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Optimal glycemic target level for colon cancer patients with diabetes

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ABSTRACT

Aims: The aim of this study was to evaluate the differences in mortality among colon cancer patients with or without diabetes and to determine optimal glycemic target level for colon cancer patients with diabetes.

Methods: A total of 741 patients with colon cancer between April 1999 and December 2010 were reviewed. The non-diabetes group had a fasting plasma glucose <126 mg/dL, and the diabetes group had a fasting plasma glucose ⩾126 mg/dL. Patients with diabetes were further divided based on glycemic control into either the uncontrolled subgroup (HbA1c ⩾8%) or the well-controlled subgroup (HbA1c <8%).

Results: Patients with diabetes had significantly shorter overall survival and median survival than non-diabetes patients. Uncontrolled diabetes patients had significantly shorter overall survival and median survival than well-controlled diabetes patients. The relative risk of mortality for diabetes patients was higher than non-diabetes patients (relative risk 1.17). The relative risk of mortality in uncontrolled diabetes patients was significantly higher than in well-controlled diabetes patients (relative risk 4.58). The area under the curve for mortality and HbA1c level was 0.73. The cut off HbA1c level was 7.75%.

Conclusions: A optimal glycemic control level for colon cancer patients with diabetes should be recommended as an HbA1c of 7.8% or below.

1. Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases worldwide and constitutes a major health burden in terms of mortality and impaired quality of life [1]. Diabetes mellitus (DM) is associated with a risk of cancer and its associated mortality. Epidemiologic evidence has suggested that people with DM are at a significantly higher risk of developing various types of cancer, such as colorectal, pancreatic, lung, breast, bladder, gastric, prostate, and kidney. Mortality in DM patients with these cancers is also increased [2,3]. A number of studies have been recently conducted on the impact of type 2 diabetes on the clinical outcomes of patients with various cancers types, including gynecologic cancers. These studies have demonstrated that type 2 diabetes has a negative impact on the outcome of these cancers [4]. In a study of 202 women with breast cancer, an increased risk of recurrence was noted to correlate with increased serum glucose levels [5]. A meta-analysis found that cancer patients with DM had a significantly increased risk of mortality compared to cancer patients without DM [5]. Although the biological mechanisms associated with the relationship between DM and cancer are not

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fully understood, we speculate that controlling one's current diabetic state can affect the risk of cancer.

Colorectal cancer (CRC) is one of the most common cancers in patients with type 2 diabetes. Furthermore, type 2 diabetes increases the lifetime risk of colon cancer by up to three times when compared to the general population [6]. CRC is also the second leading cause of cancer death in the world, and it has been shown that preexisting diabetes mellitus (pre DM) increases the risk of CRC-specific mortality [7]. One study on CRC patients demonstrated that poorly controlled DM, as determined by HbA1c levels, independently predicted more advanced disease and a poorer five-year survival. Among non-diabetic patients and those who had well-controlled type 2 diabetes (HbA1c <7.5%(58 mmol/mol)), the calculated five-year cancer-specific survival (64% and 74%, respectively) was significantly higher than in patients with poorly controlled type 2 diabetes (HbA1c ⩾7.5%(58 mmol/mol)) (52%, $P < 0.05$) [8]. However, until now, no additional research on the relationship between glycemic control status and mortality in colon cancer patients with DM has been reported.

In this study, we aimed to explore differences in mortality among colon cancer patients with DM compared to patients without DM. A specific aim was to examine the association between glycemic control status and mortality in colon cancer patients with DM.

2. Research design and methods

2.1. Study population

Data from patients with colon cancer who were diagnosed between April 1999 and December 2010 at Kosin University Gospel Hospital were reviewed retrospectively. Patients were eligible for inclusion in this study if they had the following criteria: 1. a histologically confirmed diagnosis of colon cancer, 2. no evidence of any other malignancies, 3. fasting plasma glucose level measured at the time of diagnosed colon cancer. Among a total of 2048 patients with colon cancer, only 741 patients had initial fasting plasma glucose levels. Finally, 741 patients were enrolled in the present study. The stage of colon cancer was classified by AJCC stage and TNM staging system [9]. All patients received tailored therapy depending on the stage of colon cancer.

2.2. Data collection

Patients were divided into two groups according to fasting plasma glucose levels. Group I ($n = 634$) included non-DM patients with a fasting plasma glucose <126 mg/dL, while group II ($n = 107$) included DM patients with a fasting plasma glucose ⩾126 mg/dL.

Patients with DM were divided into two subgroups according to their glycemic control. Subgroup I ($n = 23$) was the uncontrolled group consisting of patients with an HbA1c ⩾8%(64 mmol/mol), and subgroup II ($n = 38$) was the well-controlled group consisting of patients with an HbA1c <8% (64 mmol/mol). We compared differences in mortality according to the DM status and glycemic control.

2.3. Statistical analysis

Data were analyzed by SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). The student's *t*-test and chi square test were used for analysis of baseline characteristics. Kaplan–Meier analysis was used to assess factors affecting mortality and overall and median survival. A log-rank test was used to compare survival rates between the two groups. Overall survival was defined as the length of time from either the date of diagnosis or the start of treatment for colon cancer. We analyzed the relative risk of mortality based on the status of DM and glycemic control by using logistic regression. ROC curve analysis was performed to determine the cut off value of HbA1c that is indicative of proper glycemic control in colon cancer patients with DM. In all cases, a p-value <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Of all the study patients, 107 patients were categorized as DM, and 634 patients were categorized as non-DM. The mean age was 64.72 ± 11.60 in non-DM patients and 68.05 ± 9.95 in DM patients.

There were no significant differences in cancer staging, total cholesterol, triglyceride, HDL(high-density lipoproteins), LDL(low-density lipoproteins), neutrophil lymphocyte ratio, or CRP(C-reactive protein) levels. Patients with DM were more likely to have a higher WBC count than patients without DM. The baseline characteristics of both DM and non-DM patients are given in Table 1.

Of all DM patients, 39 patients were categorized as controlled DM, and 22 patients were categorized as uncontrolled DM. The mean age was 67.72 ± 9.91 in controlled DM patients and 67.86 ± 8.65 in uncontrolled DM patients.

There were no significant differences in cancer staging, total cholesterol, triglyceride, HDL, LDL, neutrophil lymphocyte ratio, CRP, WBC levels. The baseline characteristics of both controlled DM and uncontrolled DM patients are given in Table 2.

3.2. Mortality of colon cancer patients

A Kaplan–Meier analysis showed a significant difference in mortality based on the presence of DM and HbA1c levels (Fig. 1). Patients with DM had significantly shorter OS and MS than non-DM patients (14.0 vs 22.8 mo., $p = 0.003$ and 11.4 vs 17.7 mo., $p = 0.003$, respectively) (Fig. 1A). Among patients with DM, uncontrolled DM patients had a significantly shorter OS and MS than well-controlled DM patients (11.4 vs 17.6 mo., $p = 0.003$ and 8.0 vs 10.7 mo., $p = 0.003$, respectively) (Fig. 1B).

3.3. Relative risk of mortality

The relative risk of mortality is higher for DM patients than for non-DM patients (RR 1.17, 95% CI 0.76–1.80); however, this difference was not significant. After adjusting for age, sex, CRP, WBC, and cholesterol, it was still not significant. The