Adiponectin and Prostate Cancer Mortality: To Be or Not to Be Skinny?

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Obesity is one of the biggest public health crises of our day. In the United States, 1 in 3 adult men is obese. This rate is a staggeringly high compared with obesity rates in other countries—notably those in Asia, where obesity rates are <5%. Obesity is well known to increase the risk for numerous medical problems, such as diabetes, heart disease, and hypertension, and has been linked with the incidence of and the mortality from multiple cancers.

In terms of prostate cancer, the relationship with obesity is complex (1). In the 20 000-foot view, obesity appears to be associated with a slightly decreased risk in the incidence of prostate cancer, but it is also associated with a clear and consistent, albeit modest, increased risk of prostate cancer mortality. Multiple molecular mechanisms have been proposed to explain these observations (2). Ultimately, the contributions from each of these mechanisms remain unclear. Therefore, it is important to continue to investigate the pathways that link obesity with aggressive prostate cancer.

With that goal in mind, Li and coworkers (3) describe in this issue of Clinical Chemistry their investigation of whether prediagnostic concentrations of adipokines (leptin or adiponectin) correlated with prostate cancer incidence or disease aggressiveness/mortality. This study used frozen serum samples from nearly 1300 adult male participants nested within the Physicians’ Health Study. The strength of this analysis was the fact that samples were collected before the diagnosis of prostate cancer. The design of this prospective cohort study thus avoids the limitations of case–control studies, in which biomarkers are measured in men already known to have the disease. The problem with the case–control approach is that increased biomarker concentrations may be due to a tumor already present rather than to an increase in a biomarker that causes the tumor (i.e., a chicken-vs-egg argument). Thus, the use of a study design like the authors’ allows a better assessment of the role of the increased biomarker on developing the disease of interest, in this case prostate cancer.

In a result that mirrored the overall very weak to null association between obesity and prostate cancer incidence, the authors found no association between the prediagnostic concentration of adiponectin or leptin and prostate cancer risk. It is important to note, however, that not all prostate cancers are created equal. Many men with prostate cancer harbor a clinically indolent form of the disease that is unlikely to progress or cause serious harm during a man’s lifetime, whereas other men do indeed have life-threatening disease. This fact is reflected by the very high prostate cancer incidence (192 280 cases in 2009) relative to the low mortality (27 360 deaths in 2009) (4). Despite the relative low lethality of prostate cancer, it remains the second-leading cause of cancer death among men; thus, identification of any factors that may alter that risk is a worthwhile endeavor. In epidemiologic studies, for example, it is typical to separate high-risk from low-risk prostate cancers. Indeed, obesity may influence these 2 “types” of prostate cancer differently (5).

To investigate whether leptin and/or adiponectin concentrations influence disease aggressiveness, Li and coworkers examined the association between these measures and tumor stage and grade (3). The authors found trends for higher concentrations of adiponectin, but not of leptin, to be associated with a lower risk of high-grade and lethal cancer and among men with prostate cancer. In other words, a higher concentration of adiponectin, but not leptin, was correlated with less-aggressive prostate cancer.

Given these observations, it is important to review the typical function of adiponectin and to assess its physiological role in promoting prostate cancer growth. Adiponectin is a 27-kDa polypeptide hormone that is produced exclusively by fat cells (i.e., adipocytes), and its concentration is inversely related to obesity: The more obese a person is, the lower the adiponectin concentration. Its typical function is to activate AMP-activated protein kinase, which stimulates fatty acid oxidation, leading to improved insulin sensitivity and improved maintenance of glucose homoeostasis. Indeed, lowered adiponectin concentrations in obese people may be one of the mechanisms linking obesity with insulin resistance and diabetes. In addition to its known properties in glucose control,
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adiponectin directly inhibits inflammation and angiogenesis. Consequently, a low-adiponectin environment (i.e., obesity) would produce increased insulin resistance (and therefore greater production of the progrowth hormone insulin) coupled with higher inflammation and an increase in angiogenesis—all of which would theoretically promote tumor growth.

Despite the growing interest in the link between obesity and prostate cancer and regardless of the clear link between obesity and altered adiponectin concentrations, the literature concerning adiponectin and prostate cancer has remained scant. A PubMed search on October 14, 2009, for “adiponectin” and “prostate cancer” revealed only 35 reports, all of which were published since 2005. Of these 35 reports, 12 were reviews, 1 was related to benign prostate disease, and 1 was related to colon cancer and just mentioned the prostate in the introduction. Thus, only 21 primary research reports about adiponectin and prostate cancer have been published, and all have appeared in the last 4 years.

A review of these 21 reports reveals that many (6,7), but not all (8), of the studies found a higher adiponectin concentration to be linked with a lower prostate cancer risk, compared with controls. In contrast, 1 study found that men with locally advanced prostate cancer actually had higher adiponectin concentrations than healthy control individuals (9). Of note is that most of these reports were of case–control studies, a fact that again raises the chicken-vs-egg argument discussed above. The study that did not find such a link between prediagnostic adiponectin concentrations and overall prostate cancer risk was a case–control study by Baillargeon et al., which was nested within a prospective cohort study (8). This study agreed with the findings of Li et al. In contrast to the study of Li et al., however, Baillargeon et al. also found no association between the prediagnostic adiponectin concentration and high-grade tumors, whereas Li et al. found at least trends for a higher adiponectin concentration to be linked with fewer high-grade tumors. Whether these differences reflect true biological differences between the patient populations in the 2 studies, the smaller number of men with high-grade disease in the Baillargeon et al. study (n = 40), or the relatively short time (1.43 years) from the measurement of the “prediagnostic” adiponectin concentration to diagnosis in that study is unknown. Ultimately, additional study on that aspect is needed.

One particular observation by Li and coworkers deserves special mention. Specifically, the association between adiponectin concentration and prostate cancer mortality among men with prostate cancer was not altered by further adjustments for C-peptide, a marker of insulin secretion. Taken at face value, this finding suggests that the mechanisms through which adiponectin is linked to prostate cancer growth are not via altered insulin secretion. Thus, perhaps the antiinflammatory and antiangiogenic properties of adiponectin are the key to its antitumor activity, as has been suggested in preclinical models (10).

Ultimately, given both the exciting data that higher adiponectin concentrations may be linked with less-aggressive prostate cancer and other published studies that support this view (6,7), we must ask: What is the clinical relevance of this observation? First, the modest-to-poor link between obesity and adiponectin in both this study and other studies (11) suggests that many factors independent of adiposity influence the adiponectin concentration. More research is needed to determine to what degree modifiable factors (i.e., diet and exercise) influence adiponectin. If certain diets that favorably influence insulin concentrations (i.e., caloric restriction or low-carbohydrate diets) are also found to favorably influence adiponectin concentrations, perhaps such diets can in turn be used to slow prostate cancer growth in men with already diagnosed disease. Indeed, these diets do slow prostate cancer growth in animal models (12–14). At the least, we need to better examine the exact molecular mechanisms through which the pleiotropic hormone adiponectin influences prostate cancer growth. Given the study by Li et al. and a growing body of literature, however, we have a better sense that adiponectin likely plays a role in influencing prostate cancer aggressiveness, although determining the how and the why of this role will require further study.

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