Adipo-R1 and Adipo-R2 Expression in Colorectal Adenomas and Carcinomas

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Abstract

Background: Human adiponectin (ApN), a 30 kDa glycoprotein of 244-amino acids which is predominantly produced by adipocytes, exerts its effects via two receptors, namely adiponectin receptor-1 (adipo-R1) and adiponectin receptor-2 (adipo-R2) with differential binding affinity to globular adiponectin. Adiponectin receptor expression has been studied in several cancer tissues. However, there are no studies of colorectal adenomas which are considered to be precursors for colorectal carcinoma (CRC). Objectives: In the present study, the expression of adipo-R1 and adipo-R2 was investigated immunohistochemically in colorectal adenomas and colorectal carcinoma tissues in an attempt to determine associations with these tumors. Materials and Methods: The study enrolled 50 CRC patients with tumor resection and 82 patients who were diagnosed with adenomatous polyps, classified as negative for neoplasia, low-grade dysplasia (L-GD) or high-grade dysplasia (H-GD). Results: Expression of both adipo-R1 and adipo-R2 was found to be significantly lower in the CRCs than in colorectal adenomas (tubular and tubulovillous, p=0.009 and p<0.001, respectively). Adipo-R1 and adipo-R2 expression was also significantly lower in the CRC group when compared with the groups of patients with low grade dysplasia, high-grade dysplasia or no neoplasia (p=0.012 and p<0.001, respectively). In addition, it was observed that adipo-R2 expression was generally positive in the non-neoplastic group irrespective of the adipo-R2 expression. In the L-GD, H-GD and CRC groups, the adipo-R2 result was positive whenever adipo-R1 result was positive but some patients with negative adipo-R1 had positive adipo-R2 (p<0.001, p=0.004, p<0.001, respectively). Conclusions: This study indicated that ApN may play a role in the progression of colorectal adenomatous polyps to carcinoma through actions on adipo-R1 and adipo-R2 receptors.

Keywords: Adiponectin - adipoR1 - adipoR2 - colorectal carcinoma - polyps - progression

Introduction

Colorectal cancer is the third most prevalent cancer and third leading cause of all cancer-related deaths in both males and females (Siegel et al., 2014).

It is known that colorectal adenomas are among the factors that confer predisposition to CRC development. Current evidence indicates that CRC mostly evolves from preexisting adenomas. Adenomas grow, progressively dedifferentiate and become initially dysplastic and eventually malignant. Increased adenoma size, predominance of villous architecture, and a greater degree of nuclear atypia lead to dysplasia and in situ or invasive carcinoma (Bresalier, 2010). The progression of adenomas into carcinoma via this cascade of events necessitates elucidation of the association between adenomas and cytokines which have been implicated in cancer formation. Adiponectin is a cytokine that has been investigated for its possible association with CRC. Human adiponectin (ApN) is a 30 kDa glycoprotein of 244-amino acids which is predominantly produced by the adipocytes (Goldfine and Kahn, 2003)

ApN has insulin-sensitizing properties and was suggested to show antiatherogenic and antiadiabetic properties through inflammatory stimuli-induced NF-kappaB activation (Ouchi et al., 1999; Ouchi et al., 2000; Ouchi et al., 2001; Matsuzawa et al., 2003)

Research has demonstrated that ApN has both negative and positive effects on tumor growth (Hebbard and Ranscht, 2013). Additionally, it was suggested that adiponectin might show antitumor activity by inhibiting tumor angiogenesis and preventing goblet cell apoptosis (Brakenhielm et al., 2004; Saxena et al., 2013).

Reduced circulating levels of adiponectin have been shown in obese patients and implicated in the development of obesity-related malignancies (Cnop et al., 2003;
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Vascular endothelial growth factor and IL-6 are highly expressed by visceral fat tissue and contribute to cancer development (Lysaght et al., 2011). It has been shown that adiponectin inhibits CRC cell growth by activating adenosine monophosphate-activated protein kinase (AMPK) and suppressing the mammalian target-of-rapamycin (mTOR) pathways (Sugiyama et al., 2009). In a separate study, adiponectin showed anti-cancerogenic activity and prevented growth of colon cancer cells by stimulating AMPK activity in vitro (Kim et al., 2010).

Wei et al. reported an inverse relationship between serum ApN and CRC in male subjects (Wei et al., 2005). On the other hand, Otake et al. (2005) have shown that plasma ApN concentration was markedly reduced in colorectal adenoma patients with greater visceral fat area. In the same study, visceral fat area and adiponectin have been associated with the number, size and histology of adenomas (tubular and tubulovillous/villous). Recent studies focusing on colorectal cancer screening have underscored the importance of obesity and increased body mass index (BMI) as risk factors for development of colonic polyps (Zauber et al., 2012).

On the other hand, there are some studies which suggested that plasma ApN levels are not linked with the development of CRC in the long-term (Lukanova et al., 2006). Similarly, several adenoma studies have shown lack of any association between circulating ApN levels and colorectal adenomas (Fukumoto et al., 2008; Danese et al., 2013). ApN acts via adiponectin receptors. Two distinct receptors have been identified with different binding affinity to globular adiponectin, namely adiponectin receptor-1 (Adipo-R1) and adiponectin receptor-2 (Adipo-R2) (Yamauchi et al., 2003; Yamauchi et al., 2014). Many previous studies have reported discordant results on Adipo-R1/Adipo-R2 expression in colorectal cancer (Williams et al., 2008; Yoneda et al., 2008; Ayyildiz et al., 2014a).

No studies are available in literature that examined Adipo-R1/Adipo-R2 expression immunohistochemically in colorectal adenomas. Since adenomatous polyps are a predisposing factor for CRC, there is a need to evaluate their association with Adipo-R1/Adipo-R2 expression.

In the present study, we investigated Adipo-R1/Adipo-R2 expression immunohistochemically in cases of colorectal adenoma (a predisposing factor for CRC development) and surgically resected colorectal carcinoma in order to determine whether there is a link between Adipo-R1/Adipo-R2 expression and these tumors. Additionally, neoplastic status (negative for neoplasia, low-grade dysplasia ve high-grade dysplasia) of colorectal adenomas and various other factors such as, age and gender were also included in the analysis.

Materials and Methods

Study Protocol

This study had a retrospective design. Medical files of patients who were followed and treated in Uludag University Hospital were reviewed and pathologic specimens of those patients with adequate data were examined. The study enrolled 50 colorectal cancer patients (20 females, 30 males) and 82 patients diagnosed with adenomatous polyps (34 females, 48 males) which summed to a total of 132 subjects (54 (40.9%) females, 78 (59.1%) males). Colorectal cancer cases were selected from patients who underwent surgical resection and cases of adenomatous polyps were identified in other patients who had polypectomy.

Local ethics committee approval was obtained for the conduct of the study.

Immunohistochemical Staining

The presence of Adipo-R1 and Adipo-R2 expression in formalin fixed paraffin embedded tissues was investigated using immunohistochemical staining. Adipo-R1 and Adipo-R2 (ab126611 and ab77612, respectively; Abcam, Inc., Cambridge, MA, USA; working dilution 1/250) were used as the primary antibodies. Streptavidin-biotin methodology was used for immunohistochemical staining. Tissue sections four micrometers-thick were transferred onto lysine-coated slides and deparaffinized with overnight incubation at 60°C. They were deparaffinized and rehydrated. Then, they were boiled in a microwave oven for 20 minutes at a temperature equivalent to 750 watts. Following incubation with 3% hydrogen peroxide, the sections were kept at protein blocking antibody for 10 minutes and then incubated with the primary antibody for one hour at room temperature. Then, they were incubated with anti-rabbit biotinylated secondary antibody for 15 minutes and streptavidin-HRP for 15 minutes respectively. Subsequently, diaminobenzidine (DAB) chromogen solution was applied for 10 minutes. After counterstaining with Hematoxylin, the sections were dehydrated and cleared.

The sections were examined by two experienced pathologists under a light microscope with respect to the extent and intensity of staining. Sections with significant involvement and extension of 5% or greater were considered positive (Figures 1 and 2).

Statistical analysis

Descriptive values of study data are provided as number and percent frequencies and mean±standard deviation (SD) in tabulations and charts. Chi-square test was used to compare study groups with respect to age and gender distribution and Adipo-R1 and Adipo-R2 positivity. Additionally, associations between adenomatous polyps (tubular and tubulovillous) and neoplasia status as determined by histopathological examination (negative for neoplasia, low-grade dysplasia or high-grade dysplasia) were examined using an appropriate chi-square analysis. After completion of statistical tests, any study results with an associated p value less than or equal to 0.05 were considered statistically significant. A Predictive Analytics Software [SPSS (Statistical Package for the Social Sciences) version18] package was used for estimations.

Results

The numbers of poor, mild and well tumor differentiation of the patients with colorectal carcinomas
were 13 (26%), 36 (72%) and 1 (2%), respectively. pTNM stage 1, 2, 3 and 4 numbers were also 2 (4%), 18 (36%), 23 (46%) and 7 (14%), respectively.

Patients with adenomatous polyps were divided into three histological subgroups including negative for neoplasia, low-grade and high-grade dysplasia and compared with colorectal carcinoma patients with respect to Adipo-R1/Adipo-R2 expression, and sex and age distribution (Table 1) As seen in Table 1, Adipo-R1 positivity was significantly lower in CRC group (p=0.012). Similarly, Adipo-R2 positivity was also significantly lower in CRC group compared to other subgroups (p<0.001).

Apart from these findings, sex and age distribution of subgroups were statistically similar. In addition, patients were divided into 2 groups including those with adenomatous polyps and those with colorectal carcinoma and compared with respect to Adipo-R1 and Adipo-R2 expression (Table 1). As a result, Adipo-R1 and Adipo-R2 positivity rate among CRC patients was found to be significantly lower compared to that of patients with adenomatous polyps.

Excluding carcinoma group, patients without neoplasia were gathered in one group and those with low-grade and high-grade dysplasia in a second group in order to

Figure 1. Negative Adipo-R1/-R2 Expression in the Non-neoplastic Tissue, Low-Grade Dysplasia, High-Grade Dysplasia and Colorectal Carcinoma

Figure 2. Positive Adipo-R1/-R2 Expression in the Non-neoplastic tissue, Low-Grade Dysplasia, High-Grade Dysplasia and Colorectal Carcinoma.

Table 1. Results of Comparisons between Patients with Colonic Adenomatous Polyps and Colorectal Cancer Patients with Respect to Adipo-R1, Adipo-R2, Age and Sex

| Characteristics | Negative for Neoplasia | Low-Grade Dysplasia | High-Grade Dysplasia | Colorectal Carcinoma | Colorectal Polyp | Colorectal Carcinoma | P value |
|-----------------|------------------------|---------------------|----------------------|----------------------|-----------------|----------------------|---------|
| Category        | n (%)                  | n (%)               | n (%)                | n (%)                | n (%)           | n (%)                | P value |
| Adipo-R1        |                        |                     |                      |                      |                 |                      |         |
| Negative        | 15 (51.7)              | 7 (28)              | 8 (28.6)             | 30 (60)              | 30 (36.6)       | 20 (40)              | 0.012   |
| Positive        | 14 (48.3)              | 18 (72.0)           | 20 (71.4)            | 20 (40.0)            | 52 (63.4)       | 20 (40)              | 0.009   |
| Adipo-R2        |                        |                     |                      |                      |                 |                      |         |
| Negative        | 1 (3.4)                | 4 (16)              | 3 (10.7)             | 22 (44)              | 8 (9.8)         | 22 (44)              | <0.001  |
| Positive        | 28 (96.6)              | 21 (84.0)           | 25 (89.3)            | 28 (56.0)            | 74 (90.2)       | 28 (56)              | <0.001  |
| Sex             |                        |                     |                      |                      |                 |                      |         |
| Female          | 17 (58.6)              | 9 (36)              | 8 (28.6)             | 20 (40)              | 34 (41.5)       | 20 (40)              | 0.122   |
| Male            | 12 (41.4)              | 16 (64)             | 20 (71.4)            | 30 (60)              | 48 (58.5)       | 30 (60)              | 0.868   |
| Age             |                        |                     |                      |                      |                 |                      |         |
| <55             | 5 (17.2)               | 3 (12)              | 6 (21.4)             | 12 (24)              | 14 (17.1)       | 12 (24)              | 0.332   |
| ≥55             | 24 (82.8)              | 22 (88)             | 22 (78.6)            | 38 (76)              | 68 (82.9)       | 38 (76)              |         |

*Completely different letters located in different columns but in the same row, were shown as statistically significant results.
Table 2. Results of Comparison of Patients with Adenomatous Polyps Versus Colorectal Carcinoma Patients with Respect to Adipo-R1 and Adipo-R2 Expressions by Neoplasia Grade for Each Group Separately

|                      | Adipo-R2 | Adipo-R2 | Adipo-R2 | Adipo-R2 |
|----------------------|----------|----------|----------|----------|
|                      | Negative | Positive | Negative | Positive |
| Adipo-R1 Negative    | 1        | 14       | 4        | 3        |
| Adipo-R1 Positive    | 0        | 14       | 0        | 18       |
| P value              | 0.326    | <0.001   | 0.004    | <0.001   |

determine an association with Adipo-R1/R2 expression. It was seen that Adipo-R1 negativity rate was significantly lower in patients with neoplasia compared to those without any neoplasia (p=0.035). Negative and positivity rates of adipo-R2 expression did not significantly differ between these groups (p=0.150). In other words, although negativity rate was higher in patients with neoplasia (3.2%) in comparison to those without neoplasia (3.4%), the difference was not statistically significant.

Histopathological examination findings of subjects diagnosed with adenomatous polyps (tubular and tubulovillous adenomas) are shown that examination findings were similar for subgroups of non-neoplastic, low-grade and high-grade neoplasia (p=0.841). In addition, for the group with neoplasia, when Adipo-R1 was positive Adipo-R2 positivity was observed but when Adipo-R1 was negative, half of Adipo-R2 results were negative and other half were positive.

As the table indicates, about one third of patients with neoplasia (L-GD ve H-GD) had negative Adipo-R1 results. Adipo-R2 results were examined for those with negative Adipo-R1 results and nearly half of these patients were found to have negative Adipo-R2 results and the other half exhibited positive Adipo-R2 results. However, almost two-thirds of patients with neoplasia had positive Adipo-R1 results and all of their Adipo-R2 results were positive. Based on these findings, we might assume that, for patients with neoplasia, Adipo-R2 results would also be positive when Adipo-R1 results are positive but there will be 50:50 chance of seeing negative Adipo-R2 results when Adipo-R1 is negative.

However, for patients with colorectal carcinoma, positive Adipo-R2 results would be observed when Adipo-R1 results are positive but the majority of Adipo-R2 results would be negative and only a portion would be positive when Adipo-R1 is negative.

Discussion

Obesity and associated disorders increase the risk for development of a variety of gastrointestinal cancers. The underlying mechanism is unclear; however, chronic inflammation associated with obesity has been implicated in the process. Innate immunity, cytokines such as adiponectin and leptin, insulin-like growth factors, gut microbiota and several other factors may also be involved (Tilg and Moschen, 2014).

Clinical correlation studies have shown that lower levels of serum APN are associated with increased malignancy of various cancers. However, there are fewer studies on Adipo-R1/ Adipo-R2 expression in cancers compared to serum adiponectin-based studies. We see inconsistent results reported by previous studies examining Adipo-R1/Adipo-R2 expression in gastrointestinal tumors. While Barresi et al. reported a significant association of Adipo-R1/ Adipo-R2 expression and overall survival in gastric tumors, others suggested that there is not any such relation. Few studies exist in literature on Adipo-R1/Adipo-R2 expression in patients with colorectal cancer. One study reported that there was no difference between normal colon epithelium and colorectal cancer tissues in Adipo-R1 and Adipo-R2 expression. Canhoroz et al. have shown that adiponectin expression was not associated with overall survival in patients with stage 2 and 3 (TNM stage) colorectal carcinoma. Barresi et al. (2009a) reported that adiponectin expression does not occur in colorectal cancer patients but they observed a significant level of ApN expression in CRC tissues and particularly in histologically differentiated high-grade tumors. Contrastingly, Ayyildiz et al. found adiponectin receptor expression both in normal colon tissue and colon cancer tissue. Moreover, they reported significantly increased Adipo-R1/ Adipo-R2 expression in normal colon epithelium versus colorectal cancer tissue.

There are no studies in literature on Adipo-R1/ Adipo-R2 expression in colorectal adenomas. However, some studies exist which have established a link between serum adiponectin levels and colorectal adenomas. Danese et al. reported no association between plasma adiponectin level and development of colorectal adenoma. In a separate study, colorectal adenomas have not been associated with anthropometric measures and adiposity-related laboratory variables such as parameters of insulin resistance and serum adiponectin level. Also, Bobe et al. (2010) explored the relationship between serum levels of adiponectin and adenoma recurrence and did not find a significant association.

In the current study, patients with adenomatous polyps (tubular and tubulovillous) were divided into three histological subgroups including negative for neoplasia,
low-grade and high-grade dysplasia and compared with colorectal carcinoma patients with respect to Adipo-R1/Adipo-R2 expression. Adipo-R1/Adipo-R2 expression was significantly lower in CRC group. Similar results were obtained when adenomatous polyps were analyzed in aggregate within CRC patients and again, significantly low Adipo-R1/Adipo-R2 expression was observed. These results correlate with those of other studies (Fukumoto et al., 2008; Bobe et al., 2010; Chronis et al., 2011; Danese et al., 2013) which examined the association between serum adiponectin levels and colorectal adenomas. However, consistent with Ayyildiz et al.’s study, we observed a low level of ApN receptor expression in CRC patients (Ayyildiz et al., 2014a).

Adiponectin exerts its effect via Adipo-R1 and Adipo-R2. Considering the cascade of events that leads to progression of adenoma to colon cancer, one might expect to see decreased Adipo-R1 and Adipo-R2 expression with higher grade of neoplasia. When we reviewed our results in that context, Adipo-R1 expression was found to be significantly low in the groups with neoplasia (L-GD and H-GD) versus non-neoplastic group; Adipo-R2 expression was also reduced but not at a statistically significant level. This suggests that Adipo-R1 and Adipo-R2 expressions are correlated with transformation of adenomatous polyps to malignancies.

A noteworthy result of our study was the occurrence of Adipo-R2 expression in non-neoplastic group irrespective of Adipo-R1 expression, a finding which was not observed in patients with low-grade and high-grade dysplasia or CRC group. However, only about half of the patients in other groups showed Adipo-R2 expression when Adipo-R1 expression was absent, suggesting that there is a significant association between Adipo-R1 negativity and Adipo-R2 positivity during the malignant process. However, Adipo-R2 expression is present almost always when Adipo-R1 is expressed in dysplastic and CRC groups.

Our study has some limitations. Anthropometric measures, body mass index and dietary habits were not available for patients with adenoma. There were a small number of patients diagnosed as having only villous adenoma which precluded their inclusion in the study. We could have identified those colorectal cancer patients with concomitant adenomatous polyps if they had any, and inclusion of such tumors would have made a different contribution to our study.

In conclusion, a significantly low level of Adipo-R1/Adipo-R2 expression was found in colorectal cancer patients compared to those with colorectal adenomatous polyps in the present study. This finding strengthens the hypothesis that adiponectin may be involved in CRC pathogenesis via its receptors (Bobe et al., 2010).

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References

Ayyildiz T, Dolar E, Ugras N, Adim SB, Yerci O (2014a). Association of adiponectin receptor (adipo-r1/-r2) expression and colorectal cancer. Asian Pac J Cancer Prev, 15, 9385-90.

Ayyildiz T, Dolar E, Ugras N, et al (2014b). Lack of any prognostic relationship between adiponectin receptor (Adipo R1/R2) expression for early/advanced stage gastric cancer. Asian Pac J Cancer Prev, 15, 4711-16.

Barresi V, Grosso M, Giuffre G, Tuccari G, Barresi G (2009a). The expression of adiponectin receptors Adipo-R1 and Adipo-R2 is associated with an histological histotype and longer survival in gastric carcinoma. J Clin Pathol, 62, 705-9.

Barresi V, Tuccari G, Barresi G (2009b). Adiponectin immunohistochemical expression in colorectal cancer and its correlation with histological grade and tumour microvessels density. Pathology, 41, 533-8.

Bobe G, Murphy G, Rogers CJ, et al (2010). Serum adiponectin, leptin,C-peptide, homocysteine, and colorectal adenoma recurrence in the Polyp Prevention Trial. Cancer Epidemiol Biomarkers Prev, 19, 1441-52.

Braekenheiml E, Veitonnaki N, Cao R, et al (2004). Adiponectin-induced antiangiogenesis and anti-tumor activity involve caspase-mediated endothelial cell apoptosis. Proc Natl Acad Sci USA, 101, 2476-81.

Bresalier RS (2010). Colorectal cancer. In’Sleisenger and Fordtran’s Gastrointestinal and Liver Disease’ Eds Feldman M, Friedman LS and Brandt LJ, Saunders, an imprint of Elsevier Inc. Philadelphia, pp 2191-239.

Danese E, Minicozzi AM, Montagnana M, et al (2013). Lack of an association between circulating adiponectin levels and risk of colorectal adenoma. Clin Lab, 59, 211-4.

Goldfine AB, Kahn CR (2003). Adiponectin: linking the fat cell to insulin sensitivity. Lancet, 362, 1431-2.

Gulcelik MA, Colakoglu K, Dincer H, et al (2012). Associations between adiponectin and two different cancers: breast and colon. Asian Pac J Cancer Prev, 13, 395-8.

Hebbard L, Ranscht B (2014). Multifaceted roles of adiponectin in cancer. Best Pract Res Clin Endocrinol Metab, 28, 59-69.

Joshi RK, Lee SA (2014). Obesity related adipokines and colorectal cancer: a review and meta-analysis. Asian Pac J Cancer Prev, 15, 397-405.

Kim AY, Lee YS, Kim KH, et al (2010). Adiponectin represses colon cancer cell proliferation via Adipor1-and-R2-mediated AMPK activation. Mol Endocrinol, 24, 1441-52.

Lukanova A, Soderberg S, Kaaks R, Jellum E, Stattin P (2006). Serum adiponectin is not associated with risk of CRC. Cancer Epidemiol Biomarkers Prev, 15, 401-2.

Lysaght J, van der Stok EP, Allott EH, et al (2011). Pro-inflammatory and tumour proliferative properties of excess visceral adipose tissue. Cancer Lett, 312, 62-72.

Matsuzawa Y, Shimomura I, Kihara S, et al (2003). Importance of adipocytokines in obesityrelated diseases. Horm Res, 56, 59-69.

Ouchi N, Kihara S, Arita Y, et al (1999). Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Mol Med, 5, 247-63.

Ouchi N, Kihara S, Arita Y, et al (2000). Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. Circulation, 102, 1296-301.
Ouchi N, Kihara S, Arita Y, et al (2001). Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. Circulation, 103, 1057-63.
Otaka S, Takeda H, Suzuki Y, et al (2005). Association of visceral fat accumulation and plasma adiponectin with colorectal adenoma: evidence for participation of insulin resistance. Clin Cancer Res, 11, 3642-6.
Saxena A, Baliga MS, Ponemone V, et al (2013). Mucus and adiponectin deficiency: role in chronic inflammation-induced colon cancer. Int J Colorectal Dis, 28, 1267-79.
Siegel R, Desantis C, Jemal A (2014). Colorectal cancer statistics, 2014. CA Cancer J Clin, 64, 104-17
Sugiyama M, Takahashi H, Hosono K, et al (2009). Adiponectin inhibits colorectal cancer cell growth through the AMPK/mTOR pathway. Int J Oncol, 34, 339-44.
Tilg H, Moschen AR (2014). Mechanisms behind the link between obesity and gastrointestinal cancers. Best Pract Res Clin Gastroenterol, 28, 599-610.
Wei EK, Giovannucci E, Fuchs CS, Willet WC, Mantzoros CS (2005). Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. J Natl Cancer Inst, 97, 1688-94.
Yamauchi T, Kamon J, Ito Y, et al (2003). Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature, 423, 762-9.
Yamauchi T, Iwabu M, Okada-Iwabu M, Kadowaki T (2014). Adiponectin receptors: a review of their structure, function and how they work. Best Pract Res Clin Endocrinol Metab, 28, 15-23.
Yoneda K, Tomimoto A, Endo H, et al (2008). Expression of adiponectin receptors, AdipoR1 and AdipoR2, in normal colon epithelium and colon cancer tissue. Oncol Rep, 20, 479-83.
Zauberg AG, Winawer SJ, O’Brien MJ, et al (2012). Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med, 366, 687-96.