

Insulin regulation of muscle capillary permeability and kidney function

Introduction

It is well established that insulin has important physiologic effect on the cardiovascular system and the kidney apart from its effect on metabolism.^{1,2} Many years ago we observed that the activity of the sympathetic nervous system increased after insulin administration in diabetic patients with a blood glucose concentration above normal.^{3,4} The arterial blood pressure was unchanged indicating that the blood flow was increased in a larger part of the organism. An increase in blood flow after insulin had already been reported in 1939 shortly after insulin had been discovered.⁵

The increase in blood flow depends on several factors such as insulin dose, muscle mass and sympathetic activity. A marked increase in blood flow after insulin is seen in the calf due to the large muscle mass. In the elderly patients and in patients with autonomic neuropathy the blood pressure may decrease after insulin administration especially in the standing position. We also showed that insulin increased the transcapillary escape rate of albumin indicating that insulin increased the capillary surface exchange area (now named capillary recruitment).⁶ The insulin mediated increase in blood flow and capillary permeability during food intake may be of importance for the distribution of glucose and other substrates to muscles.⁷

Bonadonna et al.⁸ reported that insulin increased total forearm blood flow as well as muscle tissue drained by the deep forearm vein. The increase in the glucose tracer space was approximately 40%. This change cannot be explained by capillary recruitment but may be due to recruitment of previously inaccessible interstitial space (tissue recruitment). The increase in microvascular dilation induced by insulin is mediated by increments in NO.⁹

Due to better control of blood glucose concentration in diabetic patients, there has been a reduction in the number of long-term diabetic complications, but the smallest decline has been in patients with renal disease.¹⁰ The kidney is sensitive to insulin.¹ We observed that insulin administration to T1DM patients with a short duration of diabetes resulted in a transient increase in albumin excretion in the urine. There was also a reduction in glomerulus filtration rate and in plasma flow both these changes were due to a fall in blood glucose concentration. During an oral glucose load urinary excretion of albumin increased in normal subjects, but no change was seen in type T1DM patients with a short duration of diabetes of less than 10 years unless insulin was given. In long-term diabetic patients with albuminuria, insulin decreased albumin excretion. The lack of an increase in albumin excretion after insulin in these patients may be due to severe morphological changes in glomeruli. Coward et al.¹¹ Welsh et al.¹² showed that insulin is important for the function of the podocytes. Deletion of insulin receptors from podocytes resulted in albuminuria and in the development of glomerulosclerosis in the kidney. It has recently been demonstrated that defective podocyte insulin signaling, impairs podocyte function in diabetes.¹³ The significance of the increase in albumin excretion after insulin in normal subjects has not been clarified, but it could be to remove albumin around and between

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podocyte foot processes, because the glomerulus membrane is not completely effective in inhibition excretion of albumin.

Long-term diabetic complications are due to insulin deficiency, which is accompanied by hyperglycemia and glucose toxicity. T1DM and T2DM patients have a different etiology but the complications are the same. Note that obese patients with insulin resistance and normoglycemia will not develop the characteristic long-term diabetic complications such as diabetic retinopathy, nephropathy (with few exceptions) and advanced calcified atherosclerosis (medial) calcification. Medial calcification is closely related to blood flow in the calf and important for the development of gangrene. New types of treatments are clearly wanted. As pointed earlier it is unlikely that long term diabetic complications can be eliminated without a more physiologic insulin delivery system or alternatively with development of drugs that can activate insulin signaling pathways in response to a meal. SGLT-2 inhibitors are a new type of drug treatment, that reduces glucose toxicity and to some extent normalizes the podocyte insulin signaling pathway. These drugs limit the progression of cardiovascular disease and clinical important nephropathy in diabetic patients. Several new types of treatment are under consideration, so there is hope for the future.

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Conflict of interest

The author declares no conflict of interests.

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