

• CLINICAL RESEARCH •

Involvement of serum retinoids and Leiden mutation in patients with esophageal, gastric, liver, pancreatic, and colorectal cancers in Hungary

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Supported by the grant from the Hungarian Ministry of Health (ETT 595/2003)

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Received: 2005-03-10 Accepted: 2005-08-03

significantly increased in all groups of patients with GI cancer.

CONCLUSION: Retinoids (as environmental factors) are decreased significantly with increased prevalence of Leiden mutation (as a genetic factor) in patients before the clinical manifestation of histologically different (planocellular and hepatocellular carcinoma, and adenocarcinoma) GI cancer.

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Key words: Human gastrointestinal cancer; Leiden mutation; Retinoids; Vitamin A; Zeaxanthin

Mózsik G, Rumi G, Dömötör A, Figler M, Gasztonyi B, Papp E, Pár A, Pár G, Belágyi J, Matus Z, Melegh B. Involvement of serum retinoids and Leiden mutation in patients with esophageal, gastric, liver, pancreatic, and colorectal cancers in Hungary. *World J Gastroenterol* 2005; 11(48): 7646-7650 <http://www.wjgnet.com/1007-9327/11/7646.asp>

Abstract

AIM: To analyze the serum levels of retinoids and Leiden mutation in patients with esophageal, gastric, liver, pancreatic, and colorectal cancers.

METHODS: The changes in serum levels of retinoids (vitamin A, α - and β -carotene, α - and β -cryptoxanthin, zeaxanthin, lutein) and Leiden mutation were measured by high liquid performance chromatography (HPLC) and polymerase chain reaction (PCR) in 107 patients (70 males/37 females) with esophageal (0/8), gastric (16/5), liver (8/7), pancreatic (6/4), and colorectal (30/21 including 9 patients suffering from *in situ* colon cancer) cancer. Fifty-seven healthy subjects (in matched groups) for controls of serum retinoids and 600 healthy blood donors for Leiden mutation were used.

RESULTS: The serum levels of vitamin A and zeaxanthin were decreased significantly in all groups of patients with gastrointestinal (GI) tumors except for vitamin A in patients with pancreatic cancer. No changes were obtained in the serum levels of α - and β -carotene, α - and β -cryptoxanthin, zeaxanthin, lutein in patients with GI cancer. The prevalence of Leiden mutation

INTRODUCTION

The number of patients with different gastrointestinal (esophageal, gastric, liver, pancreatic, and colorectal) cancer has increased about two- to threefolds in the last decades (except for gastric cancer which has decreased 50%) in Hungary. The number of patients who died of these malignant diseases represents the second highest population of the total mortality of patients in Hungary. The second highest mortality rate of gastrointestinal (GI) tumor takes place at the second place in our country.

The causes of GI tumors are not known. However, different genetic and environmental factors play a role in the development of GI cancer. It is generally accepted that different diseases such as acute and chronic inflammatory diseases, polyposis, can be taken as precancerous states of GI cancer.

Since the year of 1980, we have studied the role of retinoids in protecting gastrointestinal mucosa in animal experiments and human observations^[1-4]. Retinoids are chemical compounds of color materials from plants and are built up from C-20 and four isoprene units, while carotenoids are built up from C-40 and eight isoprene units located in about 600 plants, and about 50 from 600

Table 1 Patients with different gastrointestinal tumors

Types of tumors	Number of patients			Histology
	Male	Female	Total	
Esophageal	8 (60±10 yr) ¹	-	8	Planocellular carcinoma
Gastric	16 (64±12 yr) ¹	5 (68±10 yr) ¹	21	Adenocarcinoma
Liver	8 (60±8 yr) ¹	7 (57±13 yr) ¹	15	Hepatocellular carcinoma
Pancreas	6 (56±11 yr) ¹	4 (63±9 yr) ¹	10	Adenocarcinoma
Colorectal	30 (66±10 yr) ¹	23 (65±11 yr) ¹	53	Adenocarcinoma
<i>In situ</i> carcinoma in colon polyps	4 (60±5 yr) ¹	5 (61±5 yr) ¹	9	Adenocarcinoma
Total	70	37	107	
Healthy subjects	29 (50±12 yr) ¹	28 (49±10 yr) ¹	57	

600 blood donors (healthy controls) for Leiden mutation study. ¹Age of patients (mean±SD).

isolated compounds are precursors of vitamin A.

Vitamin A and β -carotene (and other retinoids) have gastric mucosal protective effects in rats provoked by intragastric administration of 1 mL from 0.6 mol/L HCl, 25% NaCl, 0.2 NaOH, and 960 mL/L ethanol, without the presence of any inhibition of gastric acid secretion^[1]. Vitamin A has a higher ulcer healing effect than atropine, cimetidine DE-NOL (tripotassio-dicitrato) in patients with gastric ulcer^[2-4]. The serum level of retinoids is decreased in patients with inflammatory bowel disease^[5-8]. It was also demonstrated that the serum levels of vitamin A and zeaxanthin are also decreased in patients with GI cancer^[9], but the possible correlation between the changes in other serum retinoids and the prevalence of Leiden mutation has not been studied.

The presence of Leiden mutation (replacement of Arg by Glu of residue 506 in the factor V molecule, FVR, 506 Q) has been proven in thrombophilia^[10-13] as well as in Crohn's disease and ulcerative colitis^[14-18], meanwhile no higher prevalence of Leiden mutation has been obtained in patients with acute gastritis and hepatitis^[17]. The significant presence of Leiden mutation (APC) is responsible for blood coagulation abnormality in thrombophilia.

The aims of our present study were to evaluate the changes in serum levels of retinoids (as nutritional components of vitamin A, β -carotene, α -carotene, α - and β -cryptoxanthin, zeaxanthin, lutein) in patients with different gastrointestinal (esophageal, gastric, liver, pancreatic, and colorectal) cancer, to study the prevalence of Leiden mutation in the above mentioned patients, to find some correlation between the changes in Leiden mutation and serum level of vitamin A and zeaxanthin in GI cancer patients as well as between GI cancer development and chemical structure of retinoids, to obtain some correlation between serum levels of vitamin A and zeaxanthin in patients with different GI tumors.

MATERIALS AND METHODS

Observations were carried in 107 patients with esophageal ($n = 8$), gastric ($n = 21$), liver ($n = 15$), pancreatic ($n = 10$), colorectal ($n = 53$), and *in situ* colon ($n = 9$) cancer, including 70 males (50±12 years) and 37 females (49±10 years). Fifty-seven healthy persons (in matched group) were used as control, and 600 healthy blood donors were used for the control of Leiden mutation (Table 1). A total

of 764 patients with gastrointestinal cancer and healthy subjects were included in this study. The studies were approved by the Ethical Committee of University of Pécs, Hungary. Written informed consent was obtained from all participants and the nature of the study was fully explained (Table 1).

Physical, laboratory, iconographic, and histological examinations were carried out in the patients with gastrointestinal tumor. The diagnostic histology indicated planocellular carcinoma in esophagus, hepatocellular carcinoma in liver and adenocarcinoma in stomach, pancreas and colorectum. The control (healthy subjects) persons received physical and laboratory screening, and the medical histories were found to be negative (including the genetic backgrounds).

Measurement of serum retinoid levels

The serum levels of retinoids were measured by high performance liquid chromatography (HPLC). The serum levels of vitamin A, α - and β -carotene, α - and β -cryptoxanthin, zeaxanthin and lutein both in the control (healthy subjects) and in patients with GI tumors were measured. Blood samples were prepared for HPLC measurements: 2 mL of serum sample was shaken with 2 mL/L ethanol for 2 min, and extracted with 3 mL hexane for 2 min. The mixture was centrifuged for 5 min. As an internal standard, canthaxanthin was added to the removed homogenous organic phase, evaporated in vacuum. The residue was dissolved in 0.2 mL 1:4 dichloromethane/methanol and 0.125 mL of this solution was injected. The chromatographic system consists of a gradient former Model 250 B Glenco injector (Glycotec, Germany) and a time programmable UV-vis detector Model 166-2, equipped with Gold chromatography software (Beckmann, USA). The column is 150 mmx 4.6 mm in size packed with Chromsil-C 0.186 mm. The eluent was 30 mL/L water in methanol (A), methanol (B) and 20 v/v dichloromethane in methanol. The flow rate was 1.5 mL/min. The gradient program was 100% A for 30 s, 100% B for 3 min, to 100% for 4 min (linear steps). The time program of wavelength was 323 nm for 3.5 min (detecting vitamin A), then 450 nm (detecting other retinoids). The chromatograms were evaluated quantitatively by relating the peak areas of the individual components to canthaxanthin used as internal standard. The ratio of the molar extinctions of the authentic

Table 2 Serum retinoid level in patients with different gastrointestinal cancer (mean±SE, μmol/L)

Retinoids	Healthy subjects	Esophageal cancer	Gastric cancer	Liver cancer	Pancreatic cancer	Colon cancer	<i>In situ</i> colon cancer
Vitamin A	2.07±0.12	0.14±0.04 ^b	1.02±0.10 ^b	0.75±0.07 ^c	1.68±0.10 ^{NS}	0.35±0.02 ^c	0.30±0.02 ^c
α-Carotene	3.93±0.40	3.81±0.50 ^{NS}	3.85±0.60 ^{NS}	3.82±0.50 ^{NS}	3.90±0.40 ^{NS}	3.80±0.70 ^{NS}	3.80±0.70 ^{NS}
β-Carotene	8.59±0.40	7.50±0.30 ^{NS}	8.01±0.35 ^{NS}	8.10±0.30 ^{NS}	8.40±0.40 ^{NS}	6.80±0.40 ^{NS}	7.90±0.30 ^{NS}
α-Cryptoxanthin	4.10±0.50	4.00±0.60 ^{NS}	3.90±0.50 ^{NS}	4.00±0.40 ^{NS}	3.90±0.40 ^{NS}	4.00±0.30 ^{NS}	4.00±0.30 ^{NS}
β-Cryptoxanthin	6.00±0.60	5.90±0.40 ^{NS}	6.00±0.50 ^{NS}	5.90±0.40 ^{NS}	5.90±0.50 ^{NS}	4.95±0.40 ^{NS}	4.90±0.30 ^{NS}
Zeaxanthin	0.14±0.01	0.074±0.007 ^b	0.08±0.004 ^c	0.05±0.005 ^c	0.03±0.002 ^c	0.07±0.004 ^c	0.03±0.002 ^c
Lutein	0.11±0.007	0.10±0.04 ^{NS}	0.10±0.02 ^{NS}	0.08±0.007 ^{NS}	0.06±0.004 ^b	0.010±0.04 ^{NS}	0.10±0.04 ^{NS}

NS: not significant, ^a $P<0.05$, ^b $P<0.01$, ^c $P<0.001$ vs each group.

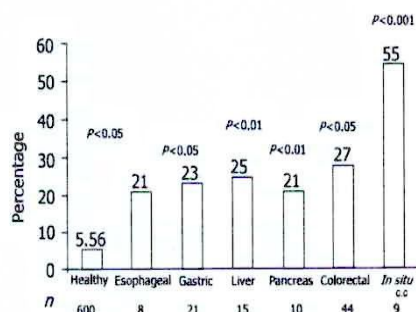


Figure 1 Prevalence of Leiden mutation in patients with different gastrointestinal tumors. The number in abscissa indicates the number of patients (600 healthy blood donors used as control).

samples to that of canthaxanthin was employed as a correction factor of the detector signals. The results were given in μmol/L, and expressed as mean±SE.

Determination of Leiden mutation

Leiden mutation was detected by polymerase-chain reaction (PCR)^[12]. The DNA was isolated from 3 mL EDTA blood.

Statistical analysis

The changes in serum levels of retinoids were detected by the method of ANOVA. The prevalence of Leiden mutation was statistically analyzed by χ^2 test. $P<0.05$ (in the changes of serum retinoids and prevalence of Leiden mutation) was considered statistically significant.

RESULTS

The serum levels of vitamin A were decreased in all groups of patients with esophageal, gastric, hepatocellular and colorectal cancer meanwhile its level remained normal in patients with pancreatic cancer. The serum levels of α- and β-carotene, as provitamins of vitamin A, were normal in different groups of patients with GI cancer. Zeaxanthin level (without presence of any vitamin A property) was decreased significantly in patients with esophageal, gastric, hepatocellular, pancreatic, and colorectal cancer. No changes were obtained in the serum levels of α- and β-cryptoxanthin and lutein in the studied cancer patients (Table 2).

Prevalence of Leiden mutation accounted for 5.56% in

600 healthy blood donors, which was significantly higher in patients with esophageal ($P<0.05$), gastric ($P<0.01$), liver ($P<0.01$), pancreatic ($P<0.05$), colorectal ($P<0.001$) cancer. The higher prevalence of Leiden mutation (55%) was found *in situ* colorectal cancer ($P<0.001$, Figures 1 and 2).

DISCUSSION

Retinoids are chemical compounds of color materials from plants. Increased intake of plant foods can prevent different types of GI cancer. We studied the possible role of different retinoids (vitamin A, α- and β-carotene, α- and β-cryptoxanthin, zeaxanthin, and lutein) in patients with different GI cancer based on previous studies^[5-9,19,20]. The location of GI tumor differed in organs (esophagus, stomach, pancreas, liver, and colon), suggesting that different etiological factors are involved in the development of different GI cancer (Barrett's esophageal metaplasia, chronic atrophic gastritis, viral infection in liver, chronic inflammatory bowel disease) in our everyday medical practice.

The serum levels of vitamin A and zeaxanthin were decreased significantly in all groups of GI cancer patients (not in patients with pancreatic cancer). Surprisingly the serum levels of provitamins were normal in patients with different GI tumor. These results indicate that transformation of provitamins into vitamin A is impaired by some factors at the level of liver, suggesting that the liver plays a key role in the development of tumor. Similar changes were observed in the serum levels of retinoids in patients with hepatocellular cancer, which offers a further proof for this hypothesis.

It is also interesting to evaluate the possible correlation between the terminal chemical structure, vitamin A activity and GI mucosal protection. Our results have clearly proved that there is no close correlation between the terminal chemical structure, vitamin A activity and GI mucosal protection (Table 3).

Similar results have been obtained in animal experiments^[12,21-24] (Table 4). At present, no information is available on the correlation between the serum and tissue levels of retinoids in patients with different GI tumor. These observations cannot be done due to the obligatory necessity of histological evaluation of tumor tissues.

In animal experiments, β-carotene has been found in gastric mucosa of indomethacin-treated rats after

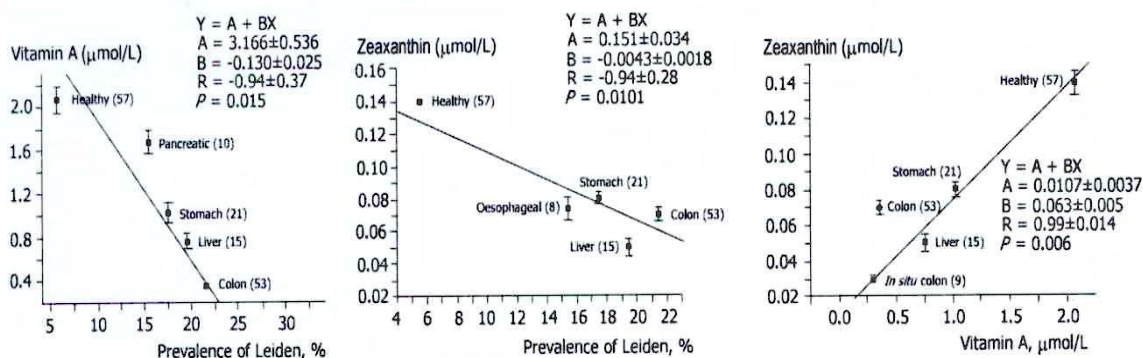


Figure 2 Correlation between the prevalence of Leiden mutation and serum level of vitamin A (A) and zeaxanthin (B) as well as between serum levels of vitamin A and zeaxanthin (C) in patients with different GI tumors. *n* indicates the number (in parenthesis) of examined patients.

Table 3 Changes of serum level of retinoids in patients with different gastrointestinal cancer

	Esophageal cancer	Gastric cancer	Hepatocellular cancer	Pancreatic cancer	Colorectal cancer	<i>In situ</i> colon cancer
Patients	8	21	15	10	44	9
Vitamin A	↓↓	↓↓	↓↓↓	NS	↓↓↓	↓↓↓
α-Carotene	NS	NS	NS	NS	NS	NS
β-Carotene	NS	NS	NS	NS	NS	NS
α-Cryptoxanthin	NS	NS	NS	NS	NS	NS
β-Cryptoxanthin	NS	NS	NS	NS	NS	NS
Zeaxanthin	↓↓	↓	↓↓↓	↓↓↓	↓↓↓	↓↓↓
Lutein	NS	NS	NS	↓↓	NS	NS

P values: between healthy controls vs each group; ↓ = *P* < 0.05 ↓↓ = *P* < 0.01 ↓↓↓ = *P* < 0.001.

Table 4 Correlation between gastric cytoprotective effects of retinoids, their chemical structure and vitamin A activity in rats

Retinoids	Terminal chemical structure	Vitamin A activity	Gastric mucosal prevention
Vitamin A	$R = a$	Yes	Yes
β-Carotene	$X = Y = a$	Yes	Yes
β-Cryptoxanthin	$X = a, Y = b$	Yes	Yes
Zeaxanthin	$X = Y = b$	None	Yes
Lutein	$X = b, Y = c$	None	Yes
Capsorubin	$X = Y = d$	None	None
Capsanthin	$X = b, Y = d$	None	None
Capsanthol	$X = b, Y = e$	None	None
Lycopene	$X = Y = f$	None	None

acute surgical vagotomy^[25,26], however no gastric mucosal protection is found, indicating that intact vagal nerve is necessary for the development of β-carotene-induced gastric cytoprotection^[26]. The mechanism of retinoids is very complex. Our earlier observations indicate that the GI mucosal protective effect of retinoids depends on intact vagal nerve and adrenals as well as on gastric mucosal biochemical changes (retinoids produce a dose-dependent inhibition on the extent of ATP-transformation into ADP in association with a simultaneous increase in the transformation of ATP into cAMP), intact function of sulfhydryl groups and scavenger properties^[9,19,28].

Retinoid-induced GI mucosal protection does not depend on the inhibition of gastric acid secretory responses, vitamin A activity, number of unsaturated double bonds, presence of a characteristic chemical structure of their terminal components and modification

of vascular permeability^[20]. These results clearly indicate that the beneficial effect of retinoids is much more complex than that of their scavengers. The results of biochemical observations suggest that different cAMP-dependent cellular regulatory mechanisms exist (including the functions of retinoid receptors, gene expressions)^[7,20,27].

The involvement of vascular events is suggested in the development of different acute inflammatory processes in the GI tract^[20]. That is the reason why we studied the potential role of Leiden mutation in acute and chronic gastrointestinal inflammatory processes (*Helicobacter pylori*-induced gastritis, viral hepatitis, Crohn's disease, ulcerative colitis). The prevalence of Leiden mutation increased in chronic inflammatory bowel diseases, but no changes were obtained in gastritis and hepatitis. The prevalence of Leiden mutation was also significantly higher in patients with esophageal, gastric, hepatocellular, pancreatic, and colorectal cancer. These results indicate that only the increased prevalence of Leiden mutation does not take place directly in the tumor genesis of human GI cancer. We compared the different results in the examined parameters in patients with acute and chronic gastrointestinal inflammatory diseases, and found a time-sequence process between the inflammatory diseases and GI cancer in patients, suggesting that retinoids play a key role in the development of precancerous state to cancerous state^[5,8,20].

In conclusion, the prevalence of Leiden mutation is significantly correlated with decrease in serum levels of vitamin A and zeaxanthin, suggesting that retinoids play a role in the human GI tumor genesis.

ACKNOWLEDGMENTS

The authors express their thanks to Ms. Katalin Vincze and Ms. Erika Kisapap for the careful preparation of the manuscript.

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