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Review Article

The Role of Adiponectin in Prostate Cancer: A Narrative Review

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ABSTRACT

Prostate cancer (PCa) is the most common type of cancer among men over 60 years old. The aggressiveness and mortality of PCa can be correlated with obesity. Adipose tissue-derived cytokines such as adiponectin may explain the correlation between PCa and obesity. Since the correlation between adiponectin and aggressive PCa is still not fully evaluated, we aimed to investigate the probable role of adiponectin in PCa. Adiponectin is considered as a link between obesity, insulin resistance and diabetes. On the other hand, adiponectin is a key mediator of systemic insulin sensitivity and glucose homeostasis. Moreover, low level of adiponectin is associated with inflammation and angiogenesis. These processes could promote tumor growth. Special effects of adiponectin are mediated via adenosine monophosphate-activated protein kinase (AMPK). AMPK activation inhibits growth of androgen-independent and androgen-sensitive PCa cell lines. Moreover, c-Jun N-terminal protein kinase (JNK) and Signal transducer and activator of transcription 3 (STAT3) signaling pathway are known as adiponectin's mediators on the metabolic syndrome and cancer. Furthermore, adiponectin acts as a tumor suppressor gene via inhibition of Epithelial-to-mesenchymal Transition (EMT) of PCa cells, but it is down regulated through hypermethylation of promoter gene in PCa cells. Therefore, according to the results of these studies, decreased concentration of adiponectin was associated with increased risk of PCa. It seems that hypoadiponectinemia may act as a promising biomarker for detection and diagnosis of PCa.

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Introduction

One of the most fatal diseases in human beings is cancer which leads to an annual death of 30000 people in Iran.[1,2] The most common type of cancer among men older than 60 years is prostate cancer (PCa).[3] PCa is the second leading cause of cancer death among American men. The highest incidence of PCa is in the United States, Canada, and northwestern Europe, but less common in Asian countries and South America so that 9% of all cancer-related deaths are among men within the European Union.[4] Since androgens play a main role in smooth muscle proliferation associated with the development of PCa, men with increased risk of PCa may show higher risk of cardiac disease.[4] Patients with PCa are often treated with androgen deprivation therapy (ADT).[5] Tumor biomarkers like prostate specific antigen (PSA), acid phosphatase (ACP) and prostatic acid phosphatase (PAP) can be used for early diagnosis, staging and monitoring of the disease.[3] Decreasing level of prostatic biomarkers in serum of PCa patients could serve as an indicator of response to the treatment.[3] Nowadays, several risk factors contributing to the development of PCa have been identified.[4] Moreover, numerous studies have shown that the aggressiveness and mortality of PCa could be correlated with obesity.[6] Adiponectin is considered as a potential biological link between obesity and PCa, but there is paucity of epidemiological data confirming this association.[7] Therefore, the aim of the current review was to assess the relationship between obesity, adiponectin, and PCa.

Adiponectin

Adiponectin is a product of the APM1 gene[8] located on

chromosome 3q27.[9] It is a 244 aminoacid polypeptide with 30 KDa molecular weight which is widely synthesized and secreted by adipose tissues.[9-15] Studies have shown a link between obesity, insulin resistance and diabetes which play an important role in diabetes and cardiovascular disease.[9]

Serum concentrations of adiponectin is in the range of 2 to 20 mg/L.[5,16,17] The mean level of adiponectin concentration is 1000 times higher than leptin and cortisol level and 1000000 times higher than cytokines like interleukin-6 and TNF-α.[18] The level of adiponectin in men is about 40% lower than in women.[16,19] It seems that it is due to androgens, since androgens have an inhibitory effect on adiponectin secretion.[17,18,20] Moreover, circulating levels of adiponectin are determined through several genetic, anthropometric, hormonal, inflammatory, dietary, and pharmacological factors.[21]

Adiponectin contains three domains including a signal peptide, a collagen-like motif and a globular domain. Moreover, circulating adiponectin exists in at least two forms; low molecular weight (LMW) oligomer that is a hexamer of two trimers and high molecular weight (HMW) oligomer containing four- six trimmers.[9] Plasma adiponectin concentrations are inversely correlated with fasting plasma insulin levels.[18] Expression of adiponectin mRNA takes place exclusively in adipose tissues;[21] however, bone, mammary glands, salivary glands and cardiac tissue may also express limited amounts of adiponectin.[10,22-24] Maturation and secretion of adiponectin is controlled through a mechanism called "thiol mediated retention",[25] so that endoplasmic reticulum chaperones such as endoplasmic reticulum protein with molecular weight of 44 kDa (ERp44) and endoplasmic reticulum oxidoreductin 1-like alpha (Ero1-La) are induced during adipogenesis.[25]

Adiponectin Receptors

Adiponectin acts via binding to main receptors; adiponectin receptor 1(AdipoR1) and adiponectin receptor 2 (AdipoR2).[26] AdipoR1 and AdipoR2 encoding genes are located on chromosomes 1p36.13-q41 and 12p13.3, respectively.[16] Expression of these receptors (AdipoR1 and AdipoR2) has been detected in monocytes, and megakaryocyte cell lines.[26]

Adiponectin and Signaling Pathway

Adiponectin inhibits inflammation by suppressing the phagocytic activity of mature macrophages and induces apoptosis in vitro.[7] Adiponectin works through many intracellular signaling pathways such as AMPK, mechanistic target of rapamycin (mTOR), Phosphatidylinositol 3-kinase (PI3K/Akt), mitogen activated protein kinase (MAPK), STAT3 and Nuclear factor-κB (NF-κB).[18] Adiponectin also inhibits the pro-inflammatory pathways via inhibition of NF-kB phosphorylation. Inhibition of NF-κB via adiponectin plays a main role in suppression of monocyte adhesion to endothelial cells.[20] Most of the effects of adiponectin are mediated via AMPK.[18] AMPK activation also inhibits growth of androgen-independent and androgen-sensitive PCa cell lines.[27] AMPK also inhibit FAS (a key lipogenic enzyme), which has been associated with colon, breast, prostate and ovarian cancer (Figure 1).[18]

The JNK and STAT3 signaling pathway are known as adiponectin's mediators in metabolic syndrome and cancer. STAT3 is activated through adipokine or cytokine-induced JAK phosphorylation, so that many cancer-related processes including cell survival and differentiation are connected to adipokine pathways. Therefore, JAK/STAT3 pathway dysregulation leads to carcinogenesis.

Another study is reported that endogenous level of adiponectin acts as a tumor suppressor via inhibition of epithelial-to-mesenchymal transition (EMT) of PCa cells, but it is down regulated through hyperrmethylation of promoter gene in PCa cell.[28]

Adiponectin and PCa

Comments of previous researchers about the role of adiponectin and obesity in PCa have been shown in Table 1.

Most of the studies showed the role of obesity in PCa except Baillargeon et al study.[34] They reported that due to small sample size they did not observe any relationship between obesity and PCa.

Obesity and Adiponectin in PCa

The relationship between obesity and aggressive PCa is still not fully evaluated. Obesity may be associated with

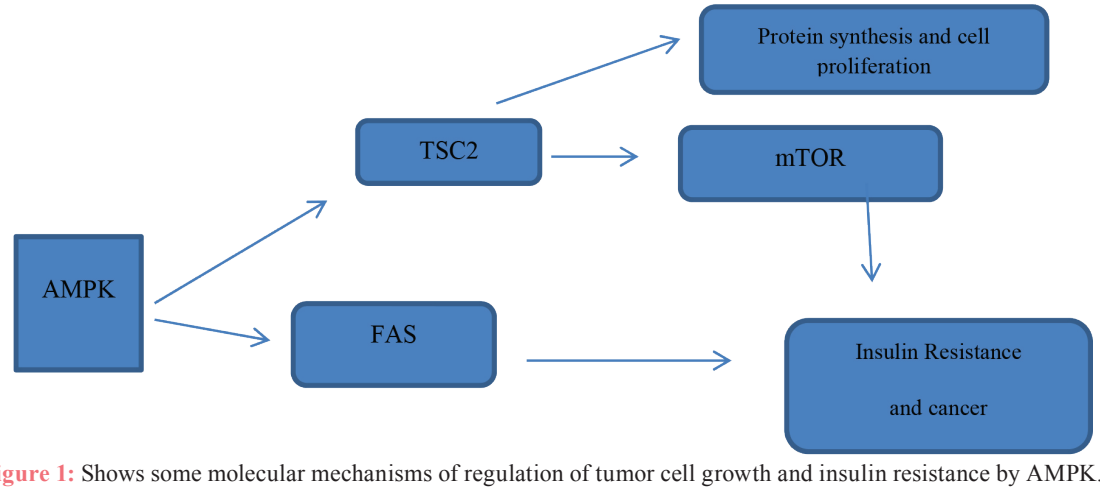

Figure 1: Shows some molecular mechanisms of regulation of tumor cell growth and insulin resistance by AMPK.[18]

Table 1: Comments of researchers about the role of adiponectin and obesity in PCa

Study	Explanations	Population	References
Stephan (2005)	Obesity was associated with altered level of adiponectin.	Maryland	29
Goktas (2005)	Plasma adiponectin level was significantly lower in the PCa group in comparison to the group with benign prostate disorders or controls.	Turkey	9
Housa (2006)	Circulating level of adiponectin is inversely associated with the risk of malignancies.	Prague	30
Bub (2006)	Adiponectin at physiological concentrations inhibited both androgen-dependent and androgen-independent PCa cell growth in vitro.	USA	31
Baillargeon (2006)	There was no significant association between obesity with PCa risk due to small sample size.	USA	32
Michalakis (2007)	Lower concentration of plasma adiponectin was found among PCa patients compared to healthy men.	Greece	33
Buschemeyer (2007)	Obesity and lower level of adiponectin increased the risk of PCa.	USA	34
Sher (2008)	Lower serum adiponectin was independently associated with high-grade PCa.	USA	35
Housa (2008)	Increased level of adiponectin has a protective effect against tumor progression in cancer patients.	Prague	36
Mistry (2008)	Low level of adiponectin may be important in driving obesity-related PCa progression.	United kingdom	37
Fontana (2009)	Adiponectin may acts as an anti-prostatic factor. Obesity may promote progression of PCa.	Argentina	38
Freedland (2010)	Higher adiponectin concentration was associated with a lower risk of PCa in comparison to controls.	North Carolina	39
Li (2010)	Men with higher adiponectin concentrations presented lower risk for developing high-grade or metastatic cancer.	USA	7
Dimmer (2010)	There was no association between Single Nucleotide Polymorphism (SNP) and PCa risk.	USA	40
Dhillon (2011)	SNP of ADIPOR1/R2 genes was not significantly associated with PCa risk.	USA	41
Alokail (2011)	There was inverse association between adiponectin level and total PSA.	Saudi Arabia	42
Lu (2012)	Lower level of adiponectin in obese people was associated with prostatic oxidative stress.	Canada	43
Izadi (2012)	There was negative correlation between adiponectin level and PCa.	Iran	44
Tewari (2013)	Higher BMI and obesity was significantly correlated to PCa.	India	45
Gao (2014)	Adiponectin suppresses proliferation but doesn't affect apoptosis of human prostate adenocarcinoma cell line.	China	46
Ikeda (2015)	Inverse correlation was seen between adiponectin and BMI.	Japan	47
Baslan (2015)	Globular adiponectin and full-length adiponectin was decreased in obese and insulin-resistant rats.	Brazil	25

increased risk of advanced disease and death in PCa patients.[27] Several factors can increase the risk of tumor initiation and progression. Environmental factors such as diet with higher content of saturated fat and obesity itself can be connected to PCa. The consumption of fat is concordantly correlated to PCa mortality rate.[36] It seems that high level of dietary fat stimulates PCa cells proliferation. Obesity and diabetes together lead to hyperinsulinemia and may promote the risk of PCa development.[27] Insulin resistance can alter the risk of PCa via diverse biologic pathways such as obesity-sex hormone pathway and non-obesity-related pathways.[9,20] Insulin resistance can increase the risk of PCa via non-obesity-linked mechanisms like inflammation, oxidative stress, and apoptosis. Therefore, it seems that many factors such as insulin resistance and obesity may be related to PCa.[9]

Obesity causes increased level of free Insulin-like growth factor (IGF-1) which stimulates growth of prostate cell lines in vitro. Moreover, obesity is related to advanced stage of PCa in humans and leads to elevated level of serum interleukin-6 in adipose tissues.[27] PCa cell line and PCa patients have been shown to be capable of increased production of IL-6 and IL-6 receptor. Circulating level of IL-6 is associated with progression of metastatic disease.[47] In addition, human PCas expressed high amounts of leptin receptor.[27,48] Moreover, studies have shown that the relationship between leptin and PCa is contradictory. Some studies have found a positive correlation between serum leptin level and PCa risk,[49,50] but others have found no association.[39] Adipose tissue-derived cytokines like adiponectin could explain the association between PCa and obesity.[50] Adipokines may provide a molecular mechanism whereby obesity exerts its effects on prostate tumor biology.[38] It seems that obesity affects prostate tumor biology via exposing of prostate cells to circulating adipokines. Adiponectin plays a main role as a molecular basis for the association between obesity and PCa.[37]

Adiponectin also increased sensitivity of insulin in various stromal and epithelial cells.[9] It seems that adiponectin has potent insulin-sensitizing actions.[27] On the other hand, adiponectin is a key mediator of systemic insulin sensitivity and glucose homeostasis. The main metabolic effects of adiponectin are suppression of hepatic glucose production and modulation of suppressing inflammatory responses in other cell types including macrophages.[25] Another study reported that the anti-neoplastic activity of adiponectin may be explained possibly by decreasing insulin resistance and hyperinsulinemia.[51]

Low levels of adiponectin could result in higher inflammatory states and angiogenesis. These processes promoted tumor growth.[39] Another study reported that the effect of adiponectin on neovascularization remains contradictory, so that it has both pro and anti-angiogenic effects.[27] Moreover, adiponectin mRNA expression is decreased in adipose tissues. This change is related to a higher risk of diabetes evolution.[39] Therefore, it is hypothesized that decreased level of adiponectin may underlie the association between PCa and obesity/ insulin resistance.[39]

Another study showed that there is inverse relationship between metformin and serum prostate-specific antigen in PCa, independent of other anti-hyperglycemic medications.[51] Metformin improves PCa recurrence and survival rate.[52] Metformin as an anti-diabetic drug caused activation of AMPK and inhibited growth of PCa cells.[7] Antineoplastic mechanism of metformin can be due to inhibition of mTOR in the PI3K/AKT/mTOR pathway.[53,54] Moreover, metformin has a main role in decreasing level of gene expression involved in mitosis.[55] Therefore, it seems that metformin therapy leads to a better prognosis in patients with PCa.[56]

Conclusion

According to the ample studies in the literature, decreased concentration of adiponectin was associated with increased risk of PCa. Therefore, it seems that hypoadiponectinemia may be a promising biomarker for early detection of PCa.

Conflict of Interest: None declared.

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