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Care of the cancer survivor: metabolic syndrome following hormone-modifying therapy

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Abstract

Emerging evidence implicates metabolic syndrome as a long-term cancer risk factor but also suggests that certain cancer therapies may increase patients' risk of developing metabolic syndrome secondary to cancer therapy. In particular, breast cancer and prostate cancer are driven in part by sex hormones, thus treatment for both diseases is often based on hormone-modifying therapy. Androgen suppression therapy in men with prostate cancer is associated with dyslipidemia, increasing risk of cardiovascular disease, and insulin resistance. Anti-estrogen therapy in women with breast cancer can affect lipid profiles, cardiovascular risk, and liver function. As the number of cancer survivors continues to grow, treating physicians must be aware of the potential risks facing patients who have previously been treated with either androgen suppression therapy or anti-estrogen therapy so that early diagnosis and intervention can be achieved.

Keywords

metabolic syndrome; breast cancer; prostate cancer; anti-estrogen therapy; androgen suppression therapy

Introduction

The symptoms of metabolic syndrome were associated as early as 1921 when Elliott Joslin published a report linking diabetes and obesity in the *Journal of the American Medical Association*.[1] Throughout the 1970's and 1980's, accumulating clinical data continued to link insulin resistance with other findings, including dyslipidemia and hypertension.[2–5] Eventually, several descriptors including metabolic syndrome, insulin resistance syndrome, or syndrome X were used to discuss the association amongst this constellation of symptoms.[6–8] Today, metabolic syndrome has an ICD-9 code and is a widely used, if still debated, description of a health risk affecting an estimated one in five Americans, or nearly 50 million people.[9,10] As a result of their metabolic abnormalities, these individuals are at a significantly elevated risk for

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cardiovascular disease, diabetes, and liver disease, while emerging evidence has begun to implicate metabolic syndrome as a long-term cancer risk factor.[11]

However, there is also accumulating evidence suggesting that certain cancer therapies may place cancer survivors at an increased risk of developing post-treatment characteristics of metabolic syndrome.[12,13] As our understanding of the health consequences of metabolic syndrome continue to expand and as more and more cancer patients become long-term survivors, it will be important to evaluate cancer therapy itself as a risk factor for the development of metabolic syndrome.

Definition

Several study groups have attempted to develop standardized diagnostic criteria for metabolic syndrome. The widely cited National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) definition established in 2001 14 was updated in 2005 by two panels of experts, the American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement (AHA/NHLBI) and the International Diabetes Federation (IDF).15 The AHA/NHLBI definition of metabolic syndrome requires that three of the following be present: elevated waist circumference (>102 cm in men or >88 cm in women), elevated triglycerides (>150 mg/dL or following specific treatment for elevated triglycerides), reduced high density lipoprotein (HDL) (<40 mg/dL in men or 50 mg/dL in women), elevated blood pressure (>130/85 or the use of medication for hypertension), and elevated fasting glucose (>100 or the use of medication for hyperglycemia). Similarly, the IDF definition is based on waist circumference greater than 94 cm in men or 80 cm for women and at least two of the following: elevated triglycerides (>150 mg/L or following specific treatment for lipid abnormalities), reduced HDL (<40 mg/dL in men or 50 mg/dL in women or following a specific treatment for HDL abnormalities), elevated blood pressure (>130/85), and elevated fasting glucose (>100 mg/L or diabetes).

Health Consequences of Metabolic Syndrome

Even in the absence of clinically evident disease, metabolic syndrome leads to a greatly elevated risk of morbidity and mortality associated with conditions that arise secondary to metabolic irregularities. Metabolic syndrome has been shown to increase the morbidity associated with cardiovascular disease,[16] while diagnosed patients are also much more likely than the general population to develop type 2 diabetes. Furthermore, nonalcoholic steatohepatitis is associated with obesity, insulin resistance, and, increasingly, with coincident metabolic syndrome.[17] Clearly, the long-term health consequences of untreated metabolic syndrome are substantial, both for the individual patient and for society at large.

However, even as prevention and treatment of metabolic syndrome have focused on modifying specific factors through intensive lifestyle modification and pharmacological therapy, there has been speculation that alterations in sex hormone levels may modify metabolism.[18–20] More recently, evidence suggests that hormone levels may play a role in the gender differences observed in metabolic syndrome.[21] Abdominal obesity is associated with androgens and is more commonly observed in men than in women. This finding is in keeping with the many studies documenting the cardioprotective benefits of estrogen in pre-menopausal women as well as the literature evaluating the metabolic irregularities in polycystic ovarian syndrome.[22,23] In addition, it has been noted that metabolic syndrome in men is often associated with low testosterone levels.[24,25] Consequently, the overall connection between sex hormones and metabolism is also of great relevance for another patient population: cancer survivors.

Cancer Patients at risk for Metabolic Syndrome

Breast cancer and prostate cancer are driven in part by sex hormones, thus treatment is often based on hormone-modifying therapy. Anti-estrogen agents including tamoxifen and aromatase inhibitors are routinely used for primary therapy as well as chemoprevention in women with estrogen receptor-positive malignancy. Similarly, medical therapy for prostate cancer can involve androgen ablation through the use of luteinizing-hormone releasing hormone (LHRH) analogs or anti-androgen agents which block the testosterone receptor. Emerging evidence now suggests that hormonal therapies for these malignancies can increase the risks of developing metabolic syndrome secondary to cancer therapy.

Significantly, the number of patients affected by these cancers is substantial. The SEER database managed by the National Cancer Institute indicates that in 2005, 210,000 new cases of breast cancer were diagnosed. Similarly, during the same year, an estimated 232,000 new diagnoses of prostate cancer were made in men. However, even as these malignancies continue to affect thousands of patients, improved cancer detection and therapy have also led to increasing numbers of cancer survivors. The five-year survival rate for breast cancer between 1996–2004 was an encouraging 88.7%, a 28% drop in mortality compared to survival rates from 1950–2005. Similarly, for men with prostate cancer, the same data indicate a 98.9% survival rate and a 22% drop in the mortality rate.

Prostate cancer patients and metabolic syndrome

Treatment for prostate cancer includes surgery, radiation, and androgen suppression therapy.[26,27] Despite the efficacy of androgen suppression therapy, accumulating evidence also indicates that this therapy may lead to metabolic syndrome. Several studies have documented adverse changes in cardiac risk factors in patients on androgen suppression therapy. A large cohort of Medicare enrollees demonstrated that such therapy was associated with increased risk of coronary artery disease, myocardial infarction, and sudden cardiac death.12 In risk regression analysis, controlling for age and pre-existing cardiovascular risk factors still demonstrates a nearly three-fold increase in risk of death from cardiovascular causes in patients undergoing androgen ablation.28 In particular, when groups of patients are directly compared, fatal myocardial infarctions seem to occur earlier in those men who were treated with androgen suppression therapy compared to men who were not. The cardiovascular risk profile associated with androgen suppression therapy is even such that in men with low-risk prostate cancer, it may contribute to lower overall disease survival due to increased cardiovascular morbidity. 29 In studies analyzing the specific risk factors for men undergoing androgen suppression therapy, compared to age-matched controls, patients in this population had higher levels of central obesity and elevated blood triglycerides.[30] Low testosterone, whether secondary to gonadal dysfunction or androgen suppression therapy has been shown to contribute to elevated total cholesterol, elevated low density lipoprotein (LDL), and elevated triglycerides, all factors associated with increased risk of cardiovascular disease.[31]

Another defining characteristic of metabolic syndrome, insulin resistance, is also a variable affected by androgen suppression therapy.[32] Several of the same studies linking cardiovascular risk factors to androgen suppression therapy in prostate cancer patients also noted increased risk of incident diabetes or hyperglycemia in this population, in some cases with calculated risk even greater than that described for cardiovascular disease.[12,30] Of particular note, these changes in hyperglycemia and diabetes risk developed independently of patient age and body mass index suggesting that androgen suppression therapy itself, not only a patient's underlying risk factors, contribute to the association between therapy and increased risk of glycemic abnormalities.[33] Studies in men with low testosterone demonstrate that decreased testosterone precedes detectable elevations in fasting glucose, insulin, and hemoglobin A1c levels,

indicating that low testosterone may be a marker of developing incident diabetes.[34] Even short-term use of androgen suppression therapy has been linked to changes in insulin sensitivity, a change that seems to occur in parallel with increasing abdominal obesity.[35] Finally, in men with pre-existing diabetes, initiation of androgen suppression therapy led to worsening of glycemic control in up to 22% of patients as measured by adverse changes in Hemoglobin A1c and serum glucose levels.[36]

Cardiovascular disease and diabetes are well known risks for patients diagnosed with metabolic syndrome, but liver disease in the form of non-alcoholic steatohepatitis has also been linked to the syndrome.[37] Although this connection is just starting to be evaluated, a recent case report did note the development of non-alcoholic steatohepatitis in a previously normal-weight patient on lupron, suggesting that liver disease may also be an emerging risk for patients undergoing androgen suppression therapy.[38]

Breast cancer patients and metabolic syndrome

Breast cancer treatment and subsequent risk of metabolic syndrome is complicated by the complexity of breast cancer treatment modalities. For estrogen receptor-positive tumors, standard of care is estrogen suppression, but as more targeted anti-estrogen agents are developed, the options for hormone suppression have multiplied. Tamoxifen, a selective estrogen receptor modulator, is an estrogen receptor antagonist in breast tissue but a partial agonist in other tissues, including the endometrium. In contrast, aromatase inhibitors block the peripheral conversion of androgens into estrogens and are thus useful in post-menopausal women. Finally, in the setting of known genetic predisposition to breast and/or ovarian cancer, women may choose to undergo bilateral oophorectomy. The risk of metabolic syndrome must consequently be evaluated in the context of the mechanism through which estrogen is suppressed.

As the cardiovascular literature has established, estrogen is cardioprotective, and by virtue of its partial estrogen agonist properties, tamoxifen has been shown to have beneficial effects on lipid profiles and the risk of coronary artery disease. Estrogen's favorable effect on lipid profiles has been widely documented,[39] and studies over the last two decades have established that post-menopausal women on tamoxifen seemed to have improved lipid profiles with an antiatherogenic effect.[40–42] Further analysis has subsequently shown that these positive trends in lipid profiles are also associated with improved cardiac risk factors and a decreased incidence of myocardial infarction, improved long-term survival, and decreased adverse events due to coronary artery disease.[40,43,44]

However, these favorable changes in cardiovascular risk factors are not observed in patients treated with aromatase inhibitors. Compared to treatment with tamoxifen, treatment with aromatase inhibitors has been shown to worsen lipid profiles, increase hypercholesterolemia, and increase risk of adverse cardiovascular outcomes.[45–47] A recent meta-analysis of several studies confirms the increased risk in grade 3 and 4 cardiovascular events in patients treated with aromatase inhibitors compared to tamoxifen.[13] Even as studies continue to support the increased efficacy of aromatase inhibitors over tamoxifen in the adjuvant treatment of breast cancer because of their overall side effect profile, there is nonetheless a consistent observation that aromatase inhibitors contribute to dyslipidemia and increased cardiovascular events compared to tamoxifen.[48] Further complicating the analysis of metabolic syndrome risk factors is the established incidence of weight gain in breast cancer survivors, in some studies reported as up to 60% of patients.[49,50] Such weight gain is associated with both adverse outcomes secondary to breast cancer recurrence but also comorbid conditions associated with obesity.[51]

Unlike androgen suppression, estrogen suppression therapy does not seem to be associated with adverse measures of glycemic control or incidence of diabetes. However, while the

incidence of non-alcoholic steatohepatitis in prostate cancer patients undergoing androgen suppression is just starting to be evaluated, the use of estrogen suppressing agents has long been associated with adverse trends in hepatic function.[52] Over a decade ago, case reports began to link tamoxifen with the onset of hepatic steatosis, and a 1991 study demonstrated that women on tamoxifen have increased visceral fat deposition and fatty liver compared to control women.[53] In a large study of women undergoing tamoxifen therapy as chemoprevention, estrogen suppression was associated with an increased incidence of non-alcoholic steatohepatitis in women who were previously overweight or obese.[54]

Finally, several recent studies show that women who undergo bilateral oophorectomy are also at risk for developing metabolic syndrome. A 2008 study in premenopausal women demonstrated bilateral oophorectomy was a risk factor for developing metabolic syndrome, even after controlling for reproductive, global health, and lifestyle variables.[55] Similarly, a large cohort study of nearly 1000 women found that during the six-year period following bilateral oophorectomy, women who had undergone the procedure were 2.5 times more likely to develop metabolic syndrome.[56] These studies indicate that surgical approaches to controlling estrogen production can have the same adverse effects as pharmacological therapy on markers of metabolic syndrome. It should also be noted that the same LHRH agonists used in men to treat prostate cancer have recently been evaluated in women with breast cancer to achieve cessation of ovarian function without surgery. Data indicates that when used in conjunction with chemotherapy or tamoxifen in women with estrogen receptor-positive tumors, these agents can be effective options for treating hormone-responsive tumors in pre-menopausal women.[57] Although studies have not yet evaluated whether LHRH agonists lead to metabolic syndrome in women the way they do in men, the data evaluating other means of estrogen suppression make it likely that this large and ever-growing patient population is also at risk of developing therapy-related components of metabolic syndrome.

Practice recommendations

The vast majority (98%) of men diagnosed with prostate cancer will survive five years, and the statistics for breast cancer have also improved significantly with better screening and the development of more specific targeted therapies. However, success in treating cancer raises the challenges of cancer survivorship: data from the American Cancer Society estimates that over ten million Americans are cancer survivors. In the specific setting of hormone-driven malignancies, the same hormone-modifying therapies that allow patients to survive their disease can also have significant effects on their health after cancer. It is therefore important that physicians caring for cancer survivors take the opportunity to intervene in ways that can promote good health and quality of life post-cancer.

First, it is essential for treating physicians to be aware of the potential risks facing patients who have previously been treated with either androgen suppression therapy or antiestrogen therapy. It is important to note that even without current manifestations of metabolic syndrome markers, cancer survivors are at increased risk of developing the syndrome over time. Consequently, part of these patients' overall health maintenance should include close monitoring of lipid profiles, liver enzymes, body habitus, and markers of glycemic function in order to promote early intervention. Emerging evidence even suggests that metformin in patients who are not yet diabetic can have beneficial effects in preventing the metabolic consequences of androgen deprivation.[58] In fact, insulin itself is being postulated as a potential therapeutic target for lifestyle or pharmacological interventions as it may represent underlying metabolic abnormalities that drive cardiovascular or endocrine risk factors as well as possibly cancer recurrence.[59–61]

Furthermore, early promotion of healthy lifestyle factors including physical activity and dietary modifications may be of particular importance in this vulnerable population. Studies have documented weight gain in patients diagnosed with cancer, due in part to decreased activity levels associated with the psychological stress of diagnosis combined with the physical stress of treatment.[51] However, in the cancer survivor population, physical activity and exercise may be one of the most significant ways to improve quality of life. Exercise may specifically help ameliorate some of the risk factors associated with hormone modifying therapy,[62] while more general analysis of the benefits of exercise have shown a direct correlation with quality of life markers, a particularly relevant issue for cancer survivors.[63] A recent study in women who had been treated for breast cancer suggests that exercise can help modify the elevated insulin levels associated with a sedentary lifestyle and help decrease hip circumference, both markers associated with the metabolic syndrome.[64]

Finally, as the cancer survivor population continues to grow and long-term studies reveal more about the risks cancer survivors face secondary to their therapy, cancer treatment protocols can continue to evolve to maximize successful cancer outcomes as well as quality of life and long-term health measures. For example, there is some evidence that in low-risk prostate cancer patient populations, short-term androgen suppression therapy can have the same degree of beneficial outcome as more lengthy hormone suppression.[65] In breast cancer patients, the risks and benefits of long-term tamoxifen therapy for chemoprevention or the choice of tamoxifen vs. aromatase inhibitors may eventually include analysis of metabolic syndrome risks. Oncology outcomes will continue to dictate primary therapy, but a consideration of therapy-driven side effects will also be an important part of both oncology and general medicine decision-making as the number of cancer survivors continues to grow. In patients with prostate cancer, androgen suppression is clearly linked to an increasing risk of symptoms consistent with metabolic syndrome. In the breast cancer population, the evaluation of a given patient's risk profile and which aspects of metabolic syndrome she is at risk of developing will depend upon a close evaluation of her health pre-therapy as well as the specific agents with which she was treated. In both settings, the role of the physician in actively managing risk factors and potential interventions cannot be overstated.

In his 1921 *JAMA* paper on the link between diabetes and obesity, Elliot Joslin pointed out one fact which is just as salient today as it was nearly 100 years ago: "The physician should take pride in the prevention of diabetes in his practice…but it is to the diabetic patient and his relatives that one can look most confidently for help in preventing diabetes."[1] Cancer is a devastating disease, but it also represents a remarkable opportunity for physicians to work with patients and family members to help preserve and promote health. As the success of multidisciplinary cancer treatment protocols allows more patients to survive malignancies that would once have been incurable, care of the cancer survivor will continue to be an important consideration for the physician.

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