Altered Glucose Metabolism During Chemoradiation for Head and Neck Cancer

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Abstract. *Platinum-based chemotherapy has been reported to induce diabetes and hyperosmolar coma in nondiabetic patients. The aim of the present study was to determine whether the administration of chemoradiation for head and neck carcinoma alters glucose metabolism during and after treatment. Patients and Methods: Weekly nonfasting serum glucose level was obtained during treatment of one hundred and six patients with locally advanced head and neck cancer who underwent chemoradiationt. Results: For the 91 non-diabetic patients, mean serum glucose level measured 97.75 before and 102.1, 102, 104.1, 109.1, 109.7, 110.3, 109.8, 113.2, 107.7 and 104.3 mg/dl during weeks 1-10 of treatment respectively. Serum glucose level elevation reached statistical significance for weeks 5-8. Conclusion: Chemoradiation for head and neck cancer may produce severe glucose metabolism alteration during treatment.*

Administration of chemoradiation for head and neck cancer may cause severe metabolic alteration during treatment (1). Weight loss and dysphagia from severe mucositis are common despite tube feedings (2). Cisplatinum (CDDP) is frequently the chosen chemotherapy agent during treatment because of demonstrated benefit on local control and survival (3). CDDP may induce electrolyte abnormalities and renal failure which compounds the effect of weight loss. In animal experiments, CDDP impairs glucose tolerance through hyperglucagonemia and deficient insulin response to hyperglycemia (4, 5).

Hyperosmolar coma has been reported during CDDP administration in various malignancies (6-8). Recently an association between diabetes mellitus and CDDP induction chemotherapy for head and neck cancer was observed (9) and prompted the Authors to conduct this retrospective study to determine whether alteration of glucose metabolism during head and neck cancer chemoradiation could indeed be detected and confirmed.

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Patients and Methods

Selection criteria. A retrospective review was performed of 106 patients with locally advanced head and neck cancer who underwent concurrent chemoradiation between May 1999 and February 2006 at the Veterans Administration Health Care System. All patients had weekly complete blood count (CBC) and serum metabolic panel (glucose, electrolytes, blood urea nitrogen and creatinine) examinations as part of routine monitoring during treatment. Nonfasting blood sugar (BS) was recorded from their electronic medical record and provided the data for the current study. Patients with nonfasting BS levels above 200 mg/dl were considered diabetics according to the American Diabetes Association guidelines (10). Except for one patient who declined tube feedings, all patients underwent percutaneous gastrostomy tube placement prior to treatment because of the expected severe mucositis.

Patient characteristics. One hundred and six patients were selected: 85 Caucasians and 21 African-Americans, with ages ranging from 34-86 (median age 59 years). The majority of tumors were of advanced stage according to the American Joint Commission staging criteria 2002 (11) and pathologists reported the histological type in 105 cases as squamous carcinoma and one case of basaloid type carcinoma. All patients had Karnofsky performance status (PS) of >70%. Patient family history with respect to diabetes was unknown. Table I summarizes patients' characteristics.

Treatment. Patients received 5-fluorouracil (5-FU) 1,000 mg/m^2 intravenously (*i.v.*) by continuous infusion on days 1-4 and 21-24, and CDDP 100 mg/m^2 on day 1 and 21 of radiation, except for nasopharyngeal carcinoma patients who received CDDP 100 mg/m^2 *i.v.* on days 1, 22, and 43 of radiation. Decadron 20 mg *i.v.* and Zofran 20 mg *i.v.* were given as antiemetic agents on day 1 of chemotherapy. Radiation therapy was delivered on a cobalt unit or a 6 mV linear accelerator. The tumor and regional lymph nodes outlined on CT scan planning were treated to a total dose of 3,960 to 4,000 cGy with two lateral fields (180-200 cGy/fraction). The posterior neck and anterior neck was treated afterward with en face electrons fields and two lateral photons fields respectively to 1,000-1,080 cGy (180-200 cGy/fraction). In the final phase, the gross tumor was boosted with two lateral fields for an additional dose of 1,600-2,200 cGy. The low neck was treated with an antero-posterior field to a total dose ranging from 5,000-5,040 cGy (180-200 cGy/fraction). The dose was prescribed to a depth of 3 cm. An anterior or lateral cheater block was added to the supraclavicular or lateral fields to avoid overdose of the spinal cord. The dose range delivered to gross tumor was 6,600-7,200 cGy (92 patients received 7000-7200 cGy to the tumor bed).

Patients were evaluated weekly during treatment, or more frequently if clinically indicated. Toxicity during treatment was assessed according to the Radiation Therapy Oncology Group (RTOG) toxicity scale (12). Weight loss was measured along with treatment delays and side-effects. These parameters were recorded at the end of the treatment.

Statistical analysis. Statistical analysis was performed with the paired *t*-test. Statistical significance was assigned to values achieving $p<0.05$.

Results

Ninety-one patients (85%) experienced grade 3-4 mucositis during the treatment, resulting in weight loss (median: 7.2 kg) and treatment breaks (median: 13 days). The nonfasting serum glucose level ranged from 62 to 207 mg/dl before treatment (mean: 102 mg/dl). Figure 1 described nonfasting glucose elevation during treatment. Serum glucose elevation reached statistical significance during weeks 5, 6, 7 and 8 for the non-diabetic group (*p*-values were 0.003, 0.007, 0.009, and 0.01 respectively). Eleven nondiabetic patients had serum glucose levels exceeding 200 mg/dL during treatment. C-peptide, fasting blood sugar, oral glucose tolerance test and serum cortisol and catecholamine levels were not determined for these patients. Ten patients were treated with subcutaneous insulin to reduce hyperglycemia. One patient with hyperosmolar diabetic coma was treated with intravenous insulin and hydration. Two of these patients died during treatment; one death was attributed to hyperosmolar glycemic coma following aspiration pneumonia. The blood glucose level normalized following treatment for six patients while three remained diabetic. Three additional patients with serum glucose elevation during treatment which did not reach the diabetic range developed diabetes following treatment. Overall six nondiabetic patients developed diabetes after treatment requiring oral hypoglycemic agents.

All fifteen patients with insulin-dependent diabetes prior to treatment continued with insulin during treatment. Their insulin dose was adjusted during chemoradiation to maintain normoglycemia. Table II summarizes characteristics of patients who had diabetic range serum glucose levels during treatment. Figure 1 summarizes the mean serum glucose levels during treatment for the whole group, nondiabetic and diabetic groups. Figure 2 summarizes the percentage increase of mean serum glucose level for nondiabetic patients.

Table I. *Patients' characteristics.*

Patient no.	106
Median age, years	59 (34-86)
Gender	
Male	105
Female	1
Race	
Caucasians	85
African-Americans	21
Disease site	
Oropharynx	55
Larynx	26
Hypopharynx	10
Nasopharynx	6
Paranasal sinus	1
Unknown	1
Stage	
II	1
III	31
IVA	55
IVB	18
Recurrence	2
Diabetes insulino-dependent before treatment	
Yes	15
No	91

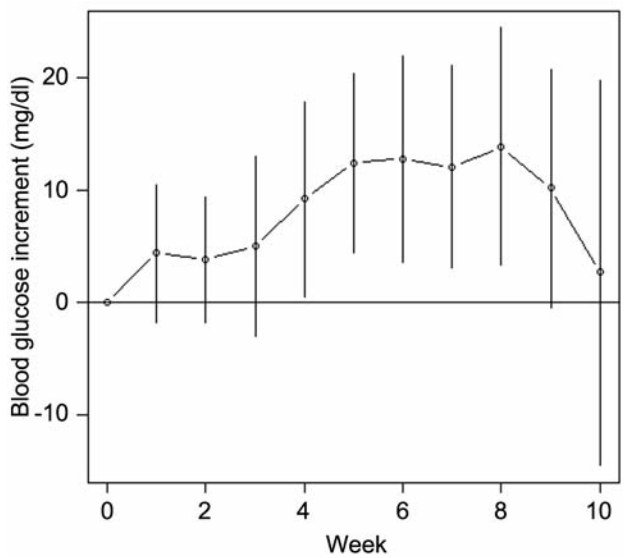

Figure 1. *Mean actual increase in serum glucose values (mg/dl) level during chemoradiation for head and neck cancer: whole group (triangle), nondiabetic patients (circle) and diabetic patients (square).*

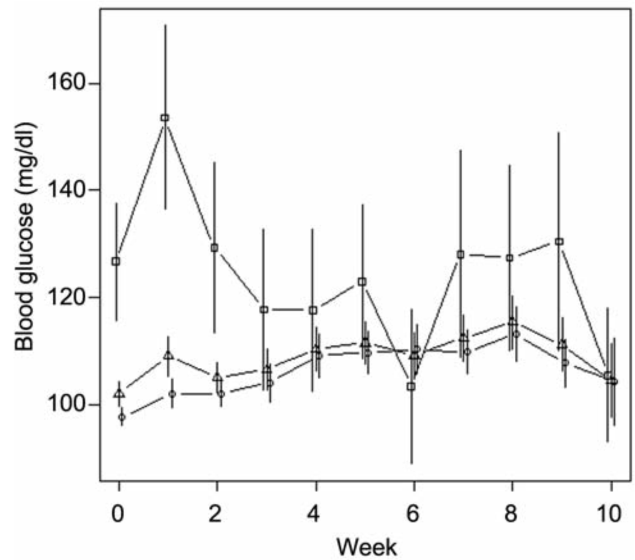

Figure 2. *Mean increase in serum glucose level (mg/dl) during chemoradiation for nondiabetic patients with head and neck cancer. The bars represent the 95% confidence intervals.*

Table II. *Characteristics of nondiabetic patients who developed hyperglycemia in the diabetic range during chemoradiation for head and neck cancer.*

	Age	Race (mg/dl)	Stage	Disease site	Peak blood glucose level		Diabetes after treatment
					Before	During treatment	
1	76	A	III	Larynx	102	273 (week 5) 285 (week 6)	Yes
2	75	A	Rec	Larynx	105	252 (week 4) 230 (week 6)	No
3	72	A	III	Larynx	159	201 (week 1) 256 (week 6)	No
4	59	C	III	Larynx	102	225 (week 3) 219 (week 4)	Yes
5	77	C	4A	Hypopharynx	84	222 (week 6)	Died during treatment
6	64	C	4A	Oral cavity	100	538*	Died during treatment
7	63	C	4B	Unknown	119	215 (week 7)	No
8	52	C	4B	Oropharynx	112	275 (week 7)	No
9	66	C	4A	Oropharynx	100	242 (week 9) 286 (week 10)	No
10	66	C	4B	Oropharynx	98	218 (week 6)	No
11	53	C	4B	Oropharynx	110	289 (week 8)	Yes

Rec: Recurrence, *Radiation therapy discontinued after week 7 because of aspiration peneumonia. A, African-American; C, Caucasian.

Discussion

To our knowledge, this is the first study to report hyperglycemia during chemoradiation for head and neck cancer, as well as development of diabetes mellitus following treatment in nondiabetic patients from a relatively large patient pool. Two of the patients died during treatment. One of these two developed hyperosmolar diabetic coma following aspiration pneumonia. A total of six out of 91 (6%) nondiabetic patients developed diabetes following treatment, requiring oral hypoglycemic agents. As this is a retrospective study, fasting blood glucose, C-peptide, oral glucose tolerance test, serum cortisol and catecholamine levels were not performed during treatment. Hyperglycemia during treatment was treated with insulin as morbidity and mortality rate of critically ill patients may be reduced with normalization of glucose levels (13, 14).

Nan *et al*. (9) observed a similar rate (5%) of diabetes in 219 head and neck cancer patients following induction chemotherapy with CDDP-based regimen. There were no reported deaths in that study. Only 10% of the patients encountered nutritional problems; in contrast, the median weight loss in our study was 7.2 kg. The elevated catabolic state may be related to the severity of mucositis observed in almost all our patients when therapeutic irradiation is combined with chemotherapy. Loss of body weight seen in various catabolic states such as burns, starvation or sepsis are frequently associated with increased levels of stress hormones (15); stress-induced hyperglycemia may result (16). Administration of CDDP may further compound the severity of hyperglycemia because of its inhibition of insulin secretion (5). Komdeur *et al*. (8) reported a case of hyperglycemic hyperosmolar coma following cycle 3 CDDP in a nondiabetic head and neck cancer patient with no prior history of obesity, glucose intolerance or a family history of diabetes. The reported patient had low insulin and C-peptide levels during the hyperglycemic episode, which corroborated animal experiments on insulin deficiency following CDDP treatment. Even though our patients received a corticosteroid for antiemetic purposes during chemotherapy, steroid-induced diabetes is usually associated with long-term use and resolves with discontinuation of the medication (17, 18). Other medications such as NSAIDS may influence the blood glucose level. The 11 nondiabetic patients who developed diabetic range hyperglycemia did not receive oral NSAIDs. The severity of the pain induced by mucositis was controlled with narcotic medication either parenterally or through their gastrostomy tubes. We do not believe that NSAIDs play a role in the development of hyperglycemia as insulin release is increased by NSAIDs, thus causing hypoglycemia (19, 20).

To our knowledge, there is no reported case of hyperglycemia associated with the administration of 5-FU. Mucositis and the stress it induces usually subside following treatment. Thus, the six patients who developed diabetes following treatment may suffer from insulin deficiency secondary to CDDP administration.

Because of the nature of the retrospective study, we lack information on their family history with respect to diabetes to determine whether they were at risk of developing diabetes secondary to altered autonomic nervous system (21).

The limitations of our study includes its retrospective nature, the lack of patient information on family history of diabetes, C-peptide levels and stress hormone levels during treatment. We cannot distinguish whether hyperglycemia during head and neck chemoradiation was the result of stress-induced therapy, chemotherapy agent (CDDP) or was drug-induced (steroid) because of the nature of the retrospective study. These limitations highlight the fact that glucose alteration is an unrecognized complication during chemoradiation for head and neck cancer. Prospective studies should be carried out to identify patients at risk of developing diabetes and to identify the mechanism responsible for hyperglycemia.

Conclusion

Head and neck cancer chemoradiation may induce glucose metabolism alterations. Diabetes may develop during and/or following treatment. Consequently, blood glucose levels should be monitored during and following treatment.

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