# Implication of visfatin levels in patients with colon cancer

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## Abstract

**Objective:** Adipocytokines have been reported to contribute to the pathogenesis of colon cancer, yet few studies have evaluated these markers. Visfatin, an adipocytokine, is thought to play a role in the pathogenesis of metabolic-syndrome-related cancers. The aim of this study was to assess the association of visfatin level with the progression of colon cancer through a case-control study.

**Methods:** Serum visfatin levels were measured in 188 Saudi female subjects (90 colon cancer patients and 98 controls) by using enzyme-linked immunosorbent assay (ELISA) method. The patient and control group were matched on age, body mass index, waist-to-hip ratio, race, and gender. Colon cancer patients were categorized into four groups based on Duke's classification (A, B, C, and D with N= 22, 20, 23, and 25; respectively). The levels of serum visfatin, anthropometric parameters and metabolic parameters were compared between patients and controls and between patients of different clinical stages of colon cancer.

**Results:** Mann-Whitney test was used for comparing patient and control group and showed that patients with colon cancer had significantly higher circulating visfatin levels than the control group (5.64±2.6 vs. 1.87±1.7ng/ml, $P< 0.0001$). Kruskal Wallis test was used to compare the levels of visfatin in different clinical stages of colon cancer and the result showed no significant differences in the levels of visfatin between the colon cancer stages ($P=0.95$). Non-significant associations with anthropometric and metabolic parameters were observed for visfatin, except that visfatin level had a significant correlation with HDL ($P=0.054$).

**Conclusions:** The observed result indicates that visfatin is not involved with tumor stage progression. However, the increased levels of visfatin in patients with colon cancer strengthen the results of previous studies and speculated that this adipocytokine may be a predictive or an important risk factor for colon cancer development. Further studies are needed to elucidate the role of serum visfatin levels in colon cancer.

**Key words:** Visfatin, colon cancer, Saudi patients.

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## Introduction

Colon cancer is a life-threatening disease. In Saudi Arabia, colon cancer occurrence ranks third among females (Al-Eid and Manalo, 2006). The incidence of colon cancer in the Kingdom of Saudi Arabia (KSA) has been on a constant rise over the past few years (Ibrahim et al., 2008). Research studies have indicated several risk factors that may increase a person's chance of developing colon cancer, but the disease still needs more investigation in its prevention and therapy. There are many known factors that increase or decrease the risk of colon cancer; some of these factors are modifiable and others are not. Abdominal obesity, that is related to the accumulation of visceral fat, has been associated with increased risk of some type of cancers (Schapira et al., 1990; Folsom et al., 1990), including colon cancer (Giovannucci et al.,1995; Murphy et al., 2000; Ceschi et al., 2007).

Metabolic changes resulting from imbalances in hormones such as adipocytokines that are derived from white adipose tissue are linked to colon cancer (Tulubas et al., 2013). Visfatin is an adipokine identified in 2004 and accordingly named for the suggestion of its high levels of expression in visceral fat cells (Fukuhara et al., 2005). Visfatin gene sequencing has been revealed to correspond to previously identified cyotokine named Pre-B-cell colony-enhancing factor (PBEF), described in 1994 as a cytokine produced by lymphocytes (Samal et al., 1994). Visfatin was also known as the formerly described Nicotinamide phosphoribosyltransferase (Nampt), the limiting enzyme in nicotinamide adenine dinucleotide (NAD) biosynthesis. Thus, it is able to regulate cellular levels of $NAD^+$, exerting an influence on cell energy metabolism and the activity of $NAD^+$ /NADH dependent enzymes (Manolescu et al., 2008).

Visfatin is not a fat-specific protein; it is released predominantly from macrophages rather than from adipocytes in visceral adipose tissue (Curat et al., 2006). In this regard, there is sufficient evidence to consider that visfatin is expressed by the macrophages infiltrating adipose tissue and is produced in response to inflammatory signals (Curat et al., 2006; Varma et al., 2007). Dendritic cells and colonic epithelial cells are also sources of visfatin (Moschen et al., 2007). In this regard, visfatin was considered as a proinflammatory adipocytokine (Alexander et al 2006; Curat et al., 2006; Varma et al., 2007). This protein is also involved in pathophysiological angiogenesis including adipose tissue angiogenesis. Kim and his colleagues demonstrated that visfatin activates migration, invasion, and tube formation in human umbilical vein endothelial cells (HUVECs). They also showed that visfatin induces activation of the extracellular signal-regulated kinase 1/2 (ERK1/2) in endothelial cells, which is closely linked to angiogenesis. Their results revealed that visfatin promotes angiogenesis via activation of mitogen-activated protein kinase ERK-dependent pathway (Kim et al., 2007).

The discovery of this adipokine has the potential to enhance our understanding of metabolic-syndrome-related cancers. The biological role of visfatin is still illusive. Association between visfatin and several medical conditions such as metabolic syndrome, insulin-mimetic effect, obesity, and diabetes are still controversial (Zhong et al., 2008; Fukuhara et al., 2005; Revollo et al., 2007; Ye et al., 2005; Berndt et al., 2005; Haider et al., 2006A; Haider et al., 2006B; Dogru et al., 2007; Toruner et al., 2009; Hammarstedt et al., 2006; Takebayashi et al., 2007; Lopez et

al., 2006). The level of visfatin in visceral fat and subcutaneous fat is also controversial (Terra et al., 2012; Sandeep et al., 2007; Berndt et al., 2005; Araki et al., 2008). With the aforementioned, the association of visfatin level with the progression of colon cancer through a case-control study was the aim of the presented project.

## Materials and Methods

### Subjects

The present study included 188 Saudi female subjects (90 colon cancer patients and 98 age, body mass index (BMI), waist-to-hip ratio (WHR), race, and gender-matched healthy controls). The case group was selected from patients diagnosed with colon cancer via colonoscopy and confirmed by tissue biopsy at King Abdul Aziz University Hospital in Jeddah, KSA, between January 2009 and December 2012. Control group was selected from subjects visited the same hospital for routine screening and diagnosed as free from colon cancer and had normal blood pressure, blood sugar level, and were not under any treatment course. All participants gave their informed consent before enrollment in the study.

### Anthropometric measurements

Standard methods were used to measure height, weight, waist circumferences (WC), and hip circumferences (HC). Body weight was measured with light clothing on, with up to 0.1kg precision. Height was measured up to 0.1cm precision. Body mass index (BMI) was calculated as weight (kg) divided by height in meters squared ($m^2$). Waist-to-hip ratio (WHR) was also calculated as WC divided by HC. BMI is used to reflect the total body fat, while WC and WHR are indirect measurements of body fat centralization.

### Biochemical measurements

Blood samples after a 12-hour overnight fasting were collected and then the serum was immediately separated and stored at –20˚C to evaluate fasting blood glucose, triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), insulin, and visfatin. Serum visfatin was measured by a commercial visfatin C-terminal enzyme-linked immunosorbent assay kit (ALPCO Diagnostics, Salem, NH) using the microplate reader (sensitivity 30pg/ml). The intra- and inter-assay coefficient of variation (CV) was 5.04% and 6.67%, respectively. The test kit is effective in the range of 0.073 to 4.8ng/ml with observed value of 80-120%. Duplicate measurements were performed in a single experiment. Lipid profiles were measured by an automatic biochemistry analyzer (Hitachi HS 2003m, Japan). This research was approved by the local ethical committee.

### Classification of the colon cancer patients

Patients with colon cancer were divided into four groups according to the size of tumors and status of lymph node metastasis. Histological grading of colon cancer was based on the Duke's classification (A, B, C, and D stages).

**Statistical analysis**

Data are presented as means ± S.D. Mann-Whitney test was used for comparing the patient and the control group. To compare visfatin levels between tumor stages, Kruskal Wallis test was performed. The correlation of serum visfatin with anthropometric parameters and metabolic parameters was analyzed by Spearman Rank order test. Differences with a *P*-value <0.05 were considered significant. All statistical analyses were carried out using the SPSS for Windows V16.0 (SPSS Inc., Chicago, Il., U.S.A)

## Results

**Comparison between the patients and the control group**

There was no significance difference in age, height, weight, BMI, WHR, cholesterol, HDL, and total lipid between the patient and the control group (Table 1). There was a statistically significant difference in waist (*P* =0.01), hip circumference (*P* =0.03), and triglycerides level (*P* =0.009) between the two groups. When serum visfatin levels were compared in cases and controls, the serum visfatin levels were significantly higher in the colon cancer group (*P* =0.0001) (Table 1). In the patient group, mean visfatin level was 5.64±2.6 and 1.87±1.7 in the control group.

**Serum visfatin levels in different clinical stages of colon cancer**

The result showed that the mean visfatin level for patients in A, B, C, and D stages were 4.9, 5.3, 4.7, and 4.9 ng/ml, respectively. In comparing visfatin levels in the stages, the result showed that there in no significant differences (*P* =0.95).

**Relationship between visfatin and other variables**

The present study investigated whether there was any relationship between the serum visfatin levels, age, BMI, WHR, waist, hip, and lipid profiles. No significant correlations with anthropometric and metabolic parameters were observed for serum visfatin level, except for HDL (*P* = 0.054).

## Discussion

In the present study, the association of visfatin level with the progression of colon cancer through a case-control study for Saudi females was evaluated. The observed result indicates that visfatin is not involved with tumor stage progression. The higher level of visfatin serum in patients with colon cancer strengthen the results of previous studies and speculates that this adipocytokine may be a predictive or an important risk factor for colon cancer development. The present study is one of few reports to evaluate visfatin level in colon cancer patients and its involvement with tumor stage progression.

Adipocytokines produced by adipose tissue have been the subject of intense investigation as novel risk markers not only of metabolic syndrome but also for

cancer (Petridou et al., 2000; Hsing et al., 2001; Miyoshi et al., 2003; Petridou et al., 2003; Stattin et al., 2004; Goktas et al., 2005; Wei et al., 2005). Visfatin is an insulinmimetic adipocytokine, which directly interacts with the insulin receptor as insulin-like growth factor receptor, and can subsequently promote cancer cell proliferation (Fukuhara, et al., 2005;Tilg and Moschen, 2008). Visfatin contributes to the generation of nicotinamide adenine dinucleotide (NAD) biosynthesis and also affects cellular metabolism, cell life span and longevity (Bi and Che, 2010). Several studies have identified changes in the circulatory levels of visfatin in diseases. Notably among them are obesity, diabetes mellitus, kidney diseases and bone disorders.

**Table1: Comparison between the patient and the control group**

| Variables | Patients Mean ± SD | Controls Mean ± SD | *P* value |
|---|---|---|---|
| Age (year) | 52.0±11.7 | 53.9±13.8 | 0.52 |
| Height (cm) | 158.1±9.1 | 155.4±7.9 | 0.25 |
| Weight (kg) | 71.6±15.9 | 65.3±14.1 | 0.11 |
| BMI (kg/cm$^2$) | 28.9±6.8 | 26.8±6.4 | 0.24 |
| Waist (cm) | 84.6±30.8 | 62.0±29.2 | 0.01* |
| Hip (cm) | 93.8±34.7 | 70.3±33.4 | 0.03* |
| WHR | 1.01±0.7 | 0.95±0.3 | 0.62 |
| Cholesterol (mg/dl) | 202.1±50.1 | 185.5±57.4 | 0.28 |
| Triglycerides (mg/dl) | 114.5±64.4 | 166.1±87.1 | 0.009** |
| HDL (mg/dl) | 60.1±26.4 | 53.7±16.4 | 0.29 |
| LDL (mgdl) | 119.7±34.2 | 98.5±54.9 | 0.12 |
| Total lipid (mg/dl) | 7.41±0.37 | 7.20± 0.53 | 0.11 |
| Visfatin (ng/ml) | 5.64±2.6 | 1.87±1.7 | 0.0001** |

*Significant, **highly significant
WHR: waist-to-hip ratio, BMI: body mass index, HDL: high-density lipoprotein, LDL: low-density lipoprotein.
Values were represented as the mean ± standard deviation.

The relationship between visfatin and colon cancer has been established, therefore Nakajima and his group suggested that it could be considered to be a new and promising biomarker of colorectal cancer (Nakajima et al., 2010). In the few published articles about visfatin serum level in colon cancer patients, there is no consensus result. A study reported that visfatin level in the malign group was not statistically significantly different from those in the benign group (Kosova et al., 2013), while others indicated that increased serum visfatin is associated with the incidence of colon cancer (Chen et al., 2013; Fazeli et al., 2013; Tuluba et al., 2013). The result of this study is in agreement with the studies that found increased levels of visfatin in patients with colon cancer than in the control group. This study confirms that patients with colon cancer are characterized with higher level of visfatin. The data postulate that higher visfatin concentrations in colon

cancer could probably serve as an early marker with prognostic value for the later development of the colon cancer. Chen et al. divided the patients into two subgroups early and advanced cancer and showed that increased level of visfatin was a strong risk factor for both early and advanced colorectal cancer in Chinese patients (Chen et al., 2013). Fazeli and his group suggested that visfatin may has a potential role in the development of colorectal cancer through mechanisms other than the direct mechanisms that are active in the association between obesity and colorectal cancer (Fazeli et al., 2013). Tuluba and his team implied that visfatin might play an important role in colon carcinogenesis (Tuluba et al., 2013). In addition, to explore the link between visfatin level and the progression of colon cancer, the levels of visfatin were compared between all the clinical stages and showed no significant differences. To our knowledge, there has not been any report comparing the level of visfatin between the clinical stages of colon cancer. This analysis may provide additional information in regard to the role of visfatin in colon cancer and the use of visfatin as a therapeutic target.

In the presented study, the analysis of visfatin levels documented no correlation with anthropometric parameters and metabolic parameters, except HDL among patients. Chen and his group observed that visfatin is not related to most anthropometric parameters and most parameters of metabolic syndrome, except HDL and LDL levels in female subjects (Chen et al., 2007). They suggested that visfatin might play a role in cholesterol homeostasis in women. Fukuhara et al. (2005) demonstrated that plasma visfatin levels correlated strongly with the visceral fat area and weakly with the subcutaneous fat area in male and female subjects. Because waist circumference and WHR are good surrogates of visceral fat, it is expected that visfatin level correlate with waist circumference and WHR. However, previous reports and this study have not found this correlation except a very recent project done be Chen et al. (2007) where they found a significant correlation with WHR among colorectal cancer patients and controls. The reason of this discrepancy is unclear. These findings may contribute to our current knowledge about visfatin in metabolic syndrome. Lipid profiles are also an important component of metabolic syndrome. The analysis showed that only HDL was associated with visfatin levels in female patients. This result and the result reported by Chen et al. (2007) in a Tawanian population showed a correlation with HDL levels in female subjects and imply a role of visfatin in homeostasis of lipid in females. However, the mechanism is currently unknown.

These findings should be considered in light of a number of limitations due to the relatively small sample size of subjects that limit the statistical power. Moreover, the possibility of misclassifications of disease status cannot be excluded, since the controls were not thoroughly examined for the absence of colon cancer. Despite these limitations, the study design was relatively strong because the controls were recruited from the same cohort as the colon cancer patients. Also the cases and controls have been matched by age, BMI, WHR, and sex.

In conclusion, visfatin is not involved with tumor stage progression and did not correlate with most anthropometric and metabolic parameters. The result of this study confirms previous findings that patients with colon cancer are characterized with higher level of visfatin and consistent with other studies linking visfatin with cancer states. Since no conclusive evidence exists so far with regards to the role of

visfatin in colon cancer, more molecular, physiological and clinical studies are needed to determine the role of visfatin in the etiology and pathogenesis of colon cancer.

**References**

1. Al Eid HS, Manalo MS. Cancer Incidence Report Saudi Arabia. Kingdom of Saudi Arabia Ministry of Health Saudi Cancer Registry. 2006. Avilable at http://www.scr.org.sa/ . Accessed on Dec /3/2010.

2. Berndt J, Kloting N, Kralisch S, Kovacs P, Fasshauer M, Schon MR, Stumvoll M, Bluher M:Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. Diabetes 2005, 54(10): 2911-2916.

3. Bi TQ, Che XM. Nampt/PBEF/visfatin and cancer. Cancer Biol Ther 2010 Jul 15, 10(2):119-25.

4. Ceschi M, Gutzwiller F, Moch H, Eichholzer M, Probst-Hensch NM. Epidemiology and Pathophysiology of obesity as a cause of cancer. Swiss Med Wkly 2007, 137(3-4): 50–56.

5. Chen CC, Li TC, Li CI, Liu CS, Lin WY, Wu MT, Lai MM, Lin CC. The relationship between visfatin levels and anthropometric and metabolicparameters: association with cholesterol levels in women. Metabolism 2007 Sep, 56(9):1216-20.

6. Chen M, Wang Y, Li Y, Zhao L, Ye S, Wang S, Yu C, Xie H. Association of plasma visfatin with risk of colorectal cancer: An observational study of Chinese patients. Asia Pac J Clin Oncol 2013 Aug 2.

7. Curat CA, Wegner V, Sengenès C, Miranville A, Tonus C, Busse R: Macrophages in human visceral adipose tissue: increased accumulation in obesity and a source of resistin and visfatin. Diabetologia 2006, 49:744-7.

8. Dogru T, Sonmez A, Tasci I, Bozoglu E, Yilmaz MI, Genc H, Erdem G, Gok M, Bingol N, Kilic S, Ozgurtas T, Bingol S: Plasma visfatin levels in patients with newly diagnosed and untreated type 2 diabetes mellitus and impaired glucose tolerance. Diabetes Res Clin Pract 2007, 76(1):24-29.

9. Fazeli MS, Dashti H, Akbarzadeh S, Assadi M, Aminian A, Keramati MR, Nabipour I. Circulating levels of novel adipocytokines in patients with colorectal cancer. Cytokine 2013 Apr, 62(1):81-5.

10. Feti T, Rafet M, Meltem O, Birol T. The role of adipocytokines in colon cancer and adenomas. J Med Biochem 2013, 32: 1-8.

11. Folsom, A. R., Kaye, S. A., Prineas, R. J., Potter, J. D., Gapstur, S. M., Wallace, R. B. (1990) Increased incidence of carcinoma of the breast associated

with abdominal adiposity in postmenopausal women. Am J Epidemiol 1990, 131: 794–803.

12. Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K, Matsuki Y, Murakami M, Ichisaka T, Murakami H, *et al*.: Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science 2005, 307(5708): 426-430.

13. Giovannucci, E. Insulin and colon cancer. Cancer Causes Control 1995, 6: 164–179.

14. Goktas S, Yilmaz MI, Caglar K, Sonmez A, Kilic S, Bedir S. Prostate cancer and adiponectin. Urology 2005, 65: 1168–72.

15. Haider DG, Schindler K, Schaller G, Prager G, Wolzt M, Ludvik B: Increased plasma visfatin concentrations in morbidly obese subjects are reduced after gastric banding. J Clin Endocrinol Metab 2006 (A), 91(4): 1578-1581.

16. Haider DG, Schaller G, Kapiotis S, Maier C, Luger A, Wolzt M: The release of the adipocytokine visfatin is regulated by glucose and insulin. Diabetologia 2006 (B), 49(8):1909-1914.

17. Hammarstedt A, Pihlajamaki J, Rotter Sopasakis V, Gogg S, Jansson PA, Laakso M, Smith U:Visfatin is an adipokine, but it is not regulated by thiazolidinediones. J Clin Endocrinol Metab 2006, 91(3):1181-1184.

18. Hsing AW, Chua S Jr, Gao YT et al. Prostate cancer risk and serum levels of insulin and leptin: a population-based study. J Natl Cancer Inst 2001, 93:783–9.

19. Ibrahim EM, Zeeneldin AA, El-Khodary TR, Al-Gahmi AM, Bin Sadiq BM. Past, Present and Future of Colorectal Cancer in the Kingdom of Saudi Arabia. SJG 2008, 14: 178–182.

20. Kosova F, Coskun T, Kaya Y, Kara E, Ari Z. Adipocytokine levels of colon cancer patients before and after treatment. Bratist Lek Listy 2013,114(7):394-7.

21. Lopez-Bermejo A, Chico-Julia B, Fernandez-Balsells M, Recasens M, Esteve E, Casamitjana R, Ricart W, Fernandez-Real JM: Serum visfatin increases with progressive beta-cell deterioration. Diabetes 2006, 55(10):2871-2875.

22. Miyoshi Y, Funahashi T, Kihara S et al. Association of serum adiponectin levels with breast cancer risk. Clin Cancer Res 2003, 9: 5699–704.

23. Moschen AR, Kaser A, Enrich B, Mosheimer B, Theurl M, Niederegger H, Tilg H. Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. J Immunol 2007, 178(3):1748-58.

24. Murphy TK, Calle EE, Rodriguez C, Kahn HS, Thun MJ. Body mass index and colon cancer mortality in a large prospective study. Am J Epidemiol 2000, 152: 847–854.

25. Nakajima TE, Yamada Y, Hamano T *et al.* Adipocytokines and squamous cell carcinoma of the esophagus. J Cancer Res Clin Oncol 2010, 136: 261–6.

26. Petridou E, Papadiamantis Y, Markopoulos C, Spanos E, Dessypris N, Trichopoulos D. Leptin and insulin growth factor I in relation to breast cancer (Greece). Cancer Causes Control 2000, 11: 383–8.

27. Petridou E, Mantzoros C, Dessypris N et al. Plasma adiponectin concentrations in relation to endometrial cancer: a case-control study in Greece. J Clin Endocrinol Metab 2003, 88: 993–7.

28. Revollo JR, Korner A, Mills KF, Satoh A, Wang T, Garten A, Dasgupta B, Sasaki Y, Wolberger C, Townsend RR, *et al.*: Nampt/PBEF/Visfatin regulates insulin secretion in beta cells as a systemic NAD biosynthetic enzyme. Cell Metab 2007, 6(5): 363-375.

29. Sandeep S, Velmurugan K, Deepa R, Mohan V. Serum visfatin in relation to visceral fat, obesity, and type 2 diabetes mellitus in Asian Indians. Metabolism 2007, 56(4):565-70.

30. Schapira, D. V., Kumar, N. B., Lyman, G. H., Cox, C. E. Abdominal obesity and breast cancer risk. Ann Intern Med 1990, 112: 182–186.

31. Stattin P, Lukanova A, Biessy C et al. Obesity and colon cancer: does leptin provide a link? Int J Cancer 2004, 109: 149–52.

32. Takebayashi K, Suetsugu M, Wakabayashi S, Aso Y, Inukai T: Association between plasma visfatin and vascular endothelial function in patients with type 2 diabetes mellitus. Metabolism 2007, 56(4):451-458.

33. Terra X, Auguet T, Quesada I, Aguilar C, Luna AM, Hernández M, Sabench F, Porras JA, Martínez S, Lucas A,Pellitero S, Llutart J, del Castillo D, Richart C. Increased levels and adipose tissue expression of visfatin in morbidly obese women: the relationship with pro-inflammatory cytokines. Clin Endocrinol (Oxf) 2012, 77(5):691-8.

34. Tilg H, Moschen AR. Role of adiponectin and PBEF/visfatin as regulators of inflammation: involvement in obesity-associated diseases.*Clin Sci (Lond)* 2008, 114: 275–88.

35. Toruner F, Altinova AE, Bukan N, Arslan E, Akbay E, Ersoy R, Arslan M: Plasma visfatin concentrations in subjects with type 1 diabetes mellitus. Horm Res 2009, 72(1):33-37.

36. Varma V, Yao-Borengasser A, Rasouli N, Bodles AM, Phanavanh B, Lee MJ, Starks T, Kern LM, Spencer HJ, McGehee RE Jr, Fried SK, Kern PA: Human visfatin expression: relationship to insulin sensitivity, intramyocellular lipids, and inflammation. J Clin Endocrinol Metab 2007, 92:666-672

37. Wei EK, Giovannucci E, Fuchs CS, Willett WC, Mantzoros CS. Low plasma

adiponectin levels and risk of colorectal cancer in men: a prospective study. J Natl Cancer Inst 2005, 97: 1688–94.

38. Ye SQ, Simon BA, Maloney JP, Zambelli-Weiner A, Gao L, Grant A, Easley RB, McVerry BJ, Tuder RM, Standiford T, *et al.*: Pre-B-cell colony-enhancing factor as a potential novel biomarker in acute lung injury. Am J Respir Crit Care Med 2005, 171(4): 361-370.

39. Zhong M, Tan HW, Gong HP, Wang SF, Zhang Y, Zhang W: Increased serum visfatin in patients with metabolic syndrome and carotid atherosclerosis. Clin Endocrinol (Oxf) 2008, 69(6):878-884.