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. Anthropometric 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 Republic). 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\textsubscript{1c} by cation-exchange chromatography (MQ-2000PT, Shanghai Hui Zhong Medical Technology Co.Ltd). This method was traceable with reference 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 pathology department. All paraffin blocks were stained with hematoxilen 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 association 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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References

1. Botteri E, Iodice S, Raimondi S, Maisonneuve P, Lowenfels AB (2008) Cigarette
smoking and adenomatous polyps: a meta-analysis. Gastroenterology 134 (2):388-395. doi:10.1053/j.gastro.2007.11.007

2. Fung T, Hu FB, Fuchs C, Giovannucci E, Hunter DJ, Stampfer MJ, Colditz GA, Willett WC (2003) Major dietary patterns and the risk of colorectal cancer in women. Archives of internal medicine 163 (3):309-314

3. Keku TO, Millikan RC, Martin C, Rahkra-Burris TK, Sandler RS (2003) Family history of colon cancer: what does it mean and how is it useful? American journal of preventive medicine 24 (2):170-176

4. Schoen RE, Tangen CM, Kuller LH, Burke GL, Cushman M, Tracy RP, Dobs A, Savage PJ (1999) Increased blood glucose and insulin, body size, and incident colorectal cancer. Journal of the National Cancer Institute 91 (13):1147-1154

5. Dai Z, Xu YC, Niu L (2007) Obesity and colorectal cancer risk: a meta-analysis of cohort studies. World journal of gastroenterology : WJG 13 (31):4199-4206

6. Morita T, Tabata S, Mineshita M, Mizoue T, Moore MA, Kono S (2005) The metabolic syndrome is associated with increased risk of colorectal adenoma development: the Self-Defense Forces health study. Asian Pacific journal of cancer prevention : APJCP 6 (4):485-489

7. Otake S, Takeda H, Suzuki Y, Fukui T, Watanabe S, Ishihama K, Saito T, Togashi H, Nakamura T, Matsuzawa Y, Kawata S (2005) Association of visceral fat accumulation and plasma adiponectin with colorectal adenoma: evidence for participation of insulin resistance. Clinical cancer research : an official journal of the American Association for Cancer Research 11 (10):3642-3646. doi:10.1158/1078-0432.ccr-04-1868

8. Schoen RE, Weissfeld JL, Kuller LH, Thaete FL, Evans RW, Hayes RB, Rosen CJ (2005) Insulin-like growth factor-I and insulin are associated with the presence and advancement of adenomatous polyps. Gastroenterology 129 (2):464-475.
doi:10.1016/j.gastro.2005.05.051

9. Terzic J, Grivennikov S, Karin E, Karin M (2010) Inflammation and colon cancer. Gastroenterology 138 (6):2101-2114 e2105. doi:10.1053/j.gastro.2010.01.058

10. Yamamoto S, Nakagawa T, Matsushita Y, Kusano S, Hayashi T, Irokawa M, Aoki T, Korogi Y, Mizoue T (2010) Visceral fat area and markers of insulin resistance in relation to colorectal neoplasia. Diabetes care 33 (1):184-189. doi:10.2337/dc09-1197

11. Nomura AM, Stemmermann GN, Lee J, Pollak MN (2003) Serum insulin-like growth factor I and subsequent risk of colorectal cancer among Japanese-American men. American journal of epidemiology 158 (5):424-431

12. Kershaw EE, Flier JS (2004) Adipose tissue as an endocrine organ. The Journal of clinical endocrinology and metabolism 89 (6):2548-2556. doi:10.1210/jc.2004-0395

13. Maeda K, Okubo K, Shimomura I, Mizuno K, Matsuzawa Y, Matsubara K (1997) Analysis of an expression profile of genes in the human adipose tissue. Gene 190 (2):227-235

14. Fukumoto J, Otake T, Tajima O, Tabata S, Abe H, Mizoue T, Ohnaka K, Kono S (2008) Adiponectin and colorectal adenomas: Self Defense Forces Health Study. Cancer science 99 (4):781-786. doi:10.1111/j.1349-7006.2008.00745.x

15. Ryo M, Nakamura T, Kihara S, Kumada M, Shibazaki S, Takahashi M, Nagai M, Matsuzawa Y, Funahashi T (2004) Adiponectin as a biomarker of the metabolic syndrome. Circulation journal : official journal of the Japanese Circulation Society 68 (11):975-981

16. Miyoshi Y, Funahashi T, Kihara S, Taguchi T, Tamaki Y, Matsuzawa Y, Noguchi S (2003) Association of serum adiponectin levels with breast cancer risk. Clinical cancer research : an official journal of the American Association for Cancer Research
17. Kocak H, Oner-Iyidogan Y, Gurdol F, Oner P, Suzme R, Esin D, Issever H (2007) Advanced oxidation protein products in obese women: its relation to insulin resistance and resistin. Clinical and experimental medicine 7 (4):173-178. doi:10.1007/s10238-007-0143-x

18. Li L, Yang G, Li Q, Tang Y, Yang M, Yang H, Li K (2006) Changes and relations of circulating visfatin, apelin, and resistin levels in normal, impaired glucose tolerance, and type 2 diabetic subjects. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association 114 (10):544-548. doi:10.1055/s-2006-948309

19. MacInnis RJ, English DR, Haydon AM, Hopper JL, Gertig DM, Giles GG (2006) Body size and composition and risk of rectal cancer (Australia). Cancer causes & control : CCC 17 (10):1291-1297. doi:10.1007/s10552-006-0074-y

20. Pischon T, Lahmann PH, Boeing H, Friedenreich C, Norat T, Tjonneland A, Halkjaer J, Overvad K, Clavel-Chapelon F, Boutron-Ruault MC, Guner G, Bergmann MM, Linseisen J, Becker N, Trichopoulou A, Trichopoulos D, Sieri S, Palli D, Tumino R, Vineis P, Panico S, Peeters PH, Bueno-de-Mesquita HB, Boshuizen HC, Van Guelpen B, Palmqvist R, Berglund G, Gonzalez CA, Dorronsoro M, Barricarte A, Navarro C, Martinez C, Quiros JR, Roddam A, Allen N, Bingham S, Khaw KT, Ferrari P, Kaaks R, Slimani N, Riboli E (2006) Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). Journal of the National Cancer Institute 98 (13):920-931. doi:10.1093/jnci/djj246

21. Erarslan E, Turkay C, Koktener A, Koca C, Uz B, Bavbek N (2009) Association of visceral fat accumulation and adiponectin levels with colorectal neoplasia. Digestive diseases and sciences 54 (4):862-868. doi:10.1007/s10620-008-0440-6
22. Matsubara N (2012) Epigenetic regulation and colorectal cancer. Diseases of the colon and rectum 55 (1):96-104. doi:10.1097/DCR.0b013e318233a1ef

23. Chung YW, Han DS, Park YK, Son BK, Paik CH, Lee HL, Jeon YC, Sohn JH (2006) Association of obesity, serum glucose and lipids with the risk of advanced colorectal adenoma and cancer: a case-control study in Korea. Digestive and liver disease: official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 38 (9):668-672. doi:10.1016/j.dld.2006.05.014

24. Keku TO, Lund PK, Galanko J, Simmons JG, Woosley JT, Sandler RS (2005) Insulin resistance, apoptosis, and colorectal adenoma risk. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 14 (9):2076-2081. doi:10.1158/1055-9965.epi-05-0239

25. Tabuchi M, Kitayama J, Nagawa H (2008) Hyperglycemia and hypertriglyceridemia may associate with the adenoma-carcinoma transition in colorectal epithelial cells. Journal of gastroenterology and hepatology 23 (6):985-987. doi:10.1111/j.1440-1746.2007.05072.x

26. Yamada K, Araki S, Tamura M, Sakai I, Takahashi Y, Kashihara H, Kono S (1998) Relation of serum total cholesterol, serum triglycerides and fasting plasma glucose to colorectal carcinoma in situ. International journal of epidemiology 27 (5):794-798

27. Yun KE, Chang Y, Jung HS, Kim CW, Kwon MJ, Park SK, Sung E, Shin H, Park HS, Ryu S (2013) Impact of body mass index on the risk of colorectal adenoma in a metabolically healthy population. Cancer research 73 (13):4020-4027. doi:10.1158/0008-5472.can-12-3477

28. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K (2006) Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome.
29. Kosova F, Coskun T, Kaya Y, Kara E, Ari Z (2013) Adipocytokine levels of colon cancer patients before and after treatment. Bratislavske lekarske listy 114 (7):394-397

30. Kumor A, Daniel P, Pietruczuk M, Malecka-Panas E (2009) Serum leptin, adiponectin, and resistin concentration in colorectal adenoma and carcinoma (CC) patients. International journal of colorectal disease 24 (3):275-281. doi:10.1007/s00384-008-0605-y

31. Scheid MP, Sweeney G (2014) The role of adiponectin signaling in metabolic syndrome and cancer. Reviews in endocrine & metabolic disorders 15 (2):157-167. doi:10.1007/s11154-013-9265-5

32. Wei EK, Giovannucci E, Fuchs CS, Willett WC, Mantzoros CS (2005) Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. Journal of the National Cancer Institute 97 (22):1688-1694. doi:10.1093/jnci/dji376

33. Lukanova A, Soderberg S, Kaaks R, Jellum E, Stattin P (2006) Serum adiponectin is not associated with risk of colorectal cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 15 (2):401-402. doi:10.1158/1055-9965.epi-05-0836

34. Chronis A, Thomopoulos K, Sapountzis A, Triantos C, Kalafateli M, Kalofonos C, Nikolopoulou V (2011) Adiposity factors are not related to the presence of colorectal adenomas. Clinical and experimental gastroenterology 4:257-261. doi:10.2147/ceg.s25594

35. Bobe G, Murphy G, Rogers CJ, Hance KW, Albert PS, Laiyemo AO, Sansbury LB, Lanza E, Schatzkin A, Cross AJ (2010) Serum adiponectin, leptin, C-peptide, homocysteine, and colorectal adenoma recurrence in the Polyp Prevention Trial. Cancer
epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 19 (6):1441-1452. doi:10.1158/1055-9965.epi-09-1082

36. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA (2001) The hormone resistin links obesity to diabetes. Nature 409 (6818):307-312. doi:10.1038/35053000

37. Tiaka EK, Manolakis AC, Kapsoritakis AN, Potamianos SP (2011) The implication of adiponectin and resistin in gastrointestinal diseases. Cytokine & growth factor reviews 22 (2):109-119. doi:10.1016/j.cytogfr.2011.04.002

38. Gonullu G, Kahraman H, Bedir A, Bektas A, Yucel I (2010) Association between adiponectin, resistin, insulin resistance, and colorectal tumors. International journal of colorectal disease 25 (2):205-212. doi:10.1007/s00384-009-0828-6

39. Otake S, Takeda H, Fujishima S, Fukui T, Orii T, Sato T, Sasaki Y, Nishise S, Kawata S (2010) Decreased levels of plasma adiponectin associated with increased risk of colorectal cancer. World journal of gastroenterology : WJG 16 (10):1252-1257

40. Cox CM, D'Agostino SL, Miller MK, Heimark RL, Krieg PA (2006) Apelin, the ligand for the endothelial G-protein-coupled receptor, APJ, is a potent angiogenic factor required for normal vascular development of the frog embryo. Developmental biology 296 (1):177-189. doi:10.1016/j.ydbio.2006.04.452

41. Sorli SC, Le Gonidec S, Knibiehler B, Audigier Y (2007) Apelin is a potent activator of tumour neoangiogenesis. Oncogene 26 (55):7692-7699. doi:10.1038/sj.onc.1210573

42. Altinkaya SO, Nergiz S, Kucuk M, Yuksel H (2014) Apelin levels are higher in obese patients with endometrial cancer. The journal of obstetrics and gynaecology research. doi:10.1111/jog.12503

43. Berta J, Kenessey I, Dobos J, Tovari J, Klepetko W, Jan Ankersmit H, Hegedus B, Renyi-
Vamos F, Varga J, Lorincz Z, Paku S, Ostoros G, Rozsas A, Timar J, Dome B (2010) Apelin expression in human non-small cell lung cancer: role in angiogenesis and prognosis. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 5 (8):1120-1129. doi:10.1097/JTO.0b013e3181e2c1ff

44. Feng M, Yao G, Yu H, Qing Y, Wang K (2016) Tumor apelin, not serum apelin, is associated with the clinical features and prognosis of gastric cancer. BMC cancer 16 (1):794. doi:10.1186/s12885-016-2815-y

45. Heo K, Kim YH, Sung HJ, Li HY, Yoo CW, Kim JY, Park JY, Lee UL, Nam BH, Kim EO, Kim SY, Lee SH, Park JB, Choi SW (2012) Hypoxia-induced up-regulation of apelin is associated with a poor prognosis in oral squamous cell carcinoma patients. Oral oncology 48 (6):500-506. doi:10.1016/j.oraloncology.2011.12.015

46. Picault FX, Chaves-Almagro C, Projetti F, Prats H, Masri B, Audigier Y (2014) Tumour co-expression of apelin and its receptor is the basis of an autocrine loop involved in the growth of colon adenocarcinomas. European journal of cancer (Oxford, England : 1990) 50 (3):663-674. doi:10.1016/j.ejca.2013.11.017

Tables

Table-1: Demographic data of patients undergoing colonoscopy

|                     | With colorectal adenoma Mean±SD | Without colorectal adenoma Mean±SD | p   |
|---------------------|---------------------------------|------------------------------------|-----|
| Age                 | 50,93±12,97                     | 54,38±9,06                         | 0.23|
| BMI                 | 27,82±4,74                      | 27,60±5,02                         | 0.85|
| Waist circumference | 93,71±12,52                     | 95,65±13,45                        | 0.54|
| Mean arterial blood pressure | 92,90±11,29                   | 92,19±11,51                        | 0.80|
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    | 116.00±37.30            | 109.59±34.40                | 0.479 |
| glucose          | 5.65±0.73116            | 5.54±0.74                   | 0.587 |
| HbA1c            | 206.23±45.96            | 190.26±40.57                | 0.139 |
| Total cholesterol| 138.79±44.19            | 121.51±36.12                | 0.083 |
| LDL              | 44.35±10.39             | 47.68±11.73                 | 0.239 |
| Triglyceride     | 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 |
| Resistin         | 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<sup>st</sup>-3<sup>rd</sup> Percentiles) | Median (1<sup>st</sup>-3<sup>rd</sup> Percentiles) | Median (1<sup>st</sup>-3<sup>rd</sup> Percentiles) |       |
| HOMA-IR          | 1.62 (2.50-1.60) | 2.50 (1.75-3.62) | 1.60 (1.19-2.40) | 0.21  |
| Insulin          | 6.70 (5.11-13.16) | 10.39 (7.72-15.32) | 7.40 (5.25-9.54) | 0.22  |
| Adiponectin      | 15.55 (10.45-23.72) | 11.39 (8.51-19.03) | 17.77 (12.72-21.17) | 0.32  |
| Resistin         | 9.48 (7.00-13.22) | 10.96 (9.43-31.85) | 9.71 (7.79-10.89) | 0.33  |
| Apelin-12        | 0.58 (0.45-0.86)<sup>a</sup> | 0.56 (0.38-0.71)<sup>a</sup> | 0.85 (0.76-1.28)<sup>b</sup> | 0.01  |
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          | 0.07 |
|                  | p            | 0.142          | 0.753              | 0.702 | 0.420          | 0.55 |
| Rezistine        | r            | 0.076          | -0.210             | 0.057 | 0.195          | -0.16|
|                  | p            | 0.713          | 0.303              | 0.642 | 0.112          | 0.19 |
| Adiponectin      | r            | 0.029          | -0.414             | -0.247 | -0.075          | -0.16|
|                  | p            | 0.888          | 0.035*             | 0.042* | 0.542          | 0.19 |
| HOMA-IR          | r            | -0.277         | 0.198              | 0.250 | 0.251          | 0.18 |
|                  | p            | 0.171          | 0.332              | 0.040* | 0.039*          | 0.13 |
| Glucose          | r            | -0.261         | 0.309              | 0.437 | 0.328          | 0.16 |
|                  | p            | 0.197          | 0.125              | 0.000* | 0.006*          | 0.19 |
| Total cholesterol| r            | 0.472          | -0.015             | -0.143 | -0.109          | -0.00|
|                  | p            | 0.015*         | 0.941              | 0.246 | 0.377          | 0.97 |
| LDL              | r            | 0.517          | 0.018              | -0.073 | -0.071          | 0.00 |
|                  | p            | 0.007*         | 0.930              | 0.554 | 0.563          | 0.97 |
| HDL              | r            | 0.136          | -0.076             | -0.562 | -0.340          | -0.12|
|                  | p            | 0.508          | 0.710              | 0.000* | 0.005*          | 0.30 |
| Triglyceride     | r            | -0.161         | -0.096             | 0.307 | 0.188          | 0.10 |
|                  | p            | 0.432          | 0.642              | 0.011* | 0.125          | 0.39 |

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

Pearson chi-square test were done.

*Statistically significant
Serum level of apelin-12 levels were presented in groups according to neoplastic differentiation.