Metabolic Syndrome After Hormone-Modifying Therapy: Risks Associated With Antineoplastic Therapy

By Amanda J. Redig, MD, PhD and Hidayatullah G. Munshi, MD

The incidence of metabolic syndrome is rapidly increasing. Metabolic syndrome is associated with elevated morbidity and mortality secondary to cardiovascular disease, insulin resistance, and hepatic dysfunction. A body of evidence has already implicated metabolic syndrome as a cancer risk factor; emerging evidence now suggests that cancer survivors themselves may be at risk for developing metabolic syndrome as a result of their anti-cancer therapy. Treatment of both breast cancer and prostate cancer often involves hormone-modifying agents that have been linked to features of metabolic syndrome. Androgen suppression 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. Similar findings have been noted in men with testicular cancer treated with chemotherapy. In addition, several emerging therapies, including mammalian target of rapamycin (mTOR) inhibitors and targeted kinase inhibitors, are increasingly associated with some features of metabolic syndrome. As the number of cancer survivors continues to grow, consideration of these factors and of the risk of metabolic syndrome will become increasingly important when choosing between therapy options and managing long-term follow-up.

The last 3 decades have seen a steady increase in the prevalence of obesity, diabetes, dyslipidemia, and hypertension, most notably in the American population but also on a global scale. These trends have resulted in a marked increase in the prevalence of metabolic syndrome; this term is used to describe a specific constellation of findings, defined by the American Heart Association and the National Heart, Lung, and Blood Institute as including the following: elevated waist circumference (>102 cm in men or >88 cm in women), elevated triglyceride level (>150 mg/dL or the use of specific treatment for elevated triglycerides), reduced high-density lipoprotein (HDL) cholesterol level (<40 mg/dL in men or <50 mg/dL in women), elevated blood pressure (>130/85 mm Hg or the use of medication for hypertension), and elevated fasting glucose level (>100 mg/dL or the use of medication for hyperglycemia). Recent studies estimate that one in five Americans, or nearly 50 million people, suffer from metabolic syndrome.

Understanding, treating, and preventing metabolic syndrome has become a priority because of the tremendous health burden faced by individuals in whom the syndrome is diagnosed. Not only are patients with metabolic syndrome at a substantially elevated risk for cardiovascular disease and the development of cancer but the combined metabolic irregularities of the syndrome are also directly linked to greatly elevated morbidity and mortality associated with other conditions that arise from metabolic derangement. In addition to increasing the morbidity associated with cardiovascular disease, metabolic syndrome leads to an elevated incidence of type 2 diabetes and is increasingly associated with nonalcoholic steatohepatitis, a rising cause of liver transplantation, even in children. For the individual patient and for society, the potential long-term consequences of untreated metabolic syndrome are immense. Accumulating evidence suggests that cancer survivors may be at particular risk for developing metabolic syndrome secondary to their anti-cancer therapy. Because both estrogen and testosterone have been implicated in driving malignant cell growth, hormone-modifying agents are currently used to treat several different cancers, including breast and prostate tumors. Multiple studies indicate that changes in sex hormone levels modify metabolism and relative hormone levels may help explain the marked differences observed between the incidence of metabolic syndrome in men and the incidence in women. Metabolic changes associated with modification of either estrogen or androgen levels are consequently of direct relevance to the large and ever-growing number of cancer survivors who have received hormone-modifying agents. In addition, the newest classes of anti-cancer drugs include multiple compounds with potentially
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There are a myriad of ways in which cancer survivors can be affected by antineoplastic therapy. It is thus the aim of this review to synthesize the available data in order to assess the risk of metabolic syndrome associated with selected antineoplastic therapies.

Metabolic Syndrome in Patients With Breast Cancer

Treatment for prostate cancer includes surgery, radiation, and androgen suppression therapy.[14,15] Androgen suppression is highly successful at treating the disease, but accumulating evidence suggests that this therapy may lead to metabolic syndrome. Studies in a cohort of Medicare enrollees demonstrate that androgen suppression is linked to an increased risk of coronary artery disease, myocardial infarction (MI), and sudden cardiac death.[8] Tsai and colleagues[16] demonstrated that, even after controlling for age and pre-existing cardiovascular risk factors by regression analysis, patients who underwent androgen ablation still had a nearly three-fold increase in risk of death from cardiovascular causes. Of particular interest, when the incidence of fatal MI in a group of patients treated with androgen suppression was compared with the incidence in a group not treated with androgen suppression, the patients who received androgen suppression were found to be more likely to have a fatal MI at an earlier age.[17] In fact, the cardiovascular risk associated with androgen suppression therapy is so substantial that increased cardiovascular morbidity may even contribute to lower disease survival in men with low-risk prostate cancer.[17] When compared with age-matched controls, patients who undergo androgen suppression have higher levels of central obesity and greater elevations of blood triglyceride levels.[18] Also, the low testosterone levels associated with either gonadal dysfunction or androgen suppression therapy are also thought to raise total cholesterol levels, low-density lipoprotein (LDL) cholesterol levels, and triglyceride levels—all factors associated with increased risk of cardiovascular disease.[19]

In addition to its effect on cardiovascular risk factors, androgen suppression is also known to affect insulin resistance, another characteristic of metabolic syndrome.[20] Several studies demonstrating the link between androgen suppression and adverse changes in patients’ cardiac risk profiles also note an increased risk of incident diabetes or hyperglycemia in patients who receive androgen suppression, in some cases with a calculated risk that exceeds the risk of cardiovascular disease.[8,18] Importantly, changes in the risk of hyperglycemia and diabetes develop independently of patient age and body mass index (BMI) at time of diagnosis, suggesting that androgen suppression therapy itself can contribute to the development of glycemic irregularities.[21] In fact, in a population of men with low testosterone levels, a decreased testosterone level preceded detectable elevations in fasting glucose, insulin, and hemoglobin A1c levels, suggesting that a low testosterone level may serve as a marker for the development of incident diabetes.[22] Even short-term androgen suppression therapy has been shown to influence both abdominal obesity and insulin sensitivity.[23] Finally, in a cohort of men with pre-existing diabetes, glycemic control as measured by serum glucose levels and hemoglobin A1c levels markedly worsened in up to 22% of the cohort following initiation of androgen suppression.[24]

Metabolic Syndrome in Patients With Breast Cancer

The association between breast cancer treatment and subsequent metabolic syndrome is complicated by the complexity of breast cancer treatment modalities. Estrogen suppression is standard of care for estrogen receptor–positive tumors, but the mechanisms through which estrogen-suppressive agents work vary markedly. The selective estrogen receptor modulator tamoxifen antagonizes the estrogen receptor in breast tissue but is in fact a partial agonist in other tissues, including the endometrium. In contrast, aromatase inhibitors are used in postmenopausal women because they block the peripheral conversion of androgens into estrogens. Finally, some women whose genetic risk profile indicates they are at high risk for breast and/or ovarian cancer choose to undergo bilateral oophorectomy. Consequently, the risk of metabolic syndrome must be evaluated in the context of each mechanism of estrogen suppression.

Estrogen itself is cardioprotective and has a favorable effect on lipid profiles.[25] Because it is a partial estrogen agonist, tamoxifen can also have beneficial effects on lipid profiles and coronary artery disease risk.[26-28] Such positive trends in lipid profiles are, not surprisingly, associated with improved cardiac risk factor profiles, decreased incidence of MI, improved long-term survival, and...
decreased numbers of adverse events from coronary artery disease.[26,29,30] However, the favorable changes in cardiovascular risk factor profiles associated with tamoxifen are not seen with aromatase inhibitors. Use of these agents can worsen lipid profiles, increase hypercholesterolemia, and increase risk of adverse cardiovascular outcomes compared with treatment with tamoxifen.[31-33] A recent meta-analysis of several studies confirms that compared with treatment with tamoxifen, treatment with aromatase inhibitors increases the risk of grade 3 and 4 cardiovascular events.[9] Their overall adverse-effect profile continues to make aromatase inhibitors preferred over tamoxifen as an adjuvant treatment in postmenopausal women; however, it has been consistently observed that aromatase inhibitors contribute to dyslipidemia and increased cardiovascular events to a greater degree than tamoxifen does.[34] Unlike androgen suppression, estrogen suppression does not seem to lead to adverse changes in glycemic control or diabetes incidence. However, estrogen suppression has long been associated with deleterious changes in hepatic function.[35] Tamoxifen use had been linked with hepatic steatosis in case reports before a 1991 study demonstrated that compared with controls, women receiving tamoxifen had increased visceral fat deposition and fatty liver.[36] Estrogen suppression as chemoprevention is also associated with an increased incidence of nonalcoholic steatohepatitis in women who were previously overweight or obese.[37] Finally, surgical estrogen suppression via bilateral oophorectomy also increases a woman’s risk of developing metabolic syndrome. In premenopausal women, bilateral oophorectomy increases the risk of metabolic syndrome after controlling for reproductive health, global health, and lifestyle variables.[38] In a large cohort of nearly 1000 women, metabolic syndrome was 2.5 times more likely to develop in the first 6 years following oophorectomy than it was in women who had not had the surgery.[39]

**Metabolic Syndrome and Testicular Cancer**

Testicular cancer is most often treated with a combination of surgery, chemotherapy, and possibly radiation, depending on the stage of the disease at the time of diagnosis. While some testicular cancers can be remarkably aggressive, the overall 5-year survival rate is 95%. Also, the disease is most often diagnosed in men in their 20s and 30s.[40] Because of the early age at diagnosis and high survival rate, survivors of testicular cancer are at particular risk for long-term consequences of antineoplastic therapy. Both chemotherapy and mediastinal radiation appear to play a role in the adverse changes in cardiac risk factors seen in survivors of testicular cancer. Initial studies demonstrate that patients who were treated with chemotherapy are more likely to demonstrate gonadal dysfunction but have preserved adrenal and thyroid axes. This combination of effects is particularly concerning for the development of metabolic syndrome, given the known importance of androgens in this process.[41] In fact, of the various treatment modalities used in testicular cancer, chemotherapy has been associated with the most worrisome cardiac risk profile in survivors.[41-44] Even when the gross number of cardiovascular events is low, the young age of the patients involved makes this increase in risk a real concern. In one Dutch study, follow-up in 87 patients identified 8% of the cohort as having suffered an adverse cardiovascular event (defined as a documented MI, myocardial ischemia, or cerebrovascular accident).[44] Although the overall number of such events was low, what was especially striking was that they occurred in men aged 30 to 42 years, a population in which such events should be exceedingly rare. Similar findings were seen in a large Norwegian study that identified 68% of the cohort treated with chemotherapy as being at either high risk or intermediate/high risk for adverse cardiac effects following anti-cancer therapy.[45] A 2006 study with a mean follow-up of 18 years suggests that the risk of MI can be as much as doubled in nonseminoma survivors with attained ages of less than 45 years.[46] Interestingly, the risk of MI is higher in younger survivors and is actually lower in men with attained ages of more than 55 years; these data suggest a possible link between metabolism and the aging process.[46] In the same 2006 study, the use of a PVB (cisplatin, vinblastine, bleomycin) regimen instead of a BEP (bleomycin, etoposide, cisplatin) regimen also appeared to increase the rate of MI.[46] When a more comprehensive set of cardiac risk factors is considered, multiple studies have found that patients with testicular cancer treated with cisplatin-based chemotherapy have higher systolic blood pressure, higher diastolic blood pressure, and increased rates of hypercholesterolemia and obesity compared with both the general population and patients whose testicular cancer was treated with surgery alone.[43,44,47,48] Of note, in several of these studies there was no difference between the baseline parameters of different patient cohorts at the time of their...
diagnosis.[43,47,48] Furthermore, patients treated with high doses of cisplatin displayed the most marked changes in both blood pressure and BMI, suggesting a possible dose-dependent effect of this particular chemotherapeutic agent.[43] Finally, in a recent large-cohort follow-up study that included more than 1400 patients younger than 60 years, the specific diagnosis of metabolic syndrome was evaluated in testicular cancer survivors stratified by treatment modality. The results were compared with rates of metabolic syndrome in the general population.[49] Survivors treated with cisplatin-based chemotherapy were nearly 3 times more likely to develop metabolic syndrome than men in the general population.[49] Once again, metabolic syndrome was most prominent in those treated with high-dose cisplatin.[49]

**Emerging Therapies and Metabolic Syndrome**

Among the newest targeted therapies to reach the clinic are inhibitors of the mTOR pathway.[50] Because of the known role of mTOR as a regulator of cellular energy and metabolism, studies of adverse events in patients treated with these drugs are starting to focus on metabolic profiles.[51] Temsirolimus (Torisel) is a novel mTOR inhibitor with documented efficacy in the treatment of renal cell carcinoma.[52] In a cohort of patients treated with this agent and followed during the course of their therapy, hyperglycemia, hypertriglyceridemia, and hypercholesterolemia were noted in 9%, 3%, and 1% of patients, respectively.[53] Similar findings of elevated glucose and lipid levels were noted in a second cohort of patients in whom renal cell carcinoma was treated with the mTOR inhibitor everolimus (Afinitor).[54] Kinase inhibitors represent a second major class of anti-cancer drugs. Of these, the tyrosine kinase inhibitor imatinib is the proof-of-principle prototype for rational drug design. The effects of the different kinase inhibitors vary from agent to agent, but some evidence suggests that at least some of these compounds can lead to hypertension as an adverse effect.[55-57] Furthermore, at least one study has demonstrated that in addition to causing hypertension, sunitinib (Sutent) is also capable of inducing hypothyroidism.[55] The long-term effects of this agent on the metabolic profile of cancer survivors remain to be seen. Finally, in addition to kinase inhibitors, the anti-angiogenesis compound bevacizumab (Avastin) has also been shown to cause hypertension.[58]

**Conclusions**

Success in treating cancer has given rise to the emerging challenge of cancer survivorship. Indeed, the American Cancer Society estimates that more than 10 million Americans are cancer survivors. As has been documented first with hormone-modifying agents and now with several classes of newer cancer therapeutics, the treatments that enable patients to resume their lives also have the potential to significantly affect their quality of life and health following treatment. It is therefore important that physicians who care for cancer patients and cancer survivors intervene in ways that promote good health and quality of life post-cancer.
It is essential that treating physicians be aware of the potential risks facing patients who undergo hormone-modifying therapy, cisplatin-based chemotherapy, or treatment with emerging cancer therapeutics. Depending on an individual patient’s pre-existing risk of metabolic syndrome, the potential metabolic effects of the various available treatments may be an important factor for the oncologist to consider when choosing an agent or chemotherapy dosing regimen. For example, whenever possible, lower doses of cisplatin should be used when treating young men with testicular cancer. There is also evidence to suggest that in patients with low-risk prostate cancer, short-term androgen suppression therapy can have as beneficial an outcome as more lengthy hormone suppression.[59] Likewise, in patients with breast cancer, consideration of the risks and benefits of long-term tamoxifen therapy for chemoprevention—or of the choice of tamoxifen vs an aromatase inhibitor—may eventually include analysis of metabolic syndrome risks.

Even if they do not currently have manifestations of metabolic syndrome, cancer survivors are at increased risk for developing the syndrome over time. Consequently, overall health maintenance for these patients must include close monitoring of lipid profiles, liver enzyme levels, body habitus, and markers of glycemic function in order to facilitate early intervention. Healthy lifestyle measures,
including physical activity and dietary modifications, are also of particular importance for this vulnerable population.

Oncology outcomes will continue to dictate primary cancer therapy, but a consideration of therapy-driven adverse effects will also be an important part of both oncological and general medical decision making as the number of cancer survivors continues to grow. Furthermore, emerging evidence from the laboratory will play an important role in the development of targeted therapies that minimize adverse effects. Cancer is a devastating disease, but the success of multidisciplinary cancer treatment protocols is allowing more patients to survive malignancies that would once have been incurable. As a result, the relevance of issues related to the quality of life of cancer survivors cannot be overstated.

**Financial Disclosure:** The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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