Introduction

The incidences of gastrointestinal and pancreas cancers are increased in diabetes mellitus [1]. There is a complex relation between pancreas cancer and diabetes mellitus whose etiology has not been identified yet. Pancreatic cancer may be even considered as one of the several complications of diabetes mellitus. The prevalence of diabetes mellitus in pancreatic cancer varies from 4% to 64% [2]. Tumor markers such as CA19-9 and CEA are used for the screening of gastrointestinal cancers. Several benign conditions can also elevate tumor markers, such as hepatobiliary system inflammation, hydronephrosis, thyroid disease, acute and chronic pancreatitis, and pulmonary disease [3-6]. Elevated tumor markers in these benign conditions often lead to unnecessary invasive procedures.

There is scarce information in the literature regarding the effect of glycemic control on these tumor markers and exocrine pancreatic function. Bayramicli et al. found significantly higher CA19-9 levels in type 2 diabetic patients than controls, however they did not investigate the relation between CA19-9 and glycemic control [7]. Benhamou et al. [8] found a significant correlation between HbA1c, fasting blood glucose and CA19-9, on the other hand Banfi et al. [9] did not observe such a correlation. Gul et al., also found higher CA 19-9 levels in diabetic patients than controls [10]. Hyperglycemia may have deleterious effects on exocrine pancreas in addition to endocrine pancreas. There is a relation between endocrine and exocrine pancreas reserve [11]. To our knowledge, there is only one study investigating CEA levels in diabetes mellitus, which found lower CEA levels in diabetics than controls [12]. In the above-mentioned studies, tumor markers were not studied after euglycemia was achieved.

Previous studies were all using cross-sectional design. In this prospective study, we aimed to investigate tumor
Glycemic control affects on tumor markers and inflammation markers as well as pancreatic exocrine functions in hyperglycemic type 2 diabetic patients, and also after glycemic control was achieved.

2 Materials and Methods

A total of 98 consecutive diabetic patients, and 50 healthy controls who do not smoke and drink alcohol were included in the study. Exclusion criteria were; pregnancy, malignancy, pancreatic, hepatobiliary, hematologic diseases and renal failure. Biochemical parameters were performed before and after 3 weeks of insulin treatment. Fasting blood glucose (FBG), serum total cholesterol (TC), triglycerides (TG), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), g-glutamyltransferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), creatinine, amylase and lipase concentrations were measured enzymatically with an automatic analyzer (Konelab 60i, Thermo Fisher Scientific Inc. MA, USA). Serum high sensitive c-reactive protein (hsCRP) concentrations were measured nephelometrically with an automatic analyzer (Immage® Immunohistochemistry System, CA, USA). Serum CEA and CA19-9 concentrations were measured with chemiluminescent technology on the Beckman Coulter DxI800 (Beckman Coulter, Inc., Brea, CA, USA) platform according to the manufacturer’s specifications. The analytical sensitivity for these assays were 0.8 U/mL and 0.1 ng/ml respectively.

We performed abdominal ultrasonography for all of the patients and controls. Occult blood test in the stool was also given to all subjects. We continued the search for any occult malignancy with abdominal CT, endoscopy and colonoscopy for the patients with elevated CEA and CA19-9 values above the upper normal levels and/or positive occult blood test in the stool and/or suspicious findings on ultrasonographic examination. The local ethics committee approved the protocol. All participants provided informed written consent.

2.1 Statistical Methods

Distribution of the continuous variables was determined by the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables are expressed as percentage. For comparison of categorical variables or percentages we used Fisher’s exact and chi-square tests. Differences between numeric variables were tested with Student’s t-test or Mann-Whitney-U test. Pearson and Spearman analyses were used to identify correlations between study parameters. For all statistics, a two-sided p value below 0.05 was considered statistically significant. All analyses were performed with SPSS 15.0 for Windows.

3 Results

Ninety eight diabetic patients [(age: 59.4±11.0), (34♂, 64♀)] and 50 healthy controls [(age: 58.1±11.9), (15♂, 35♀)] were involved in the study. These two groups were similar in terms of age and gender. FBG (p<0.0001), HbA1c (p<0.0001), CA19-9 (p<0.0001), CEA (p<0.0001), hsCRP (p<0.0001), ESR (p<0.0001), TG (p<0.0001), AST (p<0.0001), ALT (p<0.0001), GGT (p<0.0001), ALP (p<0.0001), TC (p<0.0001) and LDL-C (p<0.0001) levels decreased significantly with the regulation of glycemic control (Table 1).

Amylase (p<0.0001) and lipase (p<0.0001) levels increased with the regulation of glycemic control (Table 1). After glycemic control, CA19-9 (p<0.0001) and CEA (p<0.0001) levels were still higher, whereas amylase (p<0.0001) and lipase (p<0.0001) levels were still lower in the diabetic group compared with the control group (Figure 1,2).

Basal HbA1c showed significant correlation with CA19-9 (r: 0.498, p<0.0001), CEA (r: 0.560, p<0.0001), amylase (r: -0.260, p<0.0001) and lipase (r: -0.218, p: 0.001). Basal FBG showed significant correlation with CA19-9 (r: 0.358, p<0.0001), CEA (r: 0.373, p<0.0001), amylase (r: -0.317, p<0.0001) and lipase (r: -0.304, p<0.0001). None of the patients revealed any sort of gastrointestinal malignancy.

4 Discussion

This study showed that CA19-9 and CEA levels decreased significantly, while amylase and lipase levels increased significantly with the regulation of blood glucose. After glycemic control was achieved, CA19-9 and CEA levels were still higher, whereas amylase and lipase levels were still lower in the diabetic group compared with the control group. Furthermore, basal CA19-9 and CEA levels showed significant positive correlation with HbA1c and FBG.

Chronic pancreatitis is often associated with endocrine pancreatic dysfunction, causing a secondaryform of diabetes, which accountsfor <1% of all diabetes mellitus cases. Approximately eighty percent of patients with chronic pancreatitis develop an overt diabetes mellitus in their lifetime, and diabetes mellitus is also an independent risk factor for mortality in patients.
Table 1: Comparison of laboratory characteristics before and after euglycemia was achieved (Mean ± SD).

|                        | Hyperglycemia | Euglycemia | Control | P (Hyperglycemia-Euglycemia) |
|------------------------|---------------|------------|---------|-----------------------------|
| Fasting Blood Glucose (mg/dl) | 306.7±116.1   | 126.5±39.9 | 90.0±6.8 | <0.0001                    |
| HbA1c %                | 11.9±2.67     | 11.0±2.45  | 5.9±0.46 | <0.0001                    |
| CA19-9 (ng/ml)         | 28.5±28.5     | 17.5±15.3  | 8.3±7.3  | <0.0001                    |
| CEA (U/ml)             | 2.9±1.95      | 2.0±1.16   | 1.5±1.09 | <0.0001                    |
| Amylase (U/L)          | 50.1±17.9     | 60.8±23.0  | 78.1±28.1| <0.0001                    |
| Lipase (U/L)           | 40.7±21.6     | 50.9±23.2  | 63.6±23.6| <0.0001                    |
| hsCRP (mg/dl)          | 4.6±7.12      | 2.7±4.66   | -        | <0.0001                    |
| ESR (mm/hour)          | 38.6±30.3     | 29.4±24.2  | 23.2±13.1| <0.0001                    |
| AST (U/L)              | 22.9±8.2      | 21.8±8.5   | 23.2±13.1| <0.0001                    |
| ALT (U/L)              | 23.9±11.1     | 22.4±10.2  | 22.3±18.6| <0.0001                    |
| GGT (U/L)              | 32.7±20.9     | 28.3±12.7  | 29.4±39.4| <0.0001                    |
| ALP (U/L)              | 94.8±39.4     | 73.5±26.1  | 86.4±56.2| <0.0001                    |
| Creatinine (mg/dl)     | 0.9±0.40      | 0.9±0.45   | 0.8±0.18 | 0.034                      |
| Total Cholesterol (mg/dl) | 176.8±45.9    | 157.4±41.9 | 178.9±24.4| <0.0001                    |
| LDL-cholesterol (mg/dl) | 101.2±32.9    | 87.5±27.3  | 109.6±23.6| <0.0001                    |
| Triglycerides (mg/dl)  | 201.0±114.4   | 168.5±88.7 | 91.6±37.5| <0.0001                    |
| HDL-cholesterol (mg/dl) | 42.8±12.9     | 42.7±14.2  | 48.8±11.8| NS                         |

Figure 1: Comparison of CA19-9 levels between the groups.
Glycemic control affects on tumor markers

with chronic pancreatitis [13,14]. Chronic pancreatitis and diabetes mellitus are both risk factors for pancreatic cancer [15]. It has been known that diabetes is related to various types of cancer, particularly associated with pancreatic cancer [16]. Metformin, which decreases insulin levels in blood, decreases the risk of cancer [17]. Insulin and IGF-1 signalling pathways and high blood glucose levels may be related to tumor cell proliferation [1]. CEA and CA19-9 levels are elevated in gastrointestinal malignancies [18]. The elevation of these markers may be related to the interaction between exocrine and endocrine pancreatic cells. The association between these tumor markers and HbA1c may be a sign for potential neoplastic proliferation in hyperglycemic environment. The insufficiency of insulin could result in a pancreatic exocrine deficiency and release of CA19-9 by ductal cells [19]. Chronic inflammatory changes of the exocrine pancreas was shown in diabetic patients [20]. Autopsy studies and studies on pancreas histology showed marked changes in the exocrine gland in patients with diabetes mellitus [21].

Benhamou et al. previously found a significant correlation between fasting blood glucose, HbA1c and CA19-9 levels [8]. Conversely, Banfi et al. found no correlation between CA19-9 and glycemic control in diabetic subjects [9]. Gul et al. found significant correlation between CA19-9 and HbA1c in diabetic patients [10]. There is only one study investigating CEA levels in diabetes mellitus, which found lower CEA levels in diabetics than controls, which contradicts our results [12]. The researchers also found higher CA19-9 levels, and they did not correlate these markers with HbA1c. The diabetic patients in that study, had diabetic nephropat and significant proteinuria, which may account for the discrepancies between our study and this study. In our study, we did not select patients with proteinuria. To our knowledge, this is the first study showing that glycemic control reduces CEA levels in diabetic subjects. Above-mentioned studies did not investigate the effect of glycemic control on amylase and lipase. The elevation of amylase and lipase in this study may be related to normalisation of exocrine pancreatic function with the glycemic control. Previously, impaired exocrine pancreatic function was reported in diabetic patients [22-24]. In an experimental study, hyperglycaemia led to decreased serum amylase levels and neutrophil infiltration in the exocrine pancreas of cats [25] after 1 week of insulin therapy amylase levels returned to normal. In another study, amylase activity and pancreatic transcripts were reduced in diabetic rodents, and amylase activity gradually returned to normal after

Figure 2: Comparison of CEA levels between the groups.
normalisation of glucose levels [26]. Our findings and earlier experimental studies suggest that hyperglycemia may cause cellular damage to exocrine pancreas and lead to impaired synthesis of pancreatic digestive enzymes. Exocrine pancreatic dysfunction may be attributable to the lack of the trophic effect of insulin on pancreatic acinar cells [22]. Alternatively, disturbed cellular signaling that controls both transcription and protein metabolism in the pancreas may be responsible for pancreatic exocrine insufficiency induced by hyperglycemia [27]. Loss of cellular paracrine communication and extracellular matrix remodeling fibrosis in diabetic pancreas may result in a dysfunctional endocrine-exocrine communication, resulting in pancreatic insufficiency and glucagon like peptide deficiency in prediabetes and overt diabetes mellitus in humans [28].

In conclusion, this study showed that glycemic control influences amylase, lipase, CEA and CA19-9 measurements in diabetic subjects. In patients with elevated levels of these tumor markers, hyperglycemia should be kept in mind as a potential confounder. This study also showed that exocrine pancreatic dysfunction was also improved with glycemic control. It is not clear whether elevated levels of CEA and CA19-9 is a pre-cancerous state or a mere benign condition causing confusion for the physician. Experimental studies may reveal the mechanisms of the interaction between endocrine and exocrine pancreatic dysfunction.

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Conflict of Interest: The authors have nothing to disclose.

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