function occurs. Such is the case with transplantation-induced osteoporosis, which may predispose bone marrow transplantation (BMT) survivors to earlier onset and more severe osteopenia and osteoporosis than the healthy population.

In this issue of *Blood*, Schulte and Beelen (page 3635) present a large prospective study of bone mineral density (BMD) deficits and potential risk factors for its development following allogeneic bone marrow transplantation. This study of 280 adults (median age, 38 years; range, 16-59 years) represents one of the few prospective longitudinal studies of BMD in allogeneic BMT patients. Their extensive statistical analyses of risk factors for rapid bone loss revealed a limited number of factors that directly correlate with BMD loss in this patient cohort: steroid dose, total dose of cyclosporine A, loss of body weight (particularly of muscle mass), and baseline BMD parameters. Interestingly, other potential factors such as age at transplantation, sex, primary diagnosis, pretransplantation regimen, and state of HLA match were not found to be significant factors.

The authors demonstrate that posttransplantation BMD loss is greatest in the first year following transplantation for all sites evaluated. Recovery of bone loss over the subsequent 3 to 4 years was notable and site specific, with the least recovery being seen in the femoral neck and Ward triangle. These site-specific differences suggest an increased risk for proximal femoral fractures in this relatively young patient cohort and should underscore the critical need to develop clinical guidelines directed at optimizing BMD recovery in this patient cohort.

Little information is currently available that addresses effective means of improving BMD in BMT survivors. The authors have provided us with insight into the potential utility of antiresorptive therapy in this patient cohort. They describe a subset of 35 patients in whom antiresorptive therapy was initiated as protection for and/or treatment of osteoporotic fracture after BMT. Of the 10 patients with demonstrated osteoporotic fractures, 9 were younger than 50 years (average age, 31.6 years; median, 39.5 years). Thus, this relatively young cohort seems to be at risk for osteoporotic fracture several decades earlier than the healthy population.

This long-term follow-up study by Schulte and Beelen provides needed details of temporal bone loss related to hematopoietic stem cell transplantation. As they indicate, there is a limited protective effect of younger age at the time of transplantation for spine BMD, the propensity for at least partial restitution of bone loss over time, and an increased risk for transplantation-induced osteoporotic fracture in this cohort. Their work should prompt development of large prospective longitudinal studies to refine risk factors for BMD loss and underscores the need for improved technologic assessments for bone quality, morphology, and quantification in long-term BMT survivors.

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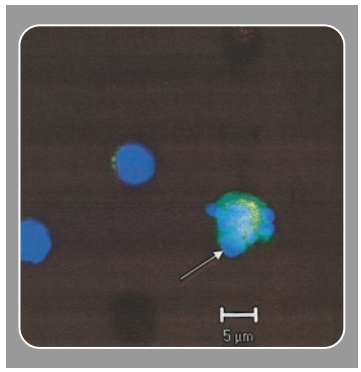
CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS

Endothelial apoptosis: the missing link between atherosclerosis and SLE?

It was proposed more than 25 years ago that atherosclerosis arises as a response of the vascular wall to endothelial injury. Evidence accumulated in the last decade showed that this injury could be due to endothelial apoptosis. Most known risk factors for atherosclerosis induce, while treatments and prophylactic interventions have the potential to decrease, endothelial apoptosis.[1] Many of the findings associated with atherosclerosis, such as endothelial dysfunction and activation, can be caused by endothelial apoptosis, and apoptotic endothelial cells are found on the surface of atherosclerotic plaques.[1-3]

Young and predominantly female patients with systemic lupus erythematosus (SLE) are an unusual group manifesting an extraordinarily strong predisposition for the development of early-onset and accelerated atherosclerosis. In addition to the usual risk factors, SLE itself predisposes to premature atherosclerosis in a manner that does not always correlate with markers of systemic inflammation or measures of disease activity.[4]

What causes premature and accelerated atherosclerosis in patients with SLE? In this issue of *Blood*, Rajagopalan and colleagues



(page 3677) describe increased numbers of apoptotic endothelial cells in the peripheral blood of patients with SLE. They compare patients with SLE to 2 control groups: healthy subjects without presence of usual risk factors for atherosclerosis, and patients with known coronary artery disease (CAD). The markedly higher numbers of apoptotic endothelial cells found in young women with SLE, when compared with the older group of predominantly male patients with CAD, suggest that endothelial apoptosis may be responsible for premature and accelerated atherosclerosis in patients with SLE. The authors fail to detect significant differences in the unequal numbers of circulating apoptotic endothelial cells between the 2 control groups in this study, which could be due to the relatively stable clinical status and the use of endothelial antiapoptotic treatments[1] (statins, aspirin, β-blockers, angiotensin-converting enzyme [ACE] inhibitors) in the CAD group. They do, however, find for the first time in human subjects a significant correlation between numbers of apoptotic endothelial cells and endothelial dysfunction; in a previously described primate model, endothelial dysfunction occurred after endothelial cell loss from the vascular wall and was due to endothelial apoptosis.[2]

The results of the study by Rajagopalan et al suggest that future investigations should focus on specific endothelial pro-apoptotic and antiapoptotic factors that may

be relevant in patients with SLE. These include the known proapoptotic (antiendothelial cell antibodies, anti-dsDNA antibodies, lupus anticoagulant, inflammatory mediators, neutrophil proteases) and antiapoptotic (glucocorticoids, cyclosporine A) agents.[1,5] One approach could involve exposure of endothelial cells in vitro to serum from patients with SLE, neutralization of known proapoptotic factors to gain an impression of their relative importance in SLE, and testing of available antiapoptotic stimuli as agents that may be useful for subsequent clinical trials. This may permit a rational advance toward therapies that will improve the prognosis in patients with SLE.

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CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS

Improving pregnancy outcome in women with thrombophilia

Pregnancy is an acquired hypercoagulable state due to an increase in procoagulants, a decrease in natural anticoagulants, and impaired fibrinolysis. While this setting may prevent bleeding, the likelihood for gestational vascular complications is increased.

Recurrent fetal loss (RFL) affects 1% to 3% of women at the reproductive age and poses a significant economic and psychologic burden. RFL has long been known to be associated with acquired thrombophilic states such as antiphospholipid syndrome. Data emerging over the past 8 years suggest that hereditary thrombophilia is a major cause of RFL.[1]

Gestational outcome in women with thrombophilia and previous RFL is poor, with an estimated live birth rate of only 20% to 50%. Heparin derivatives do not cross the placenta and are safe for women and fetus. Small-scale studies have suggested that antithrombotic prophylaxis with low-molecular-weight heparin (LMWH) significantly improves gestational outcome.[2,3]

However, in the absence of placebo-controlled trials, the optimal dose of LMWH and the role of low-dose aspirin (LDA) in this setting remained to be determined.

In a previous study, Gris et al[4] have demonstrated that enoxaparin improves gestational outcome in women with aspirin-resistant antiphospholipid syndrome.

In this issue of *Blood*, Gris and colleagues (page 3695) present the results of an elegant study comparing 40 mg/day enoxaparin to LDA in women with thrombophilia and 1 or 2 previous pregnancy losses after 10 weeks of gestation. The results clearly show the superiority of 40 mg/day enoxaparin compared with LDA in the whole group of 160 thrombophilic women as well as in subgroups of women with the specific thrombophilic defects of factor V Leiden, factor II G20210A, and protein S deficiency. In addition, Gris et al demonstrated that the presence of antibodies to protein Z and protein Z deficiency negatively affected gestational outcome. This is in accordance with previous observations that multiple hereditary[5] or acquired thrombophilic defects further increase the risk for fetal loss.

The optimal prophylactic dose of enoxaparin in women with thrombophilia and previous RFL as well as its impact on gestational outcome were evaluated by the LIVE-ENOX trial, which has recently been completed.

These are important times for women with RFL, as the role of thrombophilia is unveiled and a successful prophylaxis can be applied. The time has come to rigorously assess the role of antithrombotic prophylaxis in women with unexplained RFL without thrombophilia, and in those with thrombophilia and placental vascular complications such as early onset preeclampsia, severe intrauterine growth restriction, and placental abruption.

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GENE THERAPY

Lentiviral vector for hemophilia gene therapy

For the past decade, gene therapy for hemophilia, the X-linked bleeding disorder caused by mutations in the factor VIII (*F8* in hemophilia A) or factor IX gene (*F9* in hemophilia B), has been at the center of the efforts of many gene transfer laboratories. Several clinical trials have been carried out or are under way, and sustained, nearly curative correction of canine hemophilias A and B have been reported using viral vectors.[1] However, clear clinical success has not yet been achieved, and continuous development of novel gene transfer vectors and an improved understanding of existing vector systems are prudent.

Just a few years ago, lentiviral vectors were developed, and they have since emerged as powerful tools for gene transfer to dividing and nondividing target cells.[2] In particular, transduction of hematopoietic stem cells in murine models of β-thalassemia and sickle cell disease was achieved with spectacular efficiencies.[3,4] The latest generation of vectors are devoid of genes from the HIV parent virus and are produced using protocols with minimal potential for accidental generation of wild-type HIV through recombination.