THE LEVELS OF NITRITE, NITRATE AND VITAMIN D3 IN HUMAN WITH GASTRIC CANCER

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Abstract

Stomach cancer is one of the most observed in Van and surroundings. Dietary source of Vitamin D are helpful to survive from cancer with low mortality rates. There are so many reports on the association between nitrate intake from food and gastric cancer risk and also nitrate intake from water. The blood samples were taken patients with stomach cancer admitted to Department of Medical Oncology in Faculty of Medicine in Van. Ranging from 45-76 years old of age 32 male, 15 female patients with a total 47 were used in the research. Stomach adenocarcinoma were diagnosed from all patients with endoscopic biopsy. Then the chest X-Ray, abdominal computed tomography, biochemical and hematological analysis were done and magnetic resonance were used when it is necessary for grading. The changes of blood parameters after 3-4 cycles of chemotherapy compared to the values at the diagnosis time were analyzed. The blood samples were taken after chemotherapy and analyzed for nitrate, nitrite spectrophotometrically and vitamin D by HPLC. Comparing with control group, the nitrite levels were increased in cancer patients before and after the chemotherapy. But the levels of nitrate were high before chemotherapy then decreased after chemotherapy. Vit D levels of two groups were low then the controls. These three compounds were significantly important for gastric cancer formation in this cases.

Key Words: Nitrite, nitrate, vitamin D, gastric cancer
Introduction

Vitamin D is known mainly for the bone and Ca metabolism but lately its association with the risk of several cancer, diabetes and premature death were recognized. The low serum of 25(OH) vitamin D is the principal form of circulating vitamin D and its low levels indicate D vitamin deficiencies especially seen during fall and winter. Serum levels below 30 ng/mL are associated with risk of colon cancer, levels above 150 ng/mL suggest potential toxicity (1,2,3). There are so many reports for the beneficial effect on risk of colon, prostate ovarium cancer Vit D, Vit D metabolite, sunlight exposure are the main source of this beneficial effects. Dietary source of Vitamin D are also helpful to survive from cancer with low mortality rates (4). 1,25 Dihidro Vitamin D is synthesized in colon epithelium provides a possible explanation for lower incidence rates of colon cancer (3). Normal colon breast and prostate epithelial cells have a vitamin D receptor that is highly sensitive to 1,25 (OH)2D. This could provide mechanism of anticarcinogenic action for either circulatory or locally synthesized 1,25 (OH)2D (5).

Oxidized food may enhance the oxidation of nitrate and nitrite during their digestion in the stomach and saliva plays a role of in the lipid peroxidation of oxidized foof in stimulated gastric fluid (6,7). Green leafy vegetables, root vegetables processed meat products and water are the main source of nitrate and nitrite in the human diet. Dietary nitrate is reduced to nitrite by oral flora and absorbed from the stomach and proximal small intestinal into the plasma (8,9).

Nitrate is actively concentrated from plasma into saliva and is then resecreted into the upper intestinal tract. Under acidic concentration of the stomach nitrate is protonated to form HNO2 and decomposed to nitric oxide NO and nitrogen dioxide NO2 which is a powerful oxidizing reactive compound can stimulate lipid peroxidation and NO2 depletes antioxidant compounds from plasma (10,11).

Nitrate at pH 3 deaminates DNA bases producing mutagenic lesions. This effect was prevented by polyphenols, secondary amines in food can be converted to nitrosamine in gastric conditions by nitrite (12,13).

The release of NO from nitrite from stomach is depend on the acidic pH of stomach, inhibition of gastric secretion in the stomach prevents release of NO from nitrite (14).
Precence of reducing compounds as Vit C dietary polyphenol, enhances the reduction of Nitrit NO (2,15). In the stomach nitrite interacts easily and reversibly with dietary phenol to form S-nitrosothiols which acts as NO donors exhibits biological activity similar to that of NO (5,16). Nitrite inhibits the process of peroxidation of food lipids during digestion in the stomach. Nitrite rich meal should be consumed with rich in polyphenols antioxidant such as, fruit, vegetables tea or red wine (15,17). There is inverse association between the consumption of fruit vegetables and their product and the incidence of cancer and cardiovascular diseases (18,19).

**Material and Methods**

The blood samples were taken patients with stomach cancer admitted to Department of Medical Oncology in Faculty of Medicine in Van. Ranging from 45-76 years old of age 32 male, 15 female patients with a total 47 were used in the research. Stomach adenocarcenoma were diagnosed from all patients with endoscopic biopsy. Then the chest X-Ray, abdominal computed tomography, biochemical and hematological analysis were done and magnetic resonance were used when it is necessary for grading. The patients suitable for the surgical treatment with localized stage were excluded. Patients with locally advanced and metastatic tumors were candidate to systemic chemotherapy and used in this research.

Before starting to treatment all patients were informed and permission were taken then blood samples were taken to tubes with anticoagulant. Then cisplatin and fluorouracil-based chemotherapy given intravenously or orally were started. The clinical, radiological and laboratory results and responses to chemotherapy were evaluated. Cisplatin-5 Fluorouracil-folinic acide was given once a 14 days or cisplatin-UFT was given once a 21 days.

After 3-4 cycles all patients’ responce to this chemotherapy clinically and radiologically investigated. Clinical complains (Weight loss appetite, abdominal pains ect) were recorded, the two dimentional size of organs with tumor were examined and and the changes of blood parameters after 3-4 cycles of chemotherapy compared to the values at the diagnosis time were analyzed. Later patient were evaluated as responsive and unresponsive. The blood samples were taken after chemotherapy and analyzed for nitrate, nitrite spectrophotometrically and vitamin D by using HPLC.
Results

The plasma levels of the nitrite, nitrate and vitamin D of all patients and control group were shown in table I.

Table I: The plasma levels of the nitrite, nitrate and vitamin D.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>n</th>
<th>Control X ± SE</th>
<th>n</th>
<th>Before chemotherapy X ± SE</th>
<th>n</th>
<th>After chemotherapy X ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrite (mmol/L)</td>
<td>20</td>
<td>0.420±0.120a</td>
<td>24</td>
<td>0.560±10.210a</td>
<td>18</td>
<td>0.650±0.120a</td>
</tr>
<tr>
<td>Nitrate (mmol/L)</td>
<td>20</td>
<td>14.130±2.508c</td>
<td>24</td>
<td>34.430±15.800a</td>
<td>18</td>
<td>21.300±2.940b</td>
</tr>
<tr>
<td>Vitamin D3 (mcg/mL)</td>
<td>20</td>
<td>0.092±0.005a</td>
<td>24</td>
<td>0.030±0.004b</td>
<td>18</td>
<td>0.0421±0.0046b</td>
</tr>
</tbody>
</table>

a, b, c: Different letters in the same line difference between the carrying value of p <0.05 level of statistical significance has.

Comparing with control group, the nitrite levels were increased in cancer patients at before and after the chemotherapy. But the levels of nitrate were high before chemotherapy then decreased after chemotherapy. Vit D levels of two groups were low then the controls.

Conclusions

There are so many papers on the association between nitrate intake from food and gastric cancer risk and also nitrate intake from water. In the Netherland Van Loon et al found that no relation between higher nitrate intake from food and water and risk for gastric cancer. Human can take nitrate from vegetables and in water. Nitrate is increased in water as a consequence of the extensive use of fertilazer. Many studies have shown that metabolites of nitrite rather than nitrate are known carcinogens. Nitrate can be converted into nitrite which can react with secondary amines or amides to produce carcinogaenic N-nitroso compounds (20). Approximately 20% of the nitrite that enters the stomach arises directly from nitrite in the diet and 80% arises from the reduction of salivary nitrate (21). Ascorbic acid can inhibit nitrosation by acting as a competitive substrate for nitrite (22). Both ascorbic acid and beta-carotene may act as scavengers for free radicals, prevents gastric mucosa from oxidative damage and mutations in DNA (23). The conversion of nitrate to nitrite may be inhibited by storage of foods in the refrigerator or freezer (24). In some studies high nitrate consumption...
via ingested food showed no association with gastric cancer risk or even an inverse association.

This finding might result from the fact that vegetables - the main source of nitrate - also contain vitamin C and beta-carotene which appear to be protective factors for gastric cancer. A statistically significant inverse association was reported between nitrate intake from foods and gastric cancer risk (25,26,27), which disappeared after additional adjustment for potential confounders (mainly intake of vitamin C and beta-carotene). In all case-control studies on nitrate and gastric cancer risk, a positive association was reported (25), a non-significant inverse association between nitrate intake from foods and gastric cancer risk and no association between nitrate intake from drinking water. Van Loon et al. (20) did not find a clear association between nitrite intake from foods and gastric cancer risk. In the presented study nitrate levels were high in people with gastric cancer but decreased after chemotherapy, showed nitrate could be a reason for the formation of gastric cancer.

NO is released in some pathological conditions such as hypertension and during inflammation had detrimental effects. It inhibits the intracellular enzymes at molecular levels disrupts gene transcriptions. By disrupting the mitochondrial membranes ion exchange, it inhibits cellular respirations. Apoptosis and necrosis can be formed as a result of DNA damages (28). Dietary intake of nitrate and nitrite are converted to NO under acidic condition of stomach. Ascorbic acid induce the reduction of NO2 to NO in gastric fluid and salivary secretion (29). Peroxynitrite radicals are released as a result of synthesis of NO in the inflammation area and they play an important role in carcinogenesis by DNA mutations (30). Nitrate released from well water in rural areas, processed meat, pickled vegetables, dried fish have procarcinogen properties (31,32). In endemic areas, the high level of gastric cancers are positively correlated with the level of nitrite and nitrate in saliva (30,33).

Gastric cancers are a public health problem in Van region and the incidence of gastric cancer is very high. The majority of patient in rural area with non-healthy living conditions and harmful eating habits are the important factors in the formation of cancer (34). In another study, NO oxidation products and H.pylori prevalences were both high and this situation play an important role in the pathogenesis of gastric cancer. The nitrate and nitrite levels in some traditional foods an drinking water have been found significantly high than the controls (35).
Neoplastic cells carry Vitamin D receptors. When the 1-α hydroxilase enzyme and the levels of 25(OH) Vitamin D is high more than 30 ng/m, the 1,25(OH)_2 Vitamin D can be formed which reducts the proliferation, invasion, angiogenesis and metastasis of cancer. It was reported that Vitamin D deficiency cause high incidence of many cancers such as colon, pancreas, prostate, lung and Hodgin’s lymphoma (3,5). At the end of function of 1,25(OH)_2 in malignant cells does not pass circulation and Ca metabolism is not affected (4,18). It was reported that the intake of adequate amount of Ca with Vitamin D have protective effects on colon and rectum cancers (2). This activity could be increasingly apparent, in the people taken Vitamin D and Ca together whose Vitamin D receptor have certain polymorphic alleles. In this study the vitamin D levels of stomach cancer patients were low than healthy controls.

As conclusion, stomach cancer is one of the most observed in Van and surroundings. The analyzed parameters, nitrate, nitrite and Vitamin D, could be one of the causes of stomach cancer in our cases.
References


