; r=0.109, P=0.020, respectively).

Conclusion: A higher CA 19-9 cut-off value is needed when diagnosing malignant disease of the pancreas in patients with type II DM to prevent unnecessary invasive/noninvasive interventions.

Keywords: CA 19-9; pancreatic cancer; type II diabetes mellitus.

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ÖZET

Amaç: Pankreas kanseri (PC), karmaşık ve iyi anlaşılmayan etiyolojisi olan bir hastalıktır. PC'nin yaygın risk faktörlerinden biri diabetes mellitus'tur (DM). Artmış karbonhidrat antijeni (CA) 19-9 seviyeleri PC tanısında biyobelirteç olarak kullanılabilir. Bununla birlikte, CA 19-9 seviyelerinin bazı benign durumlarda da arttığı bildirilmiştir. Benign durumlar nedeniyle PC ile ilişkili bu tür biyobelirteçlerin artan seviyeleri gereksiz girişimsel prosedürlere yol açabilir. Bu çalışmanın amacı tip II DM'li hastalarda PC tanısı koyarken yeni bir CA 19-9 eşik değerinin gerekliliğini sorgulamaktı.

Gereç ve Yöntem: Bu retrospektif çalışmada toplam 449 hasta değerlendirildi. Hastalar iki gruba ayrıldı: normal glukoz regülasyonu (NGR) grubu (n = 292) ve tip II DM grubu (n = 157). Grupların ortalama glukoz, HbA1c, CA 19-9, insülin ve insülin direnci için homeostatik model değerlendirmesi (HOMA-IR) düzeyleri karşılaştırıldı. CA 19-9 ile glukoz, HbA1c, insülin ve HOMA-IR arasındaki korelasyon değerlendirildi.

Bulgular: Tip II DM grubu, NGR grubuna kıyasla anlamlı derecede yüksek CA19-9, glukoz, HbA1c, insülin ve de HOMA-IR seviyelerine sahipti (CA 19-9 için P=0.001 ve diğer tüm ikili karşılaştırmalarda P<0.001). CA 19-9 ile HbA1c ve HOMA-IR arasında pozitif bir korelasyon vardı (sırasıyla r=0.132, P=0.005; r=0.109, P=0.020).

Sonuç: Gereksiz invaziv/noninvaziv girişimleri önlemek için tip II DM'li hastalarda pankreasın malign hastalığı tanısını koyarken daha yüksek bir CA 19-9 cut-off değeri gereklidir.

Anahtar Kelimeler: CA 19-9; pankreas kanseri; tip II diabetes mellitus.

INTRODUCTION

Carbohydrate antigen (CA) 19-9 was first identified as a sialylated Lewis blood group antigen in early 1980s through a hybridoma of murine spleen cell and human colorectal cancer cell line that produced monoclonal antibodies (1, 2). Studies have reported increased levels of CA 19-9 in pancreatic and biliary tract tumors (3-5). The CA 19-9 increase has also been seen in other malignant tumors (ovarian, colorectal and hepatocellular carcinomas, and stomach) as well as some benign conditions associated with biliary tree (cholangitis, pancreatitis, and choledocholithiasis), pulmonary diseases, and end-stage renal failure (6-10).

Pancreatic cancer (PC) has one of the highest mortality rates, because majority of the patients are already at an advanced stage when diagnosed, and the disease has no effective medical treatment. The etiology of PC is complex and not well understood, but it has been established that diabetes mellitus (DM) increases the risk of PC incidence (11).

Elevated CA 19-9 level is one of the signs used to diagnose PC, but it should be kept in mind that CA 19-9 levels may also increase as a result of diabetes-related pancreatic tissue damage. When diagnosing PC, relying on specific cut-off values for CA 19-9, which might have increased due to benign conditions, can lead to unnecessary interventional approaches. Our aim in this study was to question the need for a new CA 19-9 cut-off value when evaluating patients with type II DM for presence of PC.

MATERIAL AND METHODS

Subjects

This retrospective study included the data of 449 patients that were treated in a tertiary hospital between January 2016 and January 2020. The patients were divided into two groups: normal glucose regulation (NGR) group (n=292) and type II DM group (n=157). In the NGR group, glucose levels were below 100 mg/dL, HbA1c levels were below 5.7%, and the patients were not diagnosed with DM (12). Patients in the type II DM group consisted of individuals who had routine follow-up with the outpatient clinics due to DM. The exclusion criteria of the study were: age <18 years, any missing data (CA 19-9, fasting serum glucose, HbA1c, fasting serum insulin), and presence of malignant disease, as well as acute or chronic pancreatitis.

Laboratory assays

Two types of tubes were used for collecting blood samples from all patients. Gel barrier containing clot-activator tubes (Becton Dickinson and Company (BD) Vacutainer® SST II Advance tube, 5 mL, 13 x 100 mm, NJ, USA) were used for CA 19-9, glucose, and insulin analyses, while tubes with K2EDTA (BD Vacutainer®, 2 mL, 13 x 75 mm, NJ, USA) were used for HbA1c analysis. The serum in SST II tubes was separated by centrifuging the tubes at 1500g for 10 minutes. Chemiluminescence immunoassay method (UniCel DxI 800, Beckman Coulter, USA) was used for detection of CA 19-9 and insulin levels in the serum. Analysis of serum glucose levels was done by an automated procedure (AU5800 autoanalyzer, Beckman Coulter Inc., USA). Boronate affinity high performance liquid chromatography method (Premier Hb9210, Trinity Biotech, USA) was used for detection of HbA1c levels.

The following formula was used for calculating homeostatic model assessment for insulin resistance (HOMA-IR): fasting insulin (μU/mL) × fasting glucose (mg/dL)/405 (13).

Statistical analysis

SPSS version 25 software package (SPSS Inc., Chicago, USA) was used for statistical analyses. Shapiro–Wilk test was used to assess whether the normality of data distribution. Parametric test (independent samples t-test) was utilized to infer statistical differences between the groups for normally distributed data, while nonparametric test (Mann–Whitney U) was used for non-normally distributed data. Gender analysis was done by using the chi-square test. The results were expressed as mean ± standard deviation or median and interquartile range. Spearman rank correlation coefficient was used for correlation analyses of the non-normally distributed data. Results with P <0.05 were accepted as statistically significant.

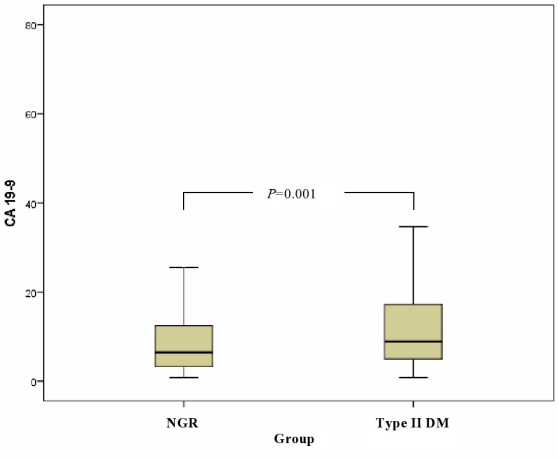
Ethical considerations

Local ethics committee approved our study (Resolution Number 2020/5-12, dated April 04, 2020).

RESULTS

Demographic characteristics and analyte levels of NGR and type II DM groups are presented in Table 1. The groups' gender distribution was not significantly different (P=0.119). Type II DM group had significantly higher age, CA 19-9, fasting serum glucose, HbA1c, fasting serum insulin, and HOMA-IR compared to NGR group (P=0.001 for CA 19-9 and P<0.001 for all pairwise comparisons) (Table 1 and Figure 1).

The results of the correlation analyses between CA 19-9 and routine biochemical analytes were presented in table 2. CA 19-9 was positively correlated with HbA1c and HOMA-IR (r=0.132, P=0.005; r=0.109, P=0.020, respectively). However, the r values presented above indicates a weak correlation (14).



Figüre 1. Comparison of CA 19-9 levels between NGR and Type II DM groups.

Abbr: NGR, normal glucose regulation; DM, diabetes mellitus.

Table 1. Demographic characteristics and analytes levels in the NGR and type II DM groups.

Parameter	NGR group (n=292)	Type II DM group (n=157)	*P*
Age, years mean ± SD	44.0 ± 13.5	64.0 ± 11.2	**<0.001**
Sex, Female, n (%)	191 (65.4)	91 (58.0)	0.119
CA 19-9, U/mL median (IQR)	6.5 (3.3-12.5)	8.9 (5.0-17.3)	**0.001**
Fasting Serum Glucose, mg/dL median (IQR)	87.0 (82.0-92.0)	135.0 (121.0-160.0)	**<0.001**
HbA1c, % median (IQR)	5.4 (5.2-5.5)	7.1 (6.6-7.9)	**<0.001**
Fasting Serum Insulin, μU/mL median (IQR)	6.8 (4.4-9.2)	9.8 (5.8-15.8)	**<0.001**
HOMA-IR, median (IQR)	1.4 (0.9-2.0)	3.1 (2.0-5.9)	**<0.001**

P value <0.05 was considered statistically significant; Statistically significant *P* values shown in bold.

Abbr: NGR, normal glucose regulation; HOMA-IR, homeostatic model assessment for insulin resistance; DM, diabetes mellitus; SD, standard deviation; IQR, interquartile range (25^{th}–75^{th} percentile).

Table 2. The correlation of CA 19-9 with routine biochemical analytes.

Parameter	CA 19-9	
	r	*P*
Fasting Serum Glucose	0.092	0.051
HbA1c	0.132	**0.005**
Fasting Serum Insulin	0.053	0.261
HOMA-IR	0.109	**0.020**

P value <0.05 was considered statistically significant; Statistically significant *P* values shown in bold.
Abbr: HOMA-IR, homeostatic model assessment for insulin resistance.

DISCUSSION

The most important finding in our study was that CA 19-9 levels of the type II DM group were significantly higher compared to those of the NGR group. Moreover, CA 19-9 was positively correlated with HbA1c and HOMA-IR.

CA 19-9's sensitivity as PC's diagnostic marker varies between 70-90%, while its specificity ranges from 68% to 91% (15). Various non-malignant disease including thyroid and ovarian disease, as well as obstructive jaundice also lead to elevated CA 19-9 levels. However, close relationship between the endocrine and exocrine functions in the pancreas makes the use of CA 19-9 in patients with DM contentious. Bayramicli et al. reported seeing higher levels of CA 19-9 in patients with type II DM compared to controls and a positive correlation between CA 19-9 and diabetes irrespective of glucose and HbA1c levels, age, and gender (16). However, their study population was relatively small. In another study, Nakamura et al. reported that patients with poorer glucose control had higher levels of CA 19-9 (17). The caveat of their study was relatively small population size, which included 60 DM patients and 40 controls (17). Larger sample size was analyzed in our study and our finding of higher levels of CA 19-9 in type II DM group was in concordance with the previous studies. However, there are also results in the literature that do not agree with the studies mentioned above. In contrast with the results of our study, Ritts et al. reported that in patients with DM CA 19-9 levels did not exceed 40 U/mL (18).

Although it is not known how diabetes leads to the increased serum CA19-9 levels, there have been some hypotheses. One of the

most notable among these is that increase in CA19-9 is associated with cellular dysfunction. Insulin deficiency in DM can lead to insufficient exocrine functions of the pancreas and stimulate ductal cells to secrete CA19-9. From this point of view, it is stated that the spike in serum CA19-9 is positively correlated with the magnitude of cellular dysfunctions (19). Previous studies that evaluated pancreatic functions in DM showed presence of pancreatic exocrine insufficiency in a significant proportion of patients with DM. Terzin et al. reported seeing insufficient pancreatic exocrine functions in type II DM patients with poor glycemic control (20). In addition, autopsy studies and pancreatic histology studies have shown that patients with DM showed significant changes in the exocrine glands compared to non-diabetic controls (21).

Murai et al. proposed a different mechanism involving elevated levels of CA 19-9 in patients with DM. They stated that in patients with DM, the prolonged CA 19-9 half-life possibly due to decrease in CA19-9's catabolism, may result in elevated tumor marker levels. They also noted that a decrease in catabolism might be due to a surge in the glycation of CA 19-9 and/or glycation of proteins involved in the catabolism of CA 19-9 (22).

The fact that the HbA1c test, which is used to assess long-term glycemic control, is the most common diagnostic and screening tool used for type II DM management and research has led us to include it in our study (23). HbA1c is used to identify treatment goals and predict complications (24). In our study, HbA1c was evaluated as a marker of chronic glucose toxicity and was found to be higher in the type II DM group. According to Benhamou et al., patients that had the highest levels of CA 19-9 were the ones with the worst metabolic control. In Benhamou's study, the levels of CA 19-9 were significantly higher in patients whose HbA1c >7.5% compared to those with HbA1c <7.5%. Similar to Benhamou et al., we also found that HbA1c levels were positively correlated with CA 19-9 (25).

HOMA-IR evaluation was included in our study to exclude the effects of insulin resistance in the NGR group (26). We found that the median HOMA-IR value was below 2.5 in NGR group.

PC is usually diagnosed based on physical examination, patient history, clinical tests, and imaging techniques (27). Among the clinical tests, CA 19-9 is of particularly important for PC diagnosis. However, it is important to use accurate cut-off values to avoid unnecessary invasive and non-invasive interventions. In our study, we detected higher CA 19-9 values in patients with type II DM, which revealed the necessity to determine new cut-off value for this patient group when diagnosing PC.

There are several limitations of this study. First, similar to other retrospective studies, we cannot completely rule out the impact of selection bias. Second, there was a significant difference between groups in terms of age. However, according to the reference of the manufacturer of chemiluminescence immunoassay method, the reference range of CA19-9, which is between 0-35 U/mL, does not differ based on age.

In conclusion, the present study points out the need to use a higher CA 19-9 cut-off value in differentiating malignant disease of the pancreas in patients with type II DM to prevent unnecessary invasive/noninvasive interventions.

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