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Role of reduced insulin-stimulated bone blood flow in the pathogenesis of metabolic insulin resistance and diabetic bone fragility

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ABSTRACT

Worldwide, 387 million adults live with type 2 diabetes (T2D) and an additional 205 million cases are projected by 2035. Because T2D has numerous complications, there is significant morbidity and mortality associated with the disease. Identification of early events in the pathogenesis of insulin resistance and T2D might lead to more effective treatments that would mitigate health and monetary costs. Here, we present our hypothesis that impaired bone blood flow is an early event in the pathogenesis of whole-body metabolic insulin resistance that ultimately leads to T2D. Two recent developments in different fields form the basis for this hypothesis. First, reduced vascular function has been identified as an early event in the development of T2D. In particular, before the onset of tissue or whole body metabolic insulin resistance, insulin-stimulated, endothelium-mediated skeletal muscle blood flow is impaired. Insulin resistance of the vascular endothelium reduces delivery of insulin and glucose to skeletal muscle, which leads to tissue and whole-body metabolic insulin resistance. Second is the paradigm-shifting discovery that the skeleton has an endocrine function that is essential for maintenance of whole-body glucose homeostasis. Specifically, in response to insulin signaling, osteoblasts secret osteocalcin, which stimulates pancreatic insulin production and enhances insulin sensitivity in skeletal muscle, adipose, and liver. Furthermore, the skeleton is not metabolically inert, but contributes to whole-body glucose utilization, consuming 20% that of skeletal muscle and 50% that of white adipose tissue. Without insulin signaling or without osteocalcin activity, experimental animals become hyperglycemic and insulin resistant. *Currently, it is not known if insulin-stimulated, endothelium-mediated blood flow to bone plays a role in the development of whole body metabolic insulin resistance. We hypothesize that it is a key, early event.* Microvascular dysfunction is a primary cause of diabetic nephropathy, retinopathy and neuropathy and poor bone blood flow is associated with bone loss. *Therefore, we also hypothesize that dysfunction of the bone vascular endothelium contributes to the bone fragility observed in T2D.* The most important consequence of our-dual hypothesis is the public health significance. Namely, identification of the proximal cause of T2D and associated bone complications allows pursuit of the appropriate therapeutic target to treat and prevent T2D. If our hypothesis that reduced bone blood flow is an early event in the pathogenesis of T2D and diabetic bone fragility is correct, then the endothelium of the bone vasculature should be a therapeutic target.

Introduction

Worldwide, 387 million adults live with type 2 diabetes (T2D) and an additional 205 million cases are projected by 2035 [1]. Because T2D has numerous complications, there is significant morbidity and mortality associated with diabetes. It is estimated that 50 million adults aged 20–79 years died as a result of diabetes in 2015. The US alone spent $348 billion to treat diabetes and prevent complications [1]. Identification of early events in the pathogenesis of insulin resistance and T2D might lead to more effective treatments that would mitigate the health and monetary costs associated with the disease.

Here, we present our hypothesis that impaired bone blood flow is an early event in the pathogenesis of whole-body metabolic insulin resistance that ultimately leads to T2D. Two recent developments in different fields form the basis for this hypothesis. First, reduced vascular function has been identified as an early event in the development of T2D [2]. In particular, before the onset of tissue or whole body metabolic insulin resistance, insulin-stimulated, endothelium-mediated skeletal muscle blood flow is impaired [3]. Insulin resistance of the vascular endothelium reduces delivery of insulin and glucose to skeletal muscle [4–6], which leads to

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tissue (e.g., myocyte) and whole-body metabolic insulin resistance [2,7]. Second is the paradigm-shifting discovery that the skeleton has an endocrine function that is essential for maintenance of whole-body glucose homeostasis [8,9]. Specifically, in response to insulin signaling, osteoblasts secret osteocalcin, which stimulates pancreatic insulin production and enhances insulin sensitivity in skeletal muscle, adipose, and liver [8,9]. Furthermore, the skeleton is not metabolically inert, but contributes to whole-body glucose utilization, consuming 20% that of skeletal muscle and 50% that of white adipose tissue [10]. Without insulin signaling or without osteocalcin activity, experimental animals become hyperglycemic and insulin resistant [9–11]. *Currently, it is not known if insulin-stimulated, endothelium-mediated blood flow to bone plays a role in the development of whole body metabolic insulin resistance. We hypothesize that it is a key, early event.*

Recently, bone fragility fracture was added to the list of T2D complications [12] that already includes cardiovascular disease, blindness, kidney disease, and limb amputation. Because microvascular dysfunction is a primary cause of diabetic nephropathy [13], retinopathy [14] and neuropathy [15] and because poor bone blood flow is associated with bone loss [16], we also hypothesize that dysfunction of the bone vascular endothelium contributes to the bone fragility observed in T2D.

The hypothesis

We hypothesize that impaired insulin-stimulated bone blood flow is an early event both in a feed-forward loop that accelerates the progression of whole body insulin resistance to T2D and in the deterioration of bone strength observed in T2D (Fig. 1). Our hypothesis is based on the dual functions of the osteoblast—maintenance of whole body glucose homeostasis and bone formation. Specifically, we hypothesize that reduced insulin-stimulated, endothelium-mediated bone blood flow decreases delivery of essential insulin and glucose to osteoblasts. Because osteoblast differentiation and function are dependent on insulin and glucose [10,11], reduced bone blood flow results in impaired osteoblastogenesis and reduced activity of mature osteoblasts, namely synthesis of bone matrix and related proteins. One of these peptides is the Gla-protein osteocalcin [17]. The uncarboxylated form of osteocalcin stimulates pancreatic β-cell insulin secretion and increases insulin-sensitivity of adipose, skeletal muscle, and liver [8,9,11]. Consequently, a decrease in osteoblast osteocalcin production, secondary to reduced insulin and glucose availability, would exacerbate whole-body metabolic insulin resistance, causing further decrements in insulin-mediated vascular function and therefore in osteoblast differentiation and function. Reduced osteoblastogenesis and reduced activity of mature osteoblasts negatively impact bone remodeling, leading to a deterioration of bone quality. Ultimately, this downward spiral leads to frank T2D and altered bone structural and material properties that increase bone fragility and fracture risk.

Evaluation of the hypothesis

Our hypothesis is based on relatively recent developments in the fields of bone biology, integrative physiology and metabolism considered in the context of the long-recognized fact that bone blood flow is essential for normal bone structure and function. These recent developments are as follows: (1) Bone is an endocrine organ that acts via osteoblast secretion of osteocalcin to maintain whole-body glucose homeostasis [8]; (2) Osteoblast differentiation and function require insulin and glucose [9–11]; and, (3) Insulin, via its actions on the vascular endothelium, regulates its own delivery to target tissues, e.g., skeletal muscle [18].

Healthy bone is dependent on bone blood flow

The skeleton accounts for 10–15% of resting cardiac output [19] and bone blood flow is essential for nutrient delivery, mineral homeostasis and maintenance of interstitial fluid flow, which is needed for mechanotransduction [16]. Bone blood flow is also a

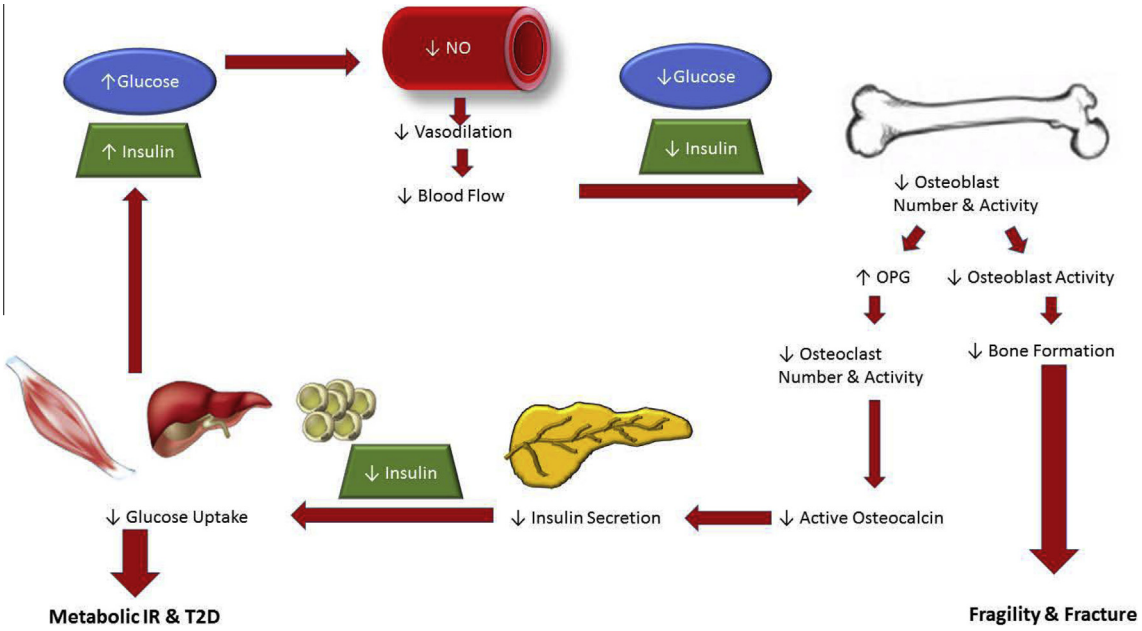

Fig. 1. Hypothetical role of reduced bone blood flow in the pathogenesis of whole-body insulin resistance and T2D and associated bone fragility. Impaired insulin-stimulated vasodilation in bone vasculature results in reduced insulin and glucose delivery to osteoblasts. Because osteoblasts require insulin and glucose for differentiation and function, including bone formation and release of osteocalcin, are impaired. Reduced insulin availability to osteoblasts also increases osteoblast expression of osteoprotegerin (OPG), which suppression osteoclastogenesis and osteoclast activity. The net result is reduced circulating undercarboxylated OC and therefore, reduced insulin secretion and peripheral insulin sensitivity, accelerating the progression of insulin resistance/T2D and deterioration of bone structural and material properties.