

Obesity in the Elderly – On the Role of Adipokines in Prostate Cancer Progression

Adriano Angelucci¹ and Mauro Bologna²

1. Assistant Professor of Immunology; 2. Professor of General Pathology, Department of Experimental Medicine, University of L'Aquila

Abstract

The prostate is the most frequent site of cancer in men aged 68 years and older. Although prostate cancer is frequently a slow-progressing cancer, the increase in lifespan is posing new challenges in order to avoid prostate cancer-associated mortality. Epidemiological studies have clearly demonstrated that the westernised lifestyle and diet may fuel prostate cancer incidence and mortality, and the associated current pandemic of obesity is becoming one of the principal risk factors for age-related chronic diseases. Obesity and ageing seem to contribute independently to deregulating adipose tissue homeostasis and in turn systemic metabolism. Nowadays, adipose tissue is recognised as an active and complex endocrine and immunological organ able to control the homeostasis of different distant organs through the release of a variety of factors, collectively termed adipokines. These factors are master regulators of energy balance and immune response and may account for some of the most frequent obesity- and age-related health problems, including cancer. The dissection of mechanisms leading to altered metabolic control by adipose tissue will eventually indicate a new preventive strategy for prostate cancer.

Keywords

Obesity, ageing, adipokines, prostate cancer, inflammation, leptin, adiponectin, macrophages

Disclosure: The authors have no conflicts of interest to declare.

Received: 5 December 2011 **Accepted:** 12 January 2012 **Citation:** *European Oncology & Haematology*, 2012;8(1):46–51 DOI: 10.17925/EOH.2012.08.01.46

Correspondence: Adriano Angelucci, Department of Experimental Medicine, University of L'Aquila, Via Vetoio, Coppito 2, 67100 L'Aquila, Italy.

E: adriano.angelucci@univaq.it

Today, health operators are mainly worried about two worldwide trends in human conditions: the remarkable increases in life expectancy and in obesity prevalence. These two aspects appear interconnected, and in the last decades a progressive gain in the body weight of older people has been observed. Considering 65 years of age as the threshold of access into the elderly population, it is expected that the number of older adults will increase to approximately 20 % of the US population by 2030,¹ and the large majority of these older people will be overweight. In fact, in the US population for men aged 60 or over the median body mass index (BMI) was progressively increasing in the last ten years of the past century.² As a result, in most developed countries middle-aged and elderly adults are more likely to be obese than people in any other age group.

The prevalence of obesity, defined as an excess amount of body fat, has increased substantially in the past half-century, worldwide. Besides genetic background, the main causal contributors responsible for the increased prevalence of obesity include the modern lifestyle associated with reduced physical activity, food abundance and unhealthy diet. The worldwide prevalence of obesity nearly doubled between 1980 and 2008. A current estimate is that roughly one-third of US adults and one-fifth of European adults are obese.^{3,4}

Advanced age and obesity are both independent and well-known risk factors for chronic health conditions, also including several types of cancer. Growing older is the greatest risk factor for cancer and about

80 % of all cancers are diagnosed in persons aged 55 and older. Prostate cancer (PCa) is the most frequently diagnosed malignancy in American and European men. In the US the median age at the time of PCa diagnosis during 2002–2006 was 68 years, with the highest incidence rate reported in men aged 70–74.⁵ At diagnosis PCa, like many other solid tumours, has a long preceding natural history that started several years before. It is plausible that the number of years overweight has the most important impact on the risks of PCa in old age. Unfortunately, prospective studies with sufficient duration and follow-up time in this matter are lacking and the majority of epidemiological studies are limited to monitoring obesity at diagnosis. However, in consequence of recent data, it is likely that even recent onset of obesity in old age may accelerate PCa progression and worsen the associated conditions. The new key evidence supporting this hypothesis suggests that obesity-related health consequences may be exacerbated by age-related dysfunction in adipose tissue metabolism. In obese individuals the normal homeostasis in visceral fat deposits is significantly perturbed and this in turn is able to disturb the systemic metabolism. Older persons are particularly vulnerable to obesity-related dysregulation because they have a limited capacity to maintain homeostasis and to respond to internal stress. The most commonly suggested multi-system impairments in the elderly involve dysregulation of the neuromuscular, endocrine and immune systems. Low-level inflammation, sarcopenia, osteopenia and nutritional changes are diagnosed. Thus obesity may worsen the outlook of risk resulting from age – or disease-associated physiological frailty.

New Concepts about Adipose Tissue

The false belief that adipose tissue was limited in function to lipid synthesis, storage and breakdown began to be reconsidered in the early 1990s with the discovery that the pro-inflammatory cytokine tumour necrosis factor- α (TNF- α) is synthesised and released by adipocytes.⁶ Subsequent studies have permitted a multiplicity of factors secreted by adipose tissue to be identified, that are collectively termed adipokines (see *Table 1*). The diversity of adipokines renders classification difficult; however, it is now appreciated that they play a key role in the integration of systemic metabolism. Using adipokines as one of the major communication tools, adipocytes affect a large number of other tissues, such as the liver, muscle, brain, reproductive system, pancreatic β cells and vasculature. To date, adipokines have been associated with the control of energy storage, endocrine activity and immune responses. It was also proposed that the adverse health consequences of the accumulation of enlarged visceral adipocytes may tentatively be accounted for by enhanced secretion of adipokines that act as endocrine and paracrine factors on other cells.⁷ Significantly, intra-abdominal fat is metabolically more active than subcutaneous or peripheral fat, and this may explain why abdominal obesity is more closely linked to adverse health outcomes. It has become evident that in addition to absolute fat quantity, qualitative aspects of adipose tissue function and cellular composition have an important effect on the systemic metabolic phenotype.⁸ Although adipose tissue mainly comprises adipocytes, other cell types contribute essentially to its normal and pathological functions, including pre-adipocytes, macrophages, fibroblasts, vascular cells and lymphocytes (see *Table 2*). Obesity, and also old age, can lead to changes in the cellular composition of the fat pad, as well as to the modulation of individual cell phenotypes. Important changes affect the amount and activation of macrophages, the status of the vasculature and the activation of fibroblasts towards a fibrotic phenotype.⁹ All these events are associated with the induction of a pro-inflammatory status. It has been shown that obesity is associated with a state of low-grade chronic inflammation, with infiltrating macrophages within adipose tissue and elevated concentrations of inflammatory markers, including TNF- α , interleukin-6 (IL-6) and C-reactive protein.^{10,11} A strict functional analogy between pre-adipocytes and immune cells seems to exist, but the bases of this similarity are largely unexplored. Adipose tissue and bone marrow share an embryological origin, the mesoderm, and pre-adipocytes are potent phagocytes that resemble macrophages in both morphology and patterns of gene expression.¹² In addition, mature adipocytes, but mainly pre-adipocytes, share the ability to secrete cytokines and activate the complement cascade much like mononuclear immune cells. It was recently suggested that adipose tissue is the main site of direct inflammation in obesity, and a raised circulating level of inflammatory markers is not an indication of systemic inflammation. Macrophages, whose number increases in adipose tissue in parallel with obesity, have been recognised as major sources of pro-inflammatory mediators. In particular, in obesity the balance between M1 and M2 macrophage subtypes is disturbed, favouring the shift to an M1 pro-inflammatory state associated with secretion of high amounts of inflammatory mediators.¹³ In addition, inflammation may be a direct consequence of hypoxia. In fact, as adipose tissue mass expands in obesity, adipocytes distant from the vasculature become relatively low in oxygen and this leads to the stimulation of the production and release of inflammatory cytokines, chemokines and angiogenic factors to stimulate blood flow and increase vascularisation.¹⁴ In turn, the activated vascular endothelium

Table 1: Main Functions of Selected Adipokines and Principal Cell Sources in Adipose Tissue

Adipokine	Function	Principal Source
Leptin	Energy homeostasis, suppression of appetite, development of reproductive tissues	Adipocytes
Interleukin-6	Inflammation, proliferation, angiogenesis, differentiation	Macrophages, activated T cells, adipocytes
Vascular endothelial growth factor	Angiogenesis, migration, vascular permeability	Adipocytes, fibroblasts
Adiponectin	Insulin sensitisation, inhibition of proliferation, apoptosis, inhibition of macrophage pro-inflammatory activation	Adipocytes
Tumor necrosis factor- α	Inflammation, proliferation, apoptosis	Macrophages, adipocytes
Plasminogen activator inhibitor-1	Inhibition of fibrinolysis, fibrosis	Adipocytes, macrophages, endothelial cells
Monocyte chemoattractant protein-1	Recruiting monocytes and T cells	Macrophages, adipocytes, endothelial cells

Table 2. Cellular Composition of Adipose Tissue and Main Changes Associated to Obesity and Elderly

Cell Types in Adipose Tissue	Changes in Older Individuals (*)	Changes in Obese Individuals
Adipocytes	Smaller, decrease of lipolytic capacity, stable or increasing in number, leakage of fatty acid	Hypertrophy, hyperplasia, apoptosis, leakage of fatty acid
Pre-adipocytes	Stable or increase in number, decreased differentiative capacity, oxidative stress	Proliferating and differentiating
Macrophages	Activation, monocyte recruitment	Increase in number, M1-phenotype
T cells	Expansion of infiltrating T cell repertoire	Infiltrating T-helper1 cells
Vascular cells	Reduced angiogenic potential	Angiogenesis, inflamed endothelium
Fibroblasts	Not evaluated	Hypertrophy, collagen deposition
Systemic outcome	↓	↓
	Dysfunctional production of adipokines, systemic low inflammation, impaired glucose homeostasis	Increased release of adipokines (decrease in adiponectin), systemic inflammation, insulin resistance

**mainly demonstrated in murine models.*

expresses adhesion molecules and chemotactic factors that reinforce and localise inflammatory processes.

Obesity in the Elderly

Obesity is a chronic condition that can be prevented but it is difficult to reverse. Over 60 % of children who are overweight before puberty will be overweight in early adulthood. This is particularly true in older adults who are often less likely to change long-standing health behaviours. Moreover, a diminished β -adrenergically mediated thermogenesis and a decreased basal metabolic rate may contribute in older adults to a

positive energy balance and thus promote increased fat storage and obesity.¹⁵ However, the main cause of obesity in developed countries is a decrease in energy expenditure which is primarily due to decreased physical activity in conjunction with an energy-dense diet.

Obesity is considered as one of the greatest long-term health threats for humans in both developed and developing countries.⁴ Worldwide, 2.8 million people, about 8 % of total deaths due to non-communicable diseases, die each year as a result of being overweight. Obesity is undoubtedly related to several diseases and disabilities; moreover, an independent association between obesity and all-cause mortality has been demonstrated in adults.^{16,17} The risks of coronary heart disease, ischaemic stroke and type 2 diabetes mellitus increase steadily with increasing BMI, defined as weight (kg)/height² (m²), a measure widely used in epidemiological and clinical studies for the definition of obesity. Based on BMI, the general population can be classified as follows: underweight (less than 18.5), normal weight (18.5–24.9), overweight (25–29.9) and obese (30 or greater). The increase in obesity prevalence has suggested further dividing obesity into three classes: class I obesity (30–34.9), class II obesity (35–39.9) and morbid obesity (40 and greater). BMI offers a very useful operational definition for many contexts, but authors are beginning to question whether the field should adopt a more useful operational definition.¹⁸ BMI is an imperfect measure in the elderly population because of the age-dependent decrease in height and lean body mass. It was suggested that fat distribution may be more important than BMI in assessing disease risk associated with obesity, especially among older adults.¹⁹ Thus, as an alternative to BMI, it was proposed to measure abdominal obesity by waist circumference or waist:hip circumference ratio (WHR). A waist circumference of 102 cm in a man is defined as having excess abdominal fat, even if the man's BMI is normal. A high waist measurement has been demonstrated to be a better independent risk factor for chronic diseases, particularly for adults with a BMI between 25 and 34.9.²⁰ Waist circumference also appears to be a more adequate measure, because fat mass and fat tissue distribution change dramatically throughout life. In old age, fat is redistributed from subcutaneous to intra-abdominal visceral depots as well as other ectopic or less frequent sites, including bone marrow, muscle and the liver. In consequence, more fat is lost from subcutaneous than visceral fat depots after middle age. However, also considering the limitation of BMI measurement in older men, a recent meta-analysis approach has suggested that elevated BMI is associated with a risk of PCa-specific mortality in prospective cohort studies and biochemical recurrence in PCa patients.²¹

Normally, adipose tissue undergoes significant age-related changes in both quantity and composition. Age-related fat tissue dysfunction may be related to a combination of mechanisms, with reduced capacity to store lipotoxic fatty acids, fat tissue damage by fatty acids and inflammation being contributing factors. These processes are interrelated and amplify each other. Studies conducted in centenarians have demonstrated that one of the key factors for maintaining health and longevity is the preservation of a well-functioning adipose tissue. Cumulative dysregulation of multiple adipokines, including an elevation of pro-inflammatory cytokines, constituted a strong marker of poor prognosis among centenarians.²²

At a cellular level, although new fat cells are formed throughout life, and pre-adipocyte numbers also increase or remain stable in various fat deposits with ageing,²³ a decline in capacity for lipid accumulation

and pre-adipocyte differentiation was observed.^{24,25} A reduced capacity of pre-adipocytes to express differentiation-dependent proteins that bind cytotoxic fatty acids and convert them into less cytotoxic triglycerides with ageing may, in turn, diminish defence against lipotoxicity, setting up a vicious cycle that accelerates pre-adipocyte and fat tissue dysfunction.²⁶ As in obesity, perhaps also with ageing, cross-talk among different cell types in fat tissue leads to a pro-inflammatory state that may contribute to systemic metabolic dysfunction. It is known that ageing is accompanied by chronic low-grade inflammation as stated by two- to fourfold increases in serum levels of inflammatory markers. This condition is independent of pre-existing morbidity, and its causal factors are not very well understood.²⁷ Recent reports show that pro-inflammatory cytokines and chemokines are expressed predominantly in pre-adipocytes, rather than in adipocytes.^{28,29} However, fat tissue inflammation with ageing appears to be caused by changes in both pre-adipocytes and macrophages. Dysfunctional pre-adipocytes release more pro-inflammatory cytokines and chemokines that induce macrophage recruitment and activation. Importantly, an *in vivo* study has demonstrated that ageing is sufficient to modify the profile of adipose tissue macrophages towards a pro-inflammatory environment.³⁰ Thus the fat tissue deregulation that occurs in ageing and obesity may initiate self-propagating inflammatory cycles.

Obesity and Prostate Cancer

Migrant studies have clearly demonstrated that environmental factors and lifestyle may explain the geographical variation in cancer incidence. Epidemiological data are concordant in suggesting that PCa rates of Asian immigrants in the US significantly increase with respect to those in their homelands.^{31,32} One of the largest geographical disparities in incidence among cancers is observed in PCa; incidence differs 60-fold between US and Chinese men. However, the observation that Chinese- and Japanese-Americans have rates that are much higher than their counterparts in China and Japan supports a role for environmental rather than genetic factors.³³ Among the underlying risk factors present in immigrant countries, overweight and obesity account for 15–20 % of all cancer deaths.³⁴ In the last years of the past century a large increase in cancer incidence in low-risk countries has been reported, independently from an improvement in diagnosis methods.^{35,36} Such increases are concurrent with westernisation in these populations, suggesting that changes in the prevalence of certain common potential risk factors, such as dietary fat, obesity and physical activity, may have contributed at least in part to the progression and rising rates of PCa.^{37,38}

In addition to ageing, the aetiology of sporadic PCa is very heterogeneous. However, data on other risk factors, such as circulating levels of hormones, physical activity, body size, smoking, drinking, sexual behaviour and occupational exposures, are conflicting.³⁹ Genetic factors have been invoked to explain the higher incidence rates reported for African-Americans with respect to white Americans, but also in this case available data about population-based incidence rates in Africa, although incomplete and scarcely comparable, indicate much lower incidence rates than the rates reported for African-Americans.³³

Pca is a slow-growing cancer with a long latency period. The prevalence of latent tumours has been shown to be quite high in the elderly population, affecting about 50 % of men over the age of 70.⁴⁰ Thus cancer-promoting factors may significantly change the

impact of PCa on life expectancy. Because of the median age at diagnosis and the slow growing rate of the tumour, it is probable that the cause of death in patients affected by PCa will be independent of cancer. It has been stated many times that most elderly men die with PCa rather than because of PCa, since so many cases of the disease grow indolently and are clinically irrelevant. Interestingly, despite the large disparity in incidence between US and Asian men, autopsy studies have shown that there is little variation in the prevalence of latent PCa across countries.⁴¹ Thus environmental factors may be responsible for the progression from latent to clinically significant tumours.³³

Significantly, recent studies suggest a reverse association between BMI and cancer grading: reduced risk of low-grade PCa and increased risk of high-grade PCa.⁴² This phenomenon is particularly evident if patients are stratified according to age. In fact, the reduced risk of low-grade PCa was evident in younger obese men (aged <60 years).⁴³ A substantial contribution of age was also suggested by a large prospective study that reported a more pronounced risk of all grades of PCa in obese men older than 45 years.⁴⁴ Accordingly, several studies have confirmed a consistent positive association between obesity and PCa mortality.^{34,45} In the American Cancer Society cancer prevention study-II (CPS-II) nutrition cohort, a higher BMI was associated with a lower risk of non-metastatic low-grade PCa, but a higher risk of high-grade, metastatic and fatal PCa.⁴² The largest prospective trial in this area included a total of 950,000 men and found a 9 % excess of PCa in obese individuals.⁴⁴ A recent study including 441 men showed that the association of PCa with obesity could be underestimated because important diagnostic characteristics correlate with obesity. In fact, the authors found that obese men had lower prostate-specific antigen (PSA) values and larger prostate volumes and, after adjusting for confounding variables, obesity was significantly associated with a 98 % increase in PCa risk.⁴⁶

Several mechanisms have been proposed that could explain the association of obesity with PCa risk, including sex steroid hormones, insulin, insulin-like growth factor (IGF) and adipokine signalling. Particular attention was reserved for the potential role of testosterone, because of its association with the initial progression of PCa. However, obesity is generally associated with a decreased concentration of serum testosterone, and the observed association with high-grade PCa has not found a plausible molecular explanation.⁴⁷ The concomitant observation that obesity is associated with substantially lower concentrations of sex hormone-binding globulin and higher concentrations of oestrogens underscores the complex interrelations between obesity and serum sex steroids and their differential effect on PCa.⁴⁸ However, further studies are needed to resolve the possible connection.

It is well known that elderly populations suffer from vitamin D (vitD) deficiency that leads to impaired bone mineralisation. As indicated by two large studies, most older people had low serum levels, and at least 25 % of elderly people had frank vitD deficiency.^{49,50} Hypovitaminosis D has also been frequently reported in obese individuals, and multiple mechanisms have been proposed to explain this association, including metabolic factors and lifestyle.⁵¹ Fat accumulation may be an important co-factor predisposing elders to decreased bioavailability of vitD because of its deposition in body fat compartments. The adverse health effects of vitD deficiency could

extend well beyond bone disease to encompass excess risk of cardiovascular diseases, autoimmune diseases and cancer, particularly colon, prostate and breast cancer.⁵² However, a direct association between vitD levels and PCa risk in older men has not been consistently demonstrated,⁵³ necessitating rigorously controlled studies that take into account the many confounding co-factors associated with lifestyle and dietary habits.

Systemic Inflammation and Metabolic Syndrome

At present, the strongest empirical support for mechanisms to link obesity and cancer risk involves the metabolic and endocrine effects of adipokines. PCa may be influenced by adipokines in three different ways: the maintenance of chronic systemic inflammation, the induction of metabolic and endocrine perturbation or by direct action on prostate tissue. Adipose tissue inflammation, observed both in elderly and in obese men, may support many of these adverse situations. Results from the Glasgow inflammation outcome study have demonstrated that markers of systemic inflammation are powerful prognostic factors for several cancers, including PCa. Moreover, increasing age was associated with a reduced five-year overall survival.⁵⁴ The presence of high levels of C-reactive protein, at diagnosis, predicts a poor long-term cancer outcome in patients with localised PCa.⁵⁵ It was demonstrated that cancer cells may take advantage of the acquisition of an inflammation-responsive phenotype. In fact, chronic exposure to inflammatory cytokines may select for cancer clones that are able to proliferate under such conditions. Cytokines can activate in cancer cells, by autocrine, paracrine or exocrine ways, inflammatory pathways, involving nuclear factor-kb and c-Jun N-terminal kinase (JNK) and stimulating different cancer-promoting mechanisms. Furthermore, it has been reported that human PCa cells produce in an autocrine manner pro-inflammatory cytokines, including TNF- α and IL-6, sustaining their progression.^{56,57}

Insulin resistance, type 2 diabetes and atherosclerosis, as well as other components of the metabolic syndrome, were causally linked to inflammation. This parallels the growing recognition of the importance of inflammation as an element in a wide range of diseases, including those associated with ageing, such as the dementias, neurodegenerative diseases, atherosclerosis, diabetes and cancer.^{27,58} Chronic inflammation is a common feature of the metabolic syndrome, and inflammatory signals may originate within visceral adipose tissue, as this fat deposit expands in response to a chronic positive energy balance. Intriguingly, the metabolic perturbations seen during acute infection share many common features with the known characteristics of the metabolic syndrome. Most importantly, insulin resistance and hyperglycaemia are common in both conditions, and the same holds true for hypertriglyceridaemia, impaired lipolysis and increases in non-esterified fatty acids. Leptin, IL-6, TNF- α and the acute-phase reactant C-reactive protein, as well as other circulating inflammatory markers, are elevated in both conditions.⁵⁹ Serum levels of IL-6 are elevated in patients with PCa and high serum IL-6 levels are associated with a poor prognosis in men with PCa.⁶⁰

Insulin resistance is associated with increased free or bioavailable IGF-1.⁶¹ Whereas few studies have investigated the role of insulin in PCa, a positive association between IGF-1 and PCa risk was reported.⁶² However, epidemiological studies in the elderly have demonstrated this association to be particularly complex, because of the constellation of metabolic abnormalities accompanying older age. Although the more

frequent abnormalities are collectively grouped and identified as metabolic syndrome, the onset and duration of the single components may differentially influence the risk of PCa. Available data on metabolic syndrome and PCa are contradictory and insufficient to suggest a link between metabolic syndrome and PCa.^{63,64}

Leptin and Adiponectin

The dual control by adipose tissue of energy metabolism and the immune system is well demonstrated by two adipokines with opposite functions, leptin and adiponectin. In recent years, both adipokines have received particular interest for their capacity to modulate cancer cell phenotype directly.

Leptin is a small adipokine produced predominantly by adipocytes. Circulating leptin levels are higher in obese individuals with respect to lean subjects. Leptin exerts a complex control of energy homeostasis, modulating different organs and systemic metabolism. During fasting, when plasma leptin levels decline, neural pathways in the hypothalamus cause appetite to increase and energy expenditure to decrease, an attempt to restore body fat stores.⁶⁵ Leptin suppresses the appetite through the production of anorexigenic peptides by the hypothalamus. In animal models the central anorexigenic action of leptin is clearly diminished in ageing, most probably due to the impaired signal transduction in hypothalamic neurons. Because aged obese rats are leptin-resistant, these data predict that they will also have a delayed normalisation of caloric intake and exacerbated weight gain when provided with a high-fat diet. These results demonstrate that aged rats are more susceptible to the detrimental effects of a high-fat diet.⁶⁶ Whether a similar mechanism is also valid in humans remains to be proven. In addition, the fall in plasma leptin diminishes thyroid hormone production⁶⁷ and inhibits the reproductive axis, both effects that save energy during nutritionally lean times.⁶⁸ Importantly, leptin has been indicated as a key factor in the development and maintenance of murine and human reproductive tissues, including the prostate.⁶⁹ The leptin receptor is expressed on prostatic epithelial cells, and thus leptin may directly modulate the development and homeostasis of prostatic tissue. Maturation of the prostate gland continues while embryonic testosterone levels are high; however, as testosterone levels fall during the third trimester of gestation, the gland enters a quiescent state. The quiescent state persists until puberty, when testosterone levels increase again and the epithelium proliferates, giving rise to the mature gland. It is plausible that leptin may exert a role in this phase of gland reactivation just prior to the increase in testosterone levels. In fact, current evidence suggests that leptin plays a permissive role in timing sexual development.⁷⁰ The leptin dependence in prostatic epithelial cells can be reactivated in elderly men following the tumour transformation. In fact, the expression of the leptin receptor is significantly higher in PCa than in both benign prostatic hyperplasia and normal prostatic tissue.⁷¹ The higher the blood leptin concentration, the greater the negative effect on cellular differentiation and the positive one on cancer progression in PCa.⁷² The available data do not unequivocally indicate a positive correlation between blood leptin levels and PCa risk. On the contrary, there are more convincing indications that elevated plasma leptin

concentration is predictive of high-grade disease and more advanced tumours.^{73,74} Results from *in vitro* studies support such a relationship. In fact, leptin treatment of PCa cells determines the activation of intracellular signalling pathways associated with proliferation, migration and invasion.^{74,75}

Adiponectin is the most abundant circulating adipokine in lean individuals. In contrast to other adipokines, serum levels of adiponectin are negatively correlated with central obesity. Adiponectin possesses several physiological functions including modulation of glucose metabolism and energy homeostasis through the enhancement of insulin activity. Studies in ageing humans revealed that enhanced adiponectin values are a distinctive feature of centenarians. Much evidence from experimental models indicates that adiponectin protects against obesity-linked metabolic dysfunction, including type 2 diabetes and metabolic syndrome. Adiponectin is an effective immunosuppressor both at the systemic level and in adipose tissue. Plasma adiponectin levels are negatively correlated with C-reactive protein levels in obese or diabetic patients, and the administration of adiponectin in obese animals improves inflammation-associated pathological outcomes.^{76,77} In adipose tissue adiponectin can interfere in the differentiation of macrophages towards a pro-inflammatory M1 subtype, reducing the production of reactive oxygen species.⁷⁸ Adiponectin receptors are expressed in PCa cell lines and in benign and malignant human prostate tissues,⁷⁹ and it is associated with a marked reduction in the risk of PCa.⁸⁰ Lower adiponectin levels are independently associated with high-grade PCa.⁸¹

Conclusions

The recent growing prevalence of overweight and obesity among older adults has synergised with a substantial change in demographic curves in industrialised countries towards an elderly population. This synergy will have an important impact in the prevalence of chronic health conditions as well as disability among future generations of older adults. Obesity in older adults could affect the health and medical care demands of the elderly population for at least the next several decades, and even today it is only because of pharmacological tools that obesity and its comorbidities have not decreased the lifespan. PCa is one of the age-associated diseases that may be nourished by obesity. The evidence of an association of obesity with increased risk of high-grade cancer could determine in the near future an escalation of non-treatable life-threatening PCa cases. There is growing evidence that dysregulation in adipose tissue homeostasis plays a key role in adverse metabolic changes associated with both obesity and old age. The well-known modification in adipose tissue during obesity may, in the elderly population, worsen the physiological condition of frailty due to a higher susceptibility of adipose cells to various stresses. The resulting dysregulation in adipokines may represent one of the interpretation keys for understanding pathological consequences at the systemic level. However it is critical to better recognise the complex relations existing between abdominal obesity and metabolic changes taking place in the elderly population. In order to dissect these mechanisms, a clearer understanding of the cellular and molecular changes in adipose tissue is needed. ■

1. Wan H, Sengupta M, Velkoff VA, DeBarros KA, 65+ in the United States. In: US Census Bureau (ed.), *Current Population Reports*, Washington, DC: US Government Printing Office, 2005;23–209.

2. Flegal KM, Carroll CL, Ogden et al., Prevalence and trends in obesity among US adults, 1999–2000, *JAMA*, 2002;288:1723–7.

3. Wang Y, Beydoun MA, The obesity epidemic in the United

States—gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis, *Epidemiol Rev*, 2007;29:6–28.

4. Alwan A, Agis T (eds), *Global status report on noncommunicable diseases 2010*, Geneva: World Health Organization, 2011;176.

5. *Cancer Facts & Figures 2010*, Atlanta: American Cancer

Society, 2010.

6. Hotamisligil GS, Shargill NS, Spiegelman BM, Adipose expression of tumor necrosis factor- α : direct role in obesity-linked insulin resistance, *Science*, 1993;259:87–91.

7. Bray GA, Medical consequences of obesity, *J Clin Endocrinol Metab*, 2004;89:2583–9.

8. Kim JY, van de Wall E, Laplante M, et al., Obesity-associated

- improvements in metabolic profile through expansion of adipose tissue, *J Clin Invest*, 2007;117:2621–37.
9. Kahn SE, Prigeon RL, Schwartz RS, et al., Obesity, body fat distribution, insulin sensitivity and islet beta-cell function as explanations for metabolic diversity, *J Nutr*, 2001;131:354S–60S.
 10. Greenberg AS, Obin MS, Obesity and the role of adipose tissue in inflammation and metabolism, *Am J Clin Nutr*, 2006;83:461S–465S.
 11. Dandona P, Aljada A, Chaudhuri A, et al., Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation, *Circulation*, 2005;111:1448–54.
 12. Cousin B, Munoz O, Andre M, et al., A role for preadipocytes as macrophage-like cells, *FASEB J*, 1999;13:305–12.
 13. Weisberg SP, McCann D, Desai M, et al., Obesity is associated with macrophage accumulation in adipose tissue, *J Clin Invest*, 2003;112:1796–808.
 14. Trayhurn P, Wood IS, Adipokines: inflammation and the pleiotropic role of white adipose tissue, *Br J Nutr*, 2004;92:347–55.
 15. Kerckhoffs DA, Blaak EE, Van Baak, Saris WH, Effect of aging on beta-adrenergically mediated thermogenesis in men, *Am J Physiol*, 1998;274:E1075–9.
 16. Harris T, Cook EF, Garrison R, et al., Body mass index and mortality among nonsmoking older persons. The Framingham Heart Study, *JAMA*, 1988;259:1520–4.
 17. Allison DB, Gallagher D, Heo M, et al., Body mass index and all-cause mortality among people age 70 and over: the Longitudinal Study of Aging, *Int J Obes Relat Metab Disord*, 1997;21:424–31.
 18. Kragelund C, Omland T, A farewell to body-mass index?, *Lancet*, 2005;366:1589–91.
 19. Zamboni M, Mazzali G, Zoico E, et al., Health consequences of obesity in the elderly: a review of four unresolved questions, *Int J Obes (Lond)*, 2005;29:1011–29.
 20. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—The Evidence Report. National Institutes of Health, *Obes Res*, 1998;6(Suppl. 2):51S–209S.
 21. Cao Y, Ma J, Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis, *Cancer Prev Res (Phila)*, 2011;4:486–501.
 22. Arai Y, Takayama M, Gondo Y, et al., Adipose endocrine function, insulin-like growth factor-1 axis, and exceptional survival beyond 100 years of age, *J Gerontol A Biol Sci Med Sci*, 2008;63:1209–18.
 23. Kirkland JL, Dobson DE, Preadipocyte function and aging: links between age-related changes in cell dynamics and altered fat tissue function, *J Am Geriatr Soc*, 1997;45:959–67.
 24. Gregerman RI, Aging and hormone-sensitive lipolysis: reconciling the literature, *J Gerontol*, 1994;49:B135–9.
 25. Yki-Jarvinen H, Kiviluoto T, Nikkila EA, Insulin binding and action in adipocytes in vitro in relation to insulin action in vivo in young and middle-aged subjects, *Acta Endocrinol (Copenh)*, 1986;113:88–92.
 26. Guo W, Pirtskhalava T, Tchonia T, et al., Aging results in paradoxical susceptibility of fat cell progenitors to lipotoxicity, *Am J Physiol Endocrinol Metab*, 2007;292:E1041–51.
 27. Krabbe KS, Pedersen M, Bruunsgaard H, Inflammatory mediators in the elderly, *Exp Gerontol*, 2004;39:687–99.
 28. Chung S, Lapoint K, Martinez K, et al., Preadipocytes mediate lipopolysaccharide-induced inflammation and insulin resistance in primary cultures of newly differentiated human adipocytes, *Endocrinology*, 2006;147:5340–51.
 29. Harkins JM, Moustaid-Moussa N, Chung YJ, et al., Expression of interleukin-6 is greater in preadipocytes than in adipocytes of 3T3-L1 cells and C57BL/6J and ob/ob mice, *J Nutr*, 2004;134:2673–7.
 30. Lumeng CN, Liu J, Geletka L, et al., Aging Is Associated with an Increase in T Cells and Inflammatory Macrophages in Visceral Adipose Tissue, *J Immunol*, 2011;187:6208–16.
 31. Shimizu H, Ross RK, Bernstein L, et al., Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County, *Br J Cancer*, 1991;63:963–6.
 32. Lee J, Demissie K, Lu SE, Rhoads GG, Cancer incidence among Korean-American immigrants in the United States and native Koreans in South Korea, *Cancer Control*, 2007;14:78–85.
 33. Parkin DM, Whelan SL, Ferlay J, et al. (eds), *Cancer Incidence in Five Continents*, Vol. VII, Lyon: IARC Scientific Publications No 143, 1997.
 34. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ, Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults, *N Engl J Med*, 2003;348:1625–38.
 35. Shimizu H, Ross RK, Bernstein L, Possible underestimation of the incidence rate of prostate cancer in Japan, *Jpn J Cancer Res*, 1991;82:483–5.
 36. Shibata A, Whittemore AS, Genetic predisposition to prostate cancer: possible explanations for ethnic differences in risk, *Prostate*, 1997;32:65–72.
 37. Popkin BM, The nutrition transition in low-income countries: an emerging crisis, *Nutr Rev*, 1994;52:285–98.
 38. Hsing AW, Devesa SS, Jin F, Gao YT, Rising incidence of prostate cancer in Shanghai, China, *Cancer Epidemiol Biomarkers Prev*, 1998;7:83–4.
 39. Nomura AM, Kolonel LN, Prostate cancer: a current perspective, *Epidemiol Rev*, 1991;13:200–27.
 40. Villers A, Soulié M, Haillot O, Boccon-Gibod L, [Prostate cancer screening (III): risk factors, natural history, course without treatment. Characteristics of detected cancers], *Prog Urol*, 1997;7:655–61.
 41. Breslow N, Chan CW, Dhom G, et al., Latent carcinoma of prostate at autopsy in seven areas. The International Agency for Research on Cancer, Lyons, France, *Int J Cancer*, 1977;20:680–8.
 42. Rodriguez C, Freedland SJ, Deka A, et al., Body mass index, weight change, and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort, *Cancer Epidemiol Biomarkers Prev*, 2007;16:63–9.
 43. Gong Z, Neuhauser ML, Goodman PJ, et al., Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial, *Cancer Epidemiol Biomarkers Prev*, 2006;15:1977–83.
 44. Engeland A, Tretli S, Bjorge T, Height, body mass index, and prostate cancer: a follow-up of 950000 Norwegian men, *Br J Cancer*, 2003;89:1237–42.
 45. Rodriguez C, Patel AV, Calle EE, et al., Body mass index, height, and prostate cancer mortality in two large cohorts of adult men in the United States, *Cancer Epidemiol Biomarkers Prev*, 2001;10:345–53.
 46. Freedland SJ, Wen J, Wuerstle M, et al., Obesity is a significant risk factor for prostate cancer at the time of biopsy, *Urology*, 2008;72:1102–5.
 47. Platz EA, Leitzmann MF, Rifai N, et al., Sex steroid hormones and the androgen receptor gene CAG repeat and subsequent risk of prostate cancer in the prostate-specific antigen era, *Cancer Epidemiol Biomarkers Prev*, 2005;14:1262–9.
 48. Gapstur SM, Kopp P, Gann PH, et al., Changes in BMI modulate age-associated changes in sex hormone binding globulin and total testosterone, but not bioavailable testosterone in young adult men: the CARDIA Male Hormone Study, *Int J Obes (Lond)*, 2007;31:685–91.
 49. Orwoll E, Nielson CM, Marshall LM, et al., Vitamin D deficiency in older men, *J Clin Endocrinol Metab*, 2009;94:1214–22.
 50. Kuchuk NO, Pliujim SM, van Schoor NM, et al., Relationships of serum 25-hydroxyvitamin D to bone mineral density and serum parathyroid hormone and markers of bone turnover in older persons, *J Clin Endocrinol Metab*, 2009;94:1244–50.
 51. Mason RS, Sequeira VB, Gordon-Thomson C, Vitamin D: the light side of sunshine, *Eur J Clin Nutr*, 2011;65:986–93.
 52. Deeb KK, Trump DL, Johnson CS, Vitamin D signalling pathways in cancer: potential for anticancer therapeutics, *Nat Rev Cancer*, 2007;7:684–700.
 53. Barnett CM, Nielson CM, Shannon J, et al., Serum 25-OH vitamin D levels and risk of developing prostate cancer in older men, *Cancer Causes Control*, 2010;21:1297–303.
 54. Proctor MJ, Morrison DS, Talwar D, et al., An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a Glasgow Inflammation Outcome Study, *Br J Cancer*, 2011;104:726–34.
 55. McArdle PA, Qayyum T, McMillan DC, Systemic inflammatory response and survival in patients with localised prostate cancer: 10-year follow-up, *Urol Int*, 2010;84:430–5.
 56. Adler HL, McCurdy MA, Kattan MW, et al., Elevated levels of circulating interleukin-6 and transforming growth factor-beta1 in patients with metastatic prostatic carcinoma, *J Urol*, 1999;161:182–7.
 57. Angelucci A, Garofalo S, Specia S, et al., Arachidonic acid modulates the crosstalk between prostate carcinoma and bone stromal cells, *Endocr Relat Cancer*, 2008;15:91–100.
 58. Bruunsgaard H, The clinical impact of systemic low-level inflammation in elderly populations. With special reference to cardiovascular disease, dementia and mortality, *Dan Med Bull*, 2006;53:285–309.
 59. Wisse BE, The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity, *J Am Soc Nephrol*, 2004;15:2792–800.
 60. Nakashima J, Tachibana M, Horiguchi Y, et al., Serum interleukin 6 as a prognostic factor in patients with prostate cancer, *Clin Cancer Res*, 2000;6:2702–6.
 61. Nelson WG, De Marzo AM, DeWeese TL, Isaacs WB, The role of inflammation in the pathogenesis of prostate cancer, *J Urol*, 2004;172(Pt 2):S6–11; discussion S11–2.
 62. Kaaks R, Lukanova A, Sommersberg B, Plasma androgens, IGF-1, body size, and prostate cancer risk: a synthetic review, *Prostate Cancer Prostatic Dis*, 2000;3:157–72.
 63. Tande AJ, Platz EA, Folsom AR, The metabolic syndrome is associated with reduced risk of prostate cancer, *Am J Epidemiol*, 2006;164:1094–102.
 64. Lund Håheim L, Wisløff TF, Holme I, Nafstad P, Metabolic syndrome predicts prostate cancer in a cohort of middle-aged Norwegian men followed for 27 years, *Am J Epidemiol*, 2006;164:769–74.
 65. Schwartz MW, Woods SC, Porte D Jr, et al., Central nervous system control of food intake, *Nature*, 2000;404:661–71.
 66. Judge MK, Zhang J, Turner N, et al., Prolonged hyperphagia with high-fat feeding contributes to exacerbated weight gain in rats with adult-onset obesity, *Am J Physiol Regul Integr Comp Physiol*, 2008;295:R773–80.
 67. Legradi G, Emerson CH, Ahima RS, et al., Leptin prevents fasting-induced suppression of prothyrotropin-releasing hormone messenger ribonucleic acid in neurons of the hypothalamic paraventricular nucleus, *Endocrinology*, 1997;138:2569–76.
 68. Ahima RS, Prabakaran D, Mantzoros C, et al., Role of leptin in the neuroendocrine response to fasting, *Nature*, 1996;382:250–2.
 69. Nazian SJ, Cameron DF, Temporal relation between leptin and various indices of sexual maturation in the male rat, *J Androl*, 1999;20:487–91.
 70. Zhang Y, Proenca R, Maffei M, et al., Positional cloning of the mouse obese gene and its human homologue, *Nature*, 1994;372:425–32.
 71. Hoon Kim J, Lee SY, Myung SC, et al., Clinical significance of the leptin and leptin receptor expressions in prostate tissues, *Asian J Androl*, 2008;10:923–8.
 72. Saglam K, Aydur E, Yilmaz M, Göktaş S, Leptin influences cellular differentiation and progression in prostate cancer, *J Urol*, 2003;169:1308–11.
 73. Chang S, Hursting SD, Contois JH, et al., Leptin and prostate cancer, *Prostate*, 2001;46:62–7.
 74. Ribeiro R, Vasconcelos A, Costa S, et al., Overexpressing leptin genetic polymorphism (-2548 G/A) is associated with susceptibility to prostate cancer and risk of advanced disease, *Prostate*, 2004;59:268–74.
 75. Somasundar P, Frankenberry KA, Skinner H, et al., Prostate cancer cell proliferation is influenced by leptin, *J Surg Res*, 2004;118:71–82.
 76. Onuma M, Bub JD, Rummel TL, Iwamoto Y, Prostate cancer cell-adipocyte interaction: leptin mediates androgen-independent prostate cancer cell proliferation through c-Jun NH2-terminal kinase, *J Biol Chem*, 2003;278:42660–7.
 77. Ouchi N, Kihara S, Funahashi T, et al., Obesity, adiponectin and vascular inflammatory disease, *Curr Opin Lipidol*, 2003;14:561–6.
 78. Xu A, Wang Y, Keshaw H, et al., The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice, *J Clin Invest*, 2003;112:91–100.
 79. Ohashi K, Parker JL, Ouchi N, et al., Adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype, *J Biol Chem*, 2010;285:6153–60.
 80. Mistry T, Digby JE, Chen J, et al., The regulation of adiponectin receptors in human prostate cancer cell lines, *Biochem Biophys Res Commun*, 2006;348:832–8.
 81. Michalakis K, Williams CJ, Mitsiades N, et al., Serum adiponectin concentrations and tissue expression of adiponectin receptors are reduced in patients with prostate cancer: a case control study, *Cancer Epidemiol Biomarkers Prev*, 2007;16:308–13.
 82. Sher DH, Oh WK, Jacobus S, et al., Relationship between serum adiponectin and prostate cancer grade, *Prostate*, 2008;68:1592–8.