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Although it is well know that both type 1 and type 2 diabetes are associated with greater risk of cardiovascular disease (CVD) the reasons for this are not known. While these two forms of diabetes have some different risk factors, it is well established that several diabetes specific complications such as retinopathy and nephropathy are shared. We have studied factors that affect vascular disease primarily in models of insulin deficient diabetes and propose to study a factor common to all diabetics, hyperglycemia, and its effects on the bone marrow, circulating white blood cells, arterial macrophages, and atherosclerosis. Specifically, we will separate the effects of hyperglycemia from defective insulin actions and hyperlipidemia by inducing glucose reduction by inhibition of the renal sodium glucose cotransporter, SGLT2. We have shown that hyperglycemia increases blood monocyte and neutrophil levels, two know risk factors for CVD. In addition, we have reported that atherosclerotic lesions in diabetic mice have an increase in the number and inflammatory phenotype of their CD68+ cells after cholesterol reduction (regression). This application has three specific aims to define how hyperglycemia and DAMPs such as S100A8 affect the biology of circulating monocytes and neutrophils, and arterial macrophages. Aim 1 will study whether and how S100A8 and other DAMPs affect bone marrow and circulating myeloid cells. Specifically we have shown that S100A8 injection into mice increases monocyte and neurophil bone marrow precursors. We will determine whether the actions of S100A8 are additive to other effects of hyperglycemia and whether they function by interaction with RAGE or TLRs. Aim 2 will determine how models of type1 and type2 diabetes alter the number and inflammatory phenotype of circulating monocytes and neutrophils. The specific role of glucose in this process will be determined by assessing cells in diabetic glucose reduced mice. Aim 3 will study how diabetes ¿ hyperglycemia and S100A8 affect the number, emigration and phenotype of arterial CD68+ cells, as well as the recruitment of monocytes, during the progression and regression of atherosclerosis. These experiments aim to identify the major causes of increased CVD risk in both forms of diabetes and to identify new targets to prevent this complication and to allow normal regression of lesions in the setting of cholesterol reduction. PUBLIC HEALTH RELEVANCE: Patients with diabetes mellitus have a number of complications including cardiovascular disease (CVD) that might be secondary to changes in the biology of circulating white blood cells. We have created mouse models that show these changes and will isolate the effects of high glucose, as opposed to insulin signaling and lipid changes, on circulating blood cells and blood cells within arteries. Our studies will discover why diabetes leads to more cardiovascular disease and will identify targets to reduce the excess CVD in patients with diabetes.
