Journal of Drug Design and Discovery Research
JDDDR, 3(1): 109-110
www.scitcentral.com

Mini-Review: Open Access

Insulin, Capillary Permeability and Albuminuria

N J Christensen*

*Professor Emeritus, Herlev University Hospital, Denmark.

Received May 10, 2022; Revised May 25, 2022; Accepted June 8, 2022

ABSTRACT

The purpose of this brief review is to discuss new findings relevant to the development of diabetic kidney disease. It is often thought to be due to an increased filtration rate and pressure in the glomerulus. Lengthy studies of diabetic patients seem to show, that this theory is not true. Concentrations of glucose in plasma and in cells undoubtedly play a role but are difficult to control. Several studies have indicated, that insulin in low or high concentrations may play a significant role in the development of the kidney disease. Insulin dilates the smaller vessels especially the capillaries. At the same time there is an increase in capillary permeability. We showed, that insulin also had an effect on kidney function. Injection of insulin or ingestion of glucose in normal individuals resulted in a short-lived increase in urinary excretion of albumin. No increase in albumin excretion was observed in diabetic patients unless insulin was given. New studies have shown that insulin mobilizes Ca^{2}+ from the cell membrane, causing remodeling of actin and presumably of the foot processes and slits of podocytes. Insulin may therefore be important for the control of the filter function in podocytes and the short- term albuminuria.

Keywords: Insulin, Albuminuria, Ca^{2}+, diabetes, Orai1

INTRODUCTION

We observed some years ago, that administration of insulin with and without glucose led to an increase in plasma norepinephrine concentration, as an expression of an increase in sympathetic activity [1,2]. Blood pressure was unchanged, indicating that insulin caused vasodilation. Studies of patients with dysfunction of the sympathetic nervous system also showed, that insulin administration and food intake were accompanied by a drop in blood pressure [3]. In a subsequent study we found, that injection of insulin resulted in an increase in the transcapillary escape rate of labeled albumin (capillary permeability) of approximately 15% [4]. We confirmed, that insulin led to an increase in capillary permeability [5], but at the same time found that adrenaline infusion had no similar effect on capillary permeability, although adrenaline undoubtedly increased flow. We also examined the effect of insulin on endothelial cells in muscles using electron microscopy. We found that insulin led to an increased formation of microvesicles in endothelial cells [6]. A recent study showed that insulin in muscle is transported to the interstitium via fluid-phase transport possibly via vesicle formation in the endothelial cells [7]. The process was not related to insulin resistance. The above studies show that insulin has an effect on the vessels and especially the small ones, an effect that is regulated by NO [8].

RESULTS

We were therefore interested in a study to evaluate, if insulin had a permeability effect on glomerulus function and podocytes. We observed, that insulin administration to type 1 diabetic patients increased albumin excretion [9].

The finding could not be explained by changes in blood glucose, a slight increase in sympathetic activity or changes in blood pressure. Most likely it was an effect of insulin on the transglomerular passage via podocytes with their foot processes and slits. In a subsequent study [10], we found that administration of oral glucose increased the secretion of albumin in normal individuals, who had an increase in plasma insulin, but no increase in urinary albumin in patients with diabetes, who had no increase in plasma insulin. Administration of insulin to long-term diabetic patients with albuminuria reduced insulin mediated albumin secretion, probably due to morphological changes in the glomerulus.

Corresponding author: Niels Juel Christensen, Professor Emeritus, Herlev University Hospital, Denmark, Tel: 004539621966 /004524485227; E-mail: nielsjue@post4.tele.dk

Citation: Christensen NJ. (2022) Insulin, Capillary Permeability and Albuminuria. J Drug Design Discov Res, 3(1): 109-110.

The development of diabetic kidney disease is often thought to be vascular and due to hyperfiltration. It's a popular theory, but it's unlikely to be correct. Molitch [11] followed a reasonably large group of type 1 diabetic patients for 28 years. There was no evidence, that patients with early hyperfiltration had an increased risk of developing diabetic renal disease. The development of diabetic kidney disease is in part due to elevated plasma and cell glucose, which via reactive oxygen formation causes damage to the endoplasmic reticulum and mitochondrial function. In addition, a defective podocyte signaling may be due to insulin resistance. Kim and coworkers [12] have recently shown, how insulin activates store-operated Ca^{2}+ entry via Orai1, leading to podocyte actin remodeling and proteinuria. The results showed that a closely balanced control of the effect of insulin on podocyte Orai1 is important to control filter function.

CONCLUSIONS

The development of diabetic nephropathy is complicated, but it is important to find areas, that may be important for the development of new drugs. Blood glucose and cell glucose have a central location. However, the treatment is not quite satisfactory, as it is difficult to achieve normal values for glucose without complications such as hypoglycemia and more. The hypothesis that early glomerulus hyperfiltration increases the risk of developing kidney disease is probably incorrect. The study by Kim [12] is extensive and important. It explains how insulin can cause short-term albuminuria. Contraction of the podocytes especially the foot sits may increase the permeability of the filter. We wondered, if the excretion of albumin was important for cleaning of the filter for albumin and more as the filter is not completely tight. The effect of Orai1 on podocytes and actin should be the subject of further studies.

CONFLICT OF INTEREST

The author declares no competing interests.

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