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C Bogardus

Stephen Lillioja
University of Wollongong, lillioja@uow.edu.au

Publication Details

Bogardus, C. & Lillioja, S. (1990). Where all the glucose doesn't go in non-insulin-dependent diabetes mellitus. New England Journal of Medicine, 322 (4), 262-263.

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Where all the glucose doesn't go in non-insulin-dependent diabetes mellitus

Abstract

REDUCED insulin-mediated glucose uptake, or insulin resistance, is a metabolic defect characteristic of virtually all patients with non-insulin-dependent diabetes mellitus (NIDDM). The cause of insulin resistance remains unknown, but in the past decade, since the development of the hyperinsulinemic-glucoseclamp technique, considerable progress has been made in identifying the insulin-resistant tissues and metabolic pathways responsible for decreased insulin action. DeFronzo et al. l ,2 and subsequently others demonstrated that most of the glucose that leaves the plasma during hyperinsulinemia enters peripheral tissues rather than the gut or liver, and that insulin resistance in patients with NIDDM is largely a result of decreased glucose uptake by these peripheral tissues. Since little of the glucose taken up by peripheral tissues under the mediation of insulin could be recovered from adipose tissue, investigators concluded that most of the glucose was taken up by skeletal muscle.

Disciplines

Medicine and Health Sciences

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WHERE ALL THE GLUCOSE DOESN'T GO IN NON-INSULIN-DEPENDENT DIABETES MELLITUS

REDUCED insulin-mediated glucose uptake, or insulin resistance, is a metabolic defect characteristic of virtually all patients with non-insulin-dependent diabetes mellitus (NIDDM). The cause of insulin resistance remains unknown, but in the past decade, since the development of the hyperinsulinemic-glucose-clamp technique, considerable progress has been made in identifying the insulin-resistant tissues and metabolic pathways responsible for decreased insulin action. DeFronzo et al.[1,2] and subsequently others demonstrated that most of the glucose that leaves the plasma during hyperinsulinemia enters peripheral tissues rather than the gut or liver, and that insulin resistance in patients with NIDDM is largely a result of decreased glucose uptake by these peripheral tissues. Since little of the glucose taken up by peripheral tissues under the mediation of insulin could be recovered from adipose tissue, investigators concluded that most of the glucose was taken up by skeletal muscle.

Skeletal muscle oxidizes glucose to carbon dioxide and water or converts glucose to lactate or glycogen (or both) by so-called "nonoxidative" pathways. The production of carbon dioxide, and thereby the oxidation of glucose, can be measured according to the classic method of indirect calorimetry. Studies in which this technique was combined with the hyperinsulinemic-glucose-clamp procedure revealed that most of the glucose taken up by skeletal muscle was metabolized by the nonoxidative pathway and that decreased metabolism by this pathway was largely responsible for decreased glucose uptake in patients with insulin resistance, whether or not they had NIDDM.[1,3] Since little of the glucose taken up appeared as lactate, the working hypothesis was that insulin resistance in patients with NIDDM was mainly the result of decreased insulin-mediated glycogen synthesis by skeletal muscle.

Direct proof of this hypothesis was difficult. When insulin and glucose were infused, direct assay of sam-

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ples of skeletal-muscle tissue obtained by percutaneous biopsy most often showed little or no change in glycogen content. This was not surprising, however, because of the small increases in glycogen content expected in view of the large mass of skeletal muscle and the relatively low sensitivity of the methods used. Some improvement in sensitivity was obtained when radiolabeled glucose was used, and Young et al.[4] found that glycogen accumulation was decreased in the muscle of nondiabetic subjects with insulin resistance, as compared with normal subjects. Since the rate-limiting enzyme in the conversion of glucose to glycogen is glycogen synthase, the most convincing evidence, albeit indirect, that insulin-mediated, nonoxidative glucose metabolism was actually due to glycogen synthesis in skeletal muscle was the positive correlation found between the insulin-mediated, nonoxidative metabolism of glucose and the activation of skeletal-muscle glycogen synthase.[5,6] Nonetheless, without direct evidence of glycogen accumulation in skeletal muscle after insulin and glucose infusions, there was no final proof of where all the glucose was going or, more important for the diabetic patient with insulin resistance, where the glucose was not going.

In this issue of the *Journal*, Shulman et al.[7] have convincingly answered these questions, using a novel application of nuclear magnetic resonance spectroscopy. They found that the insulin-mediated, nonoxidative metabolism of glucose is due largely to glycogen synthesis by skeletal muscle. They also demonstrated the important fact that insulin resistance in patients with NIDDM is mostly a result of a defect in this metabolic pathway. Thus, we now have a clearly defined metabolic pathway that has been proved to be disturbed in NIDDM.

There are many potential sites for a defect leading to abnormalities of insulin-mediated glycogen synthesis by muscle. For insulin to act, it must first traverse the unfenestrated capillary endothelium before it is bound to its specific receptor in the muscle membrane. This binding leads to a wide range of effects, including activation of the receptor tyrosine kinase, initiation of a series of phosphorylation–dephosphorylation reactions, and stimulation of glucose transport. Already, abnormalities of insulin regulation of skeletal-muscle–receptor tyrosine kinase activity and glycogen synthase activity have been described in patients with NIDDM.[5,6,8] In addition, our colleagues have recently found that insulin activation of glycogen synthase phosphatase, an enzyme that dephosphorylates and activates glycogen synthase, is reduced in subjects with insulin resistance (unpublished data). Glucose transport in skeletal muscle has been difficult to study in humans, and few data are available on patients with diabetes. Further studies of the insulin-regulated proteins involved in glycogen synthesis by muscle should lead to the delineation of the mechanism or mechanisms of insulin resistance in NIDDM.

However, studies of patients alone will not resolve whether any observed defects precede the onset of the disease and are in some way causative, or whether these defects are secondary to the disease itself. Recent family and population studies suggest that insulin resistance is present in nondiabetic persons in whom NIDDM later develops.[9] Interestingly, Eriksson et al., in a recent article in the *Journal*,[10] found that rates of insulin-mediated, nonoxidative glucose metabolism were decreased in the first-degree relatives of patients with NIDDM. On the basis of these studies and the work of Shulman et al.,[7] the hypothesis naturally arises that a defect in insulin-mediated glycogen synthesis by skeletal muscle may underlie and contribute to the development of NIDDM.

National Institute of Diabetes and Digestive and Kidney Diseases
Phoenix, AZ 85016

CLIFTON BOGARDUS, M.D.
STEPHEN LILLIOJA, M.B., CH.B., F.R.A.C.P.

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