What happens to adiponectin, resistin and apelin-12 in colorectal adenomas? A cross sectional study.

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Abstract

Background

Colorectal adenomas are precancerous neoplastic lesions which may potentially differentiate to the colorectal carcinoma. We investigated whether adiponectin, resistin and apelin 12 serum levels might change in case of colorectal neoplasia. Aims In this study we intended to determine relationship between serum levels of adiponectin, resistin, apelin-12 and presence of colorectal adenoma using case-control approach.

Methods

Patients undergoing screening colonoscopy in the Abant Izzet Baysal University Medical Faculty Gastroenterology Polyclinics between years 2010 and 2013 were selected for study.

Results

In this study there were not any difference between groups according to age, body mass index, waist circumference and mean arterial blood pressure (all p>0.05). Adiponectin, resistin and apelin-12 serum levels were not statistically different between groups (p=0.642, p=0.890, p=0.618; respectively). On the other side: Serum apelin-12 levels were found to be statistically higher in patients with severe dysplastic adenoma group compared to both non-dysplastic and without adenoma groups (p=0.014). There was a negative correlation between the number of colorectal adenomas and serum adiponectin levels (p=0.035, r=-0.41).

Conclusion

Apelin-12 does increase in severe dysplastic adenomas. Apelin-12 is an angiogenic adipocytokine with oncogenic potential. The relation between cancer development and apelin has been shown in different types of tumors. Apelin-12 might be a candidate marker for detecting dysplastic colorectal adenomas.

Introduction

Colorectal adenomas are commonly encountered precancerous lesions which may potentially differentiate to colon carcinoma. There is a lot of risk factor in the development of colorectal adenomas. These are content of food (e.g. high-fat, low fiber, salt, smoked meat), smoking, low physical activity and family history [1–4].

There is increasing evidence that obesity is related with the development of colorectal neoplasia [5]. Increased incidence of colorectal adenoma was observed in patients with metabolic syndrome [6]. Although this, there are conflicting results related with visceral fat and colorectal adenoma risk some of which reveal increased risk, but some not [7, 8]. Chronic state of low grade inflammation is another causal relation between obesity and colorectal neoplasia [9].

Although colorectal carcinogenesis was related with visceral fat accumulation and insulin resistance; such relation has not yet been settled for adenoma development [10]. Increased level of insulin has an IGF-1 like effect on colorectal cells which induce colorectal neoplastic development [11]. It is now better understand that adipose tissue is not only an energy reservoir, but also an endocrine organ which secretes adipocyte derived cytokines such as adiponectin and resistin [12, 13]. Understanding of etiology of colorectal adenomas and identifications of risk factors for development of colorectal adenomas is an important issue for prevention of colorectal cancer.

Once adipose tissue was known to be storage organ, nowadays it is noticed to be an active organ producing various different proteins. Adiponectin an adipocyte derived adipocytokine was shown to be decreased in patients with insulin resistance, obesity and colorectal adenoma [14, 7, 15]. It probably interferes with carcinogenesis [16]. Another adipocyte derived hormone namely resistin was also shown to increase in central obesity and insulin resistance[17]. Apelin-12 is recently discovered adipocytokine, serum level of which positively correlates with insulin resistance [18].

In this study we intended to determine relationship between serum levels of adiponectin, resistin, apelin-12 and presence of colorectal adenoma using case-control approach.

Materials And Methods

Patients: Patients undergoing screening colonoscopy in the Abant Izzet Baysal University Hospital Gastroenterology Polyclinics between years 2010 and 2013 were selected for study. Antropometric measurements were performed by trained medical stuff. Patients who were smoking, known diabetes mellitus, chronic renal disease, chronic hepatic disease, malignancy, hypertension, colitis, colorectal surgery and previously performed colonoscopic examination were excluded from this study. Subjects were grouped according to whether adenoma is present or not. Study has been performed in accordance with ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The study protocol was approved by Düzce University Ethic Comity. Written informed consent was taken from all participants.

Biochemical analysis: All blood samples were obtained after fasting in the morning and centrifuged for 10 min at 1200 g. Serum specimens were stored at -70°C until laboratory analysis. Equal procedures were used in collection, handling, transport and storage of all samples to standardize preanalytical factors which could affect laboratory assessment. Laboratory analyses of samples were performed simultaneously. Resistin and Adiponectin concentrations were measured by enzyme linked immunosorbent assay (ELISA) according to the manufacturer's instructions (BioVendor Laboratomi medicina a.s., Brno, Czech Repulic). Detection range of the Resistin was 0.012-50 ng/mL. Intra-assay and inter-assay precision were % CV: < 5,2 % and < 7 %, respectively. Detection limit of the Adiponectin was 0,47 ng/mL. Intra-assay and inter-assay precision were % CV: < 3,3 % and < 5,8 %, respectively. Apellin-12 concentrations were measured by ELISA according to the manufacturer's instructions (Phoenix Pharmaceuticals, Inc., California, USA). Minimum detectable dose of Apellin-12 was 0,05 ng/mL. Intra-

assay and inter-assay precision were %CV: <10 % and <15 %, respectively. Insulin concentrations were measured by ELISA according to the manufacturer's instructions (DiaMetra S.r.l. Headquater, Segrate, Italy). Minimum detectable dose of insulin is 0.25 µIU/mL. Intra-assay and inter-assay precision were CV (%): <5 % and <10 %, respectively.

Determinations of serum glucose, total cholesterol, HDL and LDL concentrations were measured via colorimetric methods with autoanalysers according to manufacturer's instructions. (Architect c 8000, Abbot Laboratories, USA). We measured total Hb A_{1c} by cation-exchange chromatography (MQ-2000PT, Shanghai Hui Zhong Medical Technology Co.Ltd). This method was traceble with referance method of IFCC.

Colonoscopic examination: Bowel preparation was done with polyethylene glycol. Colonoscopy was performed by an experienced gastroenterologist. The colonoscope was inserted up to ileocecal valve under conscious sedation with midazolam.

Pathologic examination: All specimens were analysed in patalogy department. All paraffin blocks were stained with heamotoxilen and eosin staining and evaluated under light microscope. Adenomatous polyps were grouped as; tubuler, tubulovillous and villous. Adenomatous polyps were grouped as severe, moderate and mild dysplasic; so as to assess the risk of colon cancer development.

Statistical analysis: Kolmogorow-Smirnov test were used for testing normality distribution of numerical properties of data's. The relation between the presence of adenoma and other risk factor were done with univariate analysis. Comparisons of parameters between groups either normally distributed or not were done with Independent Sample-t test or Mann-Whitney U test respectively. The relation between presence of adenoma and categorical variables were evaluated with Pearson ki-square test. For multiple comparisons nonparametric Kruskall Wallis test was used. $P<0.05$ was accepted statistically significant. PASW (version 18) was used for statistical analysis.

Results

26 (38.2%) colorectal adenoma and 42 (61.8%) controls with normal colon were analyzed. Gender distribution was not different between groups ($p = 0.318$). There was no difference between groups in the proportions of age, BMI, WC and mean arterial blood pressure (all $p > 0.05$) (Table-1). The histology of adenomas was 23 (88.5%) tubular adenoma, 2 (7.7%) mix serrated and tubular adenoma and 1 (3.8%) serrated adenoma respectively. According to the neoplastic differentiation; 6 (23.1%) mild dysplastic adenomas, 11 (76.9%) severe dysplastic adenomas were detected. The family frequency of colorectal cancer was significantly higher in patients with adenomas ($p = 0.024$). Fat consumption and Occupation were not statistically significant between groups ($p > 0.05$ for each). HOMA-IR, adiponectin, resistin and apelin-12 serum levels were not statistically different between adenomatous and non-adenomatous groups ($p = 0.603$, $p = 0.642$, $p = 0.890$, $p = 0.618$; respectively) (Table-2). We also compared serum levels of adiponectin, resistin and apelin-12 into three groups including histological differentiation of adenomas

as non-adenoma, adenoma with mild dysplasia, adenoma with severe dysplasia. Only, the median value of the Severe dysplasia significantly higher than the other two groups. (p = 0.014) (Table-3) (Figure-1). A negative correlation between colorectal adenoma numbers and serum adiponectin levels were detected (p = 0.035, r=-0.41). There was a positive correlation between total cholesterol, LDL cholesterol and adenoma size (p = 0.015, r = 0.47; p = 0.007, r = 0.51 respectively) (Table-4).

Discussion

Serum adiponectin, resistin and apelin-12 concentrations were not different between groups. Negative correlation between serum adiponectin level and adenoma number was found. An interesting finding of the study is LDL cholesterol as a strong determinant of colorectal adenoma development. Positive correlation between adenoma size and total and LDL cholesterol was observed.

Although obesity has been linked with colon cancer, title related with the frequency of colorectal adenoma in abdominal obesity is inconclusive [19, 20]. The effect of abdominal obesity on colorectal neoplasia advancement is subject of debate [21, 8, 10]. Every step in progression of colorectal adenoma carcinoma sequence was affected by multiple factors in addition to obesity [22]. The role of obesity in colorectal adenoma development is complex and has not been thoroughly explored.

Other important subject is insulin resistance. HOMA-R measurement was not statistically different between groups. Although colorectal cancer development is more commonly associated with insulin resistance, there are conflicting data related with insulin resistance and adenoma development in patients with colorectal adenomas [23–26]. Colorectal adenomas were not related with insulin resistance in metabolically healthy obese people [27]. Further studies are necessary to identify the impact of insulin resistance on the development of colorectal adenoma.

Adiponectin insulin sensitizing adipocyte derived protein secreted from adipose tissue [28]. Adiponectin has an anti-angiogenic and anti-tumor properties. In our study serum adiponectin levels correlated with adenoma number. In terms of serum adiponectin level; there were no differences in between groups. There were conflicting data related with serum adiponectin level and colon carcinogenesis. Some reveals reduced levels of serum adiponectin levels in colorectal cancer patients while some not [21, 29–32]. Lukanova et al reported that colorectal tumorogenesis was not associated with adiponectin. [33]. Chronis A et al observed similar serum adiponectin levels between adenoma and control groups [34]. Fukumoto et al. demonstrated no protective effect of adiponectin in the development of colorectal adenoma independent from obesity [14]. Bobe G et al demonstrated no associatiation between serum adiponectin levels and adenoma recurrence in a prospective study with 4 years follow period [35]. Instead homocystine level and high fat and low fiber diet were associated with adenoma recurrence implicating importance of weight changes and diet content in colorectal carcinogenesis [35]. Probably other factors such as diets and habits play a major role in colorectal carcinogenesis other than adipocytokines.

Resistin is a protein produced by stromavascular fraction of adipose tissue [36]. Resistin has been widely accepted as a player in tumors like breast and small cell lung cancer [37].There are conflicting data

related with resistin serum levels in colorectal carcinogenesis. Some of them revealed increased serum resistin levels in colorectal cancer and adenoma [38, 30]. There is one study reported that resistin is not a risk factor in colorectal tumorogenesis [39]. In our study serum resistin levels were not significantly different between groups. The role of resistin in colorectal carcinogenesis is still yet to be elucidated.

Apelin-12 is an angiogenic adipocytokine with oncogenic potential. Apelin-12 plays a role in stimulation of endothelial growth and the development of angiogenesis in tumors like lung cancer [40, 41]. The relation between cancer development and apelin has been shown in various types of tumors [42–45]. Apelin-12 expression starts with colorectal adenoma stage and continues throughout the cancer stage in the neoplastic process [46]. Apelin-12 stimulates colorectal tumorogenesis possibly by autocrine fashion [46]. We evaluated pre-malign lesions namely colorectal adenomas instead of cancer. In our study we have detected increase in serum apelin-12 levels in severe dysplastic adenoma group compared to other groups. Serum apelin-12 level might be a good candidate as a marker for colorectal dysplastic adenoma.

There are some limitations in this study. These are low number of study sample, cross sectional design and absence of tissue sample histochemical analysis.

As a conclusion we can suggest that adiponectin and resistin did not increased in colorectal adenomas. Although this; apelin-12 does increase in severe dysplastic adenomas and might be a candidate marker for detecting dysplastic colorectal adenomas. Although this; studies with greater number of patients and prospective nature are required.

Declarations

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Conflict of interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Tables

Table-1: Demographic data of patients undergoing colonoscopy

	With colorectal adenoma	Without colorectal adenoma	p
	Mean±SD	Mean±SD	
Age	50,93±12,97	54,38±9,06	0,239
BMI	27,82±4,74	27,60±5,02	0,858
Waist circumference	93,71±12,52	95,65±13,45	0,548
Mean arterial blood pressure	92,90±11,29	92,19±11,51	0,803

BMI: Body mass index

Table-2: Biochemical data of patients undergoing colonoscopy

	With colorectal adenoma	Without colorectal adenoma	p
	Mean±SD	Mean±SD	
Glucose	95,81±11,23	95,55±11,88	0,929
Post prandial glucose	116,00±37,30	109,59±34,40	0,479
HbA1c	5,65±0,73116	5,54±0,74	0,587
Total cholesterol	206,23±45,96	190,26±40,57	0,139
LDL	138,79±44,19	121,51±36,12	0,083
HDL	44,35±10,39	47,68±11,73	0,239
Trigliceride	117,27±48,26	105,31±43,78	0,296
Insulin	8,45±3,90	9,21±5,32	0,534
HOMA-R	2,04±1,09	2,20±1,39	0,603
Adiponectin	16,14±5,89	15,40±6,54	0,642
Rezistin	11,86±7,50	10,72±4,71	0,890
Apelin-12	0,73±0,38	0,72±0,62	0,618

HOMA-IR: Homeostatic model of assessment of insulin resistance, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein

Table-3: Adipocytokines were compared between three groups.

	Without adenoma	Mild dysplasia	Severe dysplasia	p
	Median (1^{th}-3^{th} Percentiles)	Median (1^{th}-3^{th} Percentiles)	Median (1^{th}-3^{th} Percentiles)	
HOMA-IR	1.62 (2.50-1.60)	2.50 (1.75-3.62)	1.60 (1.19-2.40)	0.26
Insulin	6.70 (5.11-13.16)	10.39 (7.72-15.32)	7.40 (5.25-9.54)	0.24
Adiponectin	15.55 (10.45-23.72)	11.39 (8.51-19.03)	17.77 (12.72-21.17)	0.33
Resistin	9.48 (7.00-13.22)	10.96 (9.43-31.85)	9.71 (7.79-10.89)	0.35
Apelin-12	0.58 (0.45-0.86)[a]	0.56 (0.38-0.71)[a]	0.85 (0.76-1.28)[b]	0.014*

Kruskal Wallis test was done; HOMA-IR: Homeostatic model of assessment of insulin resistance

* Only, the median value of the Severe dysplasia significantly higher than the other two groups.

Table-4: Correlation test between biochemical parameters, variables with categorical features and adenoma properties were presented.

		Adenoma size	Adenoma number	Waist circumference	BMI	Mean arterial blood pressure
Apelin-12	r	0,296	-0,065	-0,047	-0,099	0,074
	p	0,142	0,753	0,702	0,420	0,551
Rezistine	r	0,076	-0,210	0,057	0,195	-0,160
	p	0,713	0,303	0,642	0,112	0,193
Adiponectin	r	0,029	-0,414	-0,247	-0,075	-0,160
	p	0,888	0,035*	0,042*	0,542	0,193
HOMA-IR	r	-0,277	0,198	0,250	0,251	0,185
	p	0,171	0,332	0,040*	0,039*	0,130
Glucose	r	-0,261	0,309	0,437	0,328	0,161
	p	0,197	0,125	0,000*	0,006*	0,190
Total cholesterol	r	0,472	-0,015	-0,143	-0,109	-0,003
	p	0,015*	0,941	0,246	0,377	0,979
LDL	r	0,517	0,018	-0,073	-0,071	0,004
	p	0,007*	0,930	0,554	0,563	0,977
HDL	r	0,136	-0,076	-0,562	-0,340	-0,127
	p	0,508	0,710	0,000*	0,005*	0,302
Triglyceride	r	-0,161	-0,096	0,307	0,188	0,106
	p	0,432	0,642	0,011*	0,125	0,391

HOMA-IR: Homeostatic model of assessment of insulin resistance.

Pearson chi-square test were done.

*Statistically significant

Figures

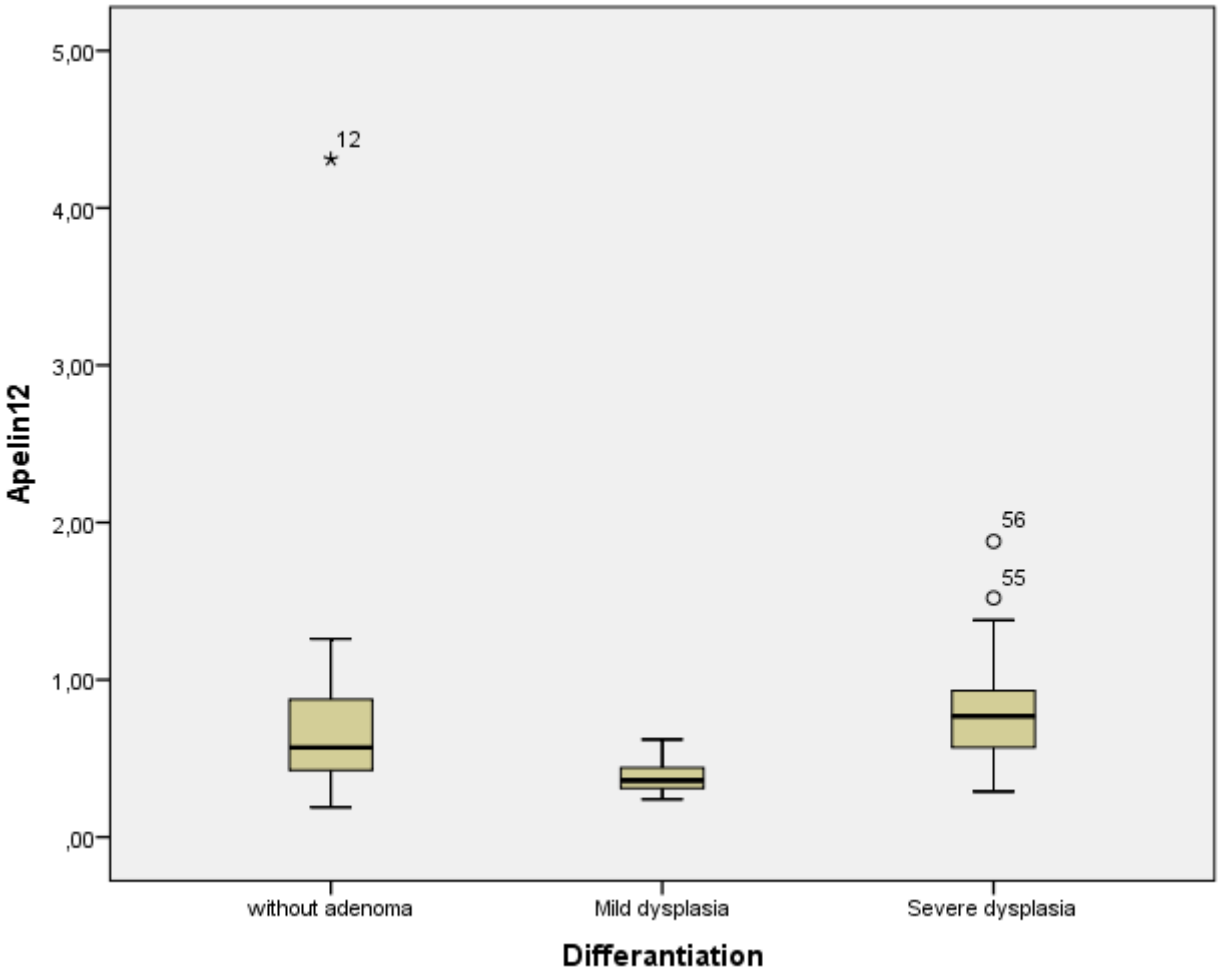

Figure 1

Serum level of apelin-12 levels were presented in groups according to neoplastic differantiation.