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INFLUENCE OF LEPTIN AND ADIPONECTIN ON PROSTATE CANCER

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Summary.- *OBJECTIVES: Many studies have investigated the association between obesity, adipose tissue-derived factors (leptin and adiponectin) and prostate cancer (CaP) but the results are still inconsistent.*

METHODS: The aim of this study was to carry out a comprehensive review of the existing evidence about the role of leptin and adiponectin in prostate carcinogenesis and to provide an overview of it.

RESULTS: Recent evidence suggests that leptin may play a rol in prostate cancer progression, while adiponectin may act as an "anti- prostatic cancer" adipokine.

CONCLUSIONS: Obesity may promote the progression of established prostate cancer and and adipokines may provide a molecular mechanism whereby obesity exerts its effects on prostate tumour biology.

Keywords: *Adiponectin. Leptin. Obesity. Prostate cancer.*

Resumen.- *OBJETIVO: Numerosos estudios han estudiado la asociación entre la obesidad, las sustancias secretadas por el tejido adiposo (leptina y adiponectina) y el cáncer de próstata (CaP), aunque los resultados no han sido concluyentes. El objetivo del presente trabajo es realizar una revisión bibliográfica sobre el rol de la leptina y la adiponectina en el desarrollo del CaP.*

MÉTODOS: Se realizó una búsqueda bibliográfica y lectura compresiva de artículos relacionados con "leptina", "adiponectina", "obesidad" y "cáncer de próstata" en Pubmed y revistas científicas; y efectuar una breve descripción sobre el tema.

RESULTADOS: Estudios recientes indican que el tejido adiposo y las diferentes sustancias que éste secreta, denominadas adipoquinas, podrían promover o prevenir el desarrollo del CaP. La leptina tendría un efecto promotor del tumor; mientras que la adiponectina tendría un efecto protector.

CONCLUSIÓN: La obesidad podría influenciar la carcinogénesis prostática mediante un mecanismo molecular en el que participarían las adipoquinas.

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INTRODUCCIÓN

Obesity, defined as "an excessive energy accumulation as fat in the organism", is acquiring the characteristics of an authentic pandemia, and constitutes one of the major current challenges for world public health, since it entails a disease with serious consequences on the health of obese people (1, 2). The consequences of overweight on the cardiovascular, respiratory, digestive, osteoarticular, reproductive and endocrine-metabolic systems are very well known as well as its relation to several types of cancer, including prostate cancer (CaP) (3). An overweight of 20% can increase 20 to 30% the incidence CaP (3).

The adipocyte has been classically considered as a cell whose main function is to "passively" store energy as triglycerids, during the periods of caloric excess, and to mobilize them when the energetic balance demands it. However, nowadays the adipose tissue is considered as an authentic organ with a high endocrine and metabolic activity (4). Recent studies have revealed the great importance of the white adipose tissue as a producer of several substances with endocrine, paracrine and autocrine activity (5, 6), known as "adipokynes". This tissue produces substances related to the inmune system (TNF-α, IL-1: IL-6), the vascular function (VEGF, angiotensin, PAI 1) and the development of insulin resistance (resistin). Besides, it has the P450 aromatase enzime that takes part in the peripheral aromatization of androgens into estrogens and secretes substances involved in the regulation of body weight, like leptin and adiponectin (Figure 1).

Numerous studies have tried to interpret the association between the quantity of body adipose tissue and CaP, although the results have not been concluding due to the great difficulty to evaluate the effects of obesity on the development of this type of tumor. This difficulty lies in that obesity not only appears as an excess of body fat but it also alters several physiological parameters that increase the aggressivity of CaP (7 – 11) (Figure 2) resulting in:

• Insulin resistance with hyperinsulinemia that leads to an increase of liver production of IGF-1. In vitro, IGF-1 stimulates the growth of prostatic cell lines androgen independent when producing a mitogenic and antiapoptotic effect on these cells, while, in vivo, IGF-1 behaves as a growth factor of multiple types of malignant tumors (12).

• Alteration of adipokyne secretion, increasing leptin, VEGF, IL-6 and TNF-α release and decreasing the adiponectin secretion. Adipokynes could be related to different carcinogenic mechanisms including cell

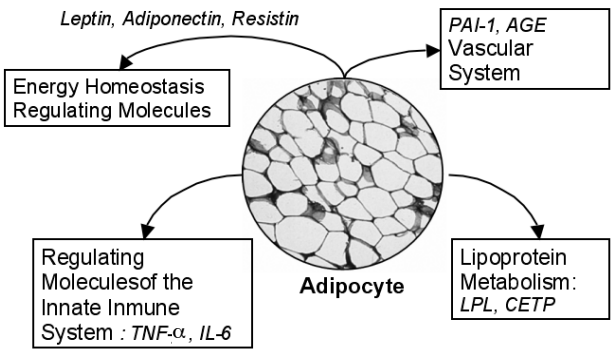

FIGURE 1. Adipocite as endocrine gland.

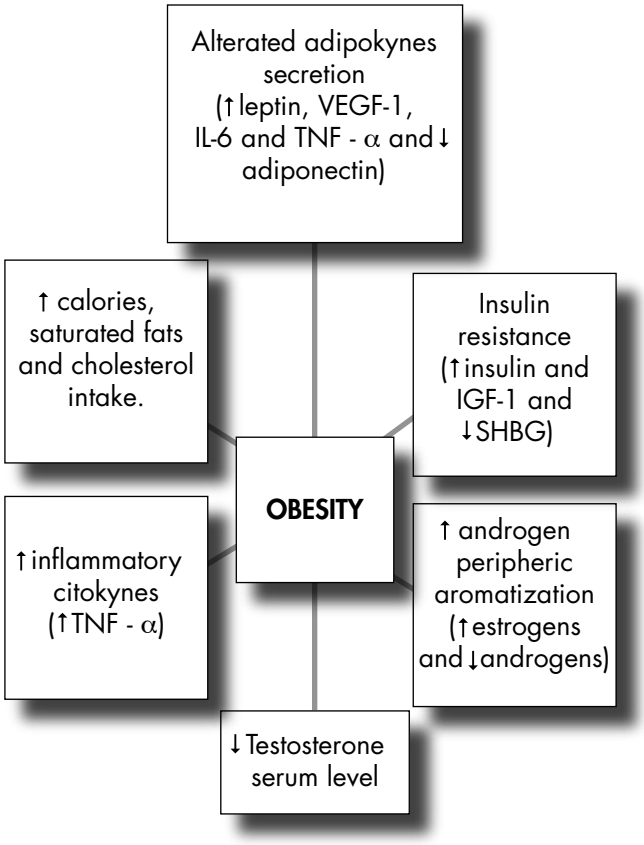

FIGURE 2. Influence of obesity on prostate cancer.

differentiation, apoptosis, cell proliferation, angiogenesis and alteration of the levels of steriodal sexual hormones (13). Numerous studies point out that leptin would have a promoting effect on CaP; while adiponectin would have a protecting one (11, 14, 15).

• Greater aromatization of androgens in the adipose tissue due to an elevated expression of P450 aromatase, increasing the plasmatic levels of estrogens and decreasing the androgen concentration. The decline of testosterone serum levels has been associated to advanced tumors and poor differentiation at the moment of diagnosis (16, 17).

• Increase of proinflammatory citokynes as IL-6 and a tumoral necrosis factor (TNF-α). The latter interferes in the insulin signaling way and leads to IR present in obesity. Also, the TNF-α induces IL-6 and leptin release. It has been recently suggested that inflammation would increase the risk of CaP, but the relation between TNF-α and CaP is still unclear (18, 19).

Likewise, obesity is highly correlated with the type of diet and the higher or lower risk of suffering a certain type of cancer. Recent epidemiologic studies show that obesity and the high intake of saturated fats could influence the development of CaP as risk factors in the initial stage and as promoting factors in the progression stage (20).

To sum up, the adipose tissue and different substances it secretes could promote or prevent the development of CaP; however, many questions remain unanswered. For this reason, the aim of the present study was to carry out a comprehensive review of the existing evidence about the role of leptin and adiponectin in prostatic carcinogenesis as well as provide an overview of this subject.

MATERIALS AND METHODS

We made a bibliographic research and comprehensive reading of articles related with "leptin", "adiponectin", "obesity", "adipokynes" and "prostate cancer" in Pubmed and scientific journals. After that, we wrote an over-view of the role of leptin and adiponectin in the development of CaP.

RESULTS AND DISCUSSION

Leptin

Leptin is a peptide of 167 aminoacids, with a molecular weight of 16kDa and codified by the gen ob located in cromosome 7q31.3 in humans. Its synthesis occurs mainly in the white adipose tissue and at a lower extent in the placenta, skeletic muscle, gastric epithelium, mammary gland, etc. (5). The leptin concentration positively correlates with the total body fat, the individual's nutritional condition and the adipocyte triglyceric content; that is why, leptin serum levels are high in obese individuals compared with individuals with a normal weight acting as a "marker" of the organism energy reserves (21).

Six isoforms of leptin receptors (obR) have been sequenced and characterized, which are made up of a membrane protein formed by 3 domains: extracellular, transmembrane and intercellular. The different isoforms of its receptor are distributed both in the central nervous system as in the periphery (ling, kidney, testicles, ovary, gastric epithelium, adipose tissue, pancreas, and so on) (5). The obRa and obRa isoforms are short receptors, predominantly located in the hematoencephalic barrier where they seem to play a transporting role. The obRb form is the structurally longest receptor, abounds in the hypothalamus and is the main maker of the actions of this adipokyne. Lastly, the obRe isoform is the soluble fraction and transports leptin through the blood stream regulating its clearance and half-life (22). Leptin circulates freely or bounded to plasmatic proteins and can be determined by radioinmunoassays or by inmunoenzimatic assays.

This adipokyne has a major function in regulating the energy homeostasis but it also has biological effects in several cellular processes such as reproduction, hematopoiesis, angiogenesis, inmune response, etc.

Numerous studies have investigated the relation between obesity, leptin and CaP (7, 9, 23, 24). High levels of leptin have been significantly correlated with testosterone and specific prostatic antigen values in subjects with CaP compared with subjects with benign prostate hyperplasia and the control group (21). Chang et al reported that high leptin concentrations are associated to tumors with a greater volume (9). There is evidence that leptin does not have the same effects in all the CaP stages. Saglam et al observed that a leptin increase is associated to a great extent to an advanced stage of the illness and to a poorly differentiated tumor (21).

Leptin could affect the risk of clinically detectable CaP by means of factors related to obesity (9). Hsing et al established that the association between leptin and the risk of CaP was limited to men with a waist-to-hip ratio higher than 0.87, suggesting that leptin could interact with the markers related to abdominal obesity, such as sexual hormones or IGF-1, to increase the risk of this neoplasia.

Stattin et al reported that leptin could be the nexus between the western life style (hypercaloric diets rich in fat and sedentarism) and the transition from a pre-neoplastic lession to a clinically detectable tumor (23). Numerous studies have observed that the aggressiveness of the tumor and mortality due to CaP increase with diets rich in fat in men over 70 (25, 26).

The hypothesis that high leptin concentrations influence the evolution of a latent CaP to a clinically detectable one is biologically feasible. In vitro and in vivo studies show that this adipokyne could promote angiogenesis as a determining factor for the growth and spreading of several types of neoplasias including CaP (6, 7, 26). Also, leptin could increase other cytokynes and growth factors such as the vascular epithelial growth factor (VEGF) which is involved in tumor transformation (27).

These studies suggest that leptin could be a promoting factor of tumor growth by promoting angiogenesis and the proliferation of vascular cells and, in this way, favouring tumor cell progression, invasion and metastasis (26). In short, leptin would affect CaP growth by means of factors related with obesity such as testosterone, IGF-1, VEFG, and could influence cell differentiation and CaP progession.

Adiponectin

Adiponectin is the most abundant circulating adipokyne and accounts for 0.05% of the total plasmatic proteins. It is a peptide with a molecular weight of 30 kDa, codified by the gen APM1 (3q27) and made up by 3 codifying exons. It is also known as Acrp30 (30 kDa adipocyte complement-related protein), AdipoQ, APM-1 or GBP28 (gelatin binding protein 28). It is exclussively produced in the white adipose tissue and increases the sensitivity to insulin in several epithelial cells and the stroma of several tissues (28).

Adiponectin can suffer proteolytic processes or posttranslational modifications, forming oligomeric associations that influence its functional capacity and its bond to the receptors. The complete form is called fAd (full-lenght adiponectin) and the smallest resulting form of the proteolysis is known as gAd (globular adiponectin). The methods to measure its plasmatic concentration include radioinmune assays that measure multimeric forms and enzimeinmune assays that recognize the denaturalized monomer.

Two types of receptors for adiponectin have been characterized and sequenced: AdipoR1. that occurs mainly in the skeletic muscle and AdipoR2, that mainly occurs in the liver (28). Cancer cells show adiponectin receptors that would mediate the inhibitory effect on cell proliferation of this adipokyne, mainly through the intracellular signalling way of MAPK (monofosfate of adenosine kinase activated by 5') (29).

Recent sutdies have shown that the complexes with high molecular weight of fAd are the ones that have an inhibitory function of adiponectin on the growth of cancer prostatic cells and suppress the proliferation stimulated by leptin, IGF-1 and dihydrotestosterone (DHT) (30). As a consequence of these observations, it has been labelled as the "anticancer" adipokyne, since it has also been able to demonstrate its inhibitory role on the growth of breast and endometrium cancer cells (31).

Adiponectin concentration also depends on the quantity and distribution of the fat mass. Unlike other adipokynes, the circulating levels of adiponectin are inversely proportional to obesity (the central one in particular), body mass index (BMI), visceral fat accumulation and insulin resistance (11). In fact, it has been demonstrated that the weight loss induced by a diet, increases the levels of ARNm of adiponectin in the abdominal adipose tissue, as well as its circulating plasmatic levels (5). It is also demonstrated that the circulating adiponectin concentrations are lower in patients with breast, endometrium, prostate and colon cancer (32). This is revealed in a study made by Michalakis et al in which the levels of plasmatic adiponectin and tissular expression of adiponectin receptors in patients with CaP, benign prostate hyperplasia (BPH) and a control group were compared. Men in the group with CaP significantly showed a lower adiponectin concentration than the patients with BPH and the control group (33). Likewise, the inmunehistochemistry of their prostatic tissue showed a weak expression of AdipoR1 and AdipoR2 receptors (33).

In addition, the lower the adiponectin levels, the higher the grade of prostatic illness is. Goktas et al made a study with the aim of observing the relation between the serum adiponectin levels and the differentiation or progression of prostatic cancer cells. With that aim, they worked with a group of subjects with CaP, another group of patients with BPH and a third one as the control group. The patients with CaP were divided into two groups: one with a localized disease and another with advanced illness, and this last group was again classified according to Gleason. They could observe that the levels of adiponectin were significantly lower in the subjects with CaP than in those with BPH and the control group (34).

Miyasaky et al have recently shown the presence of adiponectin receptors in LNCaP- FGC andro-

gen dependent, DU145 androgen-independent and PC3 prostatic cell lines (35). This study also identified a JNK kinase and STAT3 (signal transducer and activator of transcription 3) in the adiponectin signalling intracellular way. Both, JNK kinase and STAT3, play mayor roles in obesity and insulin resistance and, are also involved in the regulation of cell proloferation, differentiation and apoptosis of several physiologic and pathologic events, as tumor development (36, 37).

To summarize, the circulating low levels of adiponectin characteristic of obesity would promote insulin resistance and would be a risk factor for the development of different types of cancer, CaP among them.

CONCLUSION

As a conclusion, there is evidence that suggests an association between obesity and the development of CaP. The excess of adipose tissue in the organism could promote the progression of CaP, rather than being a risk factor. Adipokynes have an stimulating effect on prostate cancer cells inducing the promotion and progression of CaP, except for adiponectin that would have a protecting effect in face of the tumor. However, future studies are necessary to clear up even more this relation and, consequently, develop prevention and early detection measures and CaP treatment.

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