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Review

Novel roles of the IGF–IGFBP axis in etiopathophysiology of diabetic nephropathy

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Abstract

Mechanisms contributing to development of diabetic nephropathy (DN) remain unclear. High ambient glucose level transforms intracellular pathways, promoting stable phenotypic changes in the glomerulus such as mesangial cell hypertrophy, podocyte apoptosis, and matrix expansion. Insulin-like growth factors (IGFs) and the high affinity IGF binding proteins (IGFBPs) exert major effects on cell growth and metabolism. Compared with diabetic patients without microalbuminuria (MA), MA diabetic patients display perturbed GH–IGF–IGFBP homeostasis, including increased circulating IGF-I and IGFBP-3 protease activity, increased excretion of bioactive GH, IGF-I, and IGFBP-3, but decreased circulating IGFBP-3 levels. In diabetic animal models, expression of IGF-I and IGFBP-1 to -4 increases in key renal tissues and glomerular ulrafiltrate. Epithelial, mesangial, and endothelial cells derived from the kidney respond to IGF-I binding with increased protein synthesis, migration, and proliferation. This article reviews classic and emerging concepts for the roles of the GH–IGF–IGFBP axis in the etiopathophysiology, treatment, and prevention of diabetic renal disease. We report IGF-independent actions of IGFBP-3 in the podocyte for the first time.

Keywords: Diabetic nephropathy; IGF; IGFBPs; IGF receptor

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; CTGF, connective tissue growth factor; DN, diabetic nephropathy; 4E-BP1, eukaryotic initiation factor 4E-binding protein; ecNOS, endothelial constitutive nitric oxide synthase; EGF, epidermal growth factor; eIF4E, eukaryotic initiation factor 4E; ESRD, end-stage renal disease; GH, growth hormone; IGF, insulin-like growth factor; IGFBP, IGF binding protein; IGFBP-rP, IGFBP related peptides; IGF-1R, Type 1 IGF receptors; MA, microalbuminuria; MAPK, mitogen-activated protein kinase; MC, mesangial cells; MDCK, Madin–Darby canine kidney cell line; NO, nitric oxide; NRK-49F cells, rat renal interstitial cells; PI 3 kinase, phosphatidylinositol 3-kinase; rhIGF-I, recombinant human insulin-like growth factor-I; Rho GTPase, Rho guanosine triphosphatases; SNAP, nitric oxide -donors *S*-nitroso-*N*-acetylpenicillamine; T2DM, type 2 diabetes mellitus; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor

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Contents

1. Introduction

Diabetic nephropathy (DN) is defined as proteinuria resulting from reversible endovascular damage of the renal filtration capacity by long-standing diabetes mellitus. DN remains the most common origin for progression through chronic renal insufficiency to end-stage renal disease (ESRD) in developed countries. DN is the largest contributor to the total cost of diabetes care worldwide, accounting for approximately 40% of all new patients placed on dialysis therapy [1]. The vascular damage from diabetes usually involves non-renal tissues too. Thus, diabetic patients with albuminuria possess higher risk of developing myocardial infarctions, cerebrovascular accidents, severe progressive retinopathy, and peripheral and autonomic neuropathy [1].

The earliest clinical marker of DN is the appearance of small amounts of serum proteins in the urine detected by microscopy or dipstick testing. The physiologic range of proteinuria in children is below 100 mg/m^2 daily (<30 mg over 24 h for adults). An intermediate degree of proteinuria ranges 100–1000 mg/m^2 daily (30–300 mg over 24 h for adults), and the nephrotic range is above 1000 mg/m^2 daily (>300 mg over 24 h for adults). Microalbuminuria (MA) can be defined as overnight albumin excretion at least 20 μg/min for two consecutive visits.

Prevalence of microalbuminuria in children with type 1 diabetes has been reported to vary between 7 and 20% [1–3]. The growing magnitude of DN at all ages – associated with huge monetary and social costs – drive the search for early markers of hyperglycemia-induced damage and multiple efforts to prevent this disease.

DN results from the interplay of metabolic and haemodynamic factors in the renal microcirculation [1]. Prior to the onset of overt proteinuria, specific changes occur in renal functions, causing renal hyperfiltration, hyperperfusion, and increasing capillary permeability to macromolecules. Diffuse expansion of the mesangial matrix is considered the hallmark pathological feature of established DN in humans [4–7]. Tyrosine kinase growth factors have emerged as logical mechanisms contributing to the etiopathophysiology of diabetic kidney disease [8].

The growth hormone (GH)–insulin-like growth factor (IGF)–IGF binding protein (IGFBP) axis and related growth factor families [transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF)] demonstrate significant actions on the development of experimental diabetic kidney disease through defined intra-renal systems. Recently, new data have emerged supporting the concept that these growth factors initiate the earliest renal changes associated with hyperglycemia [9–11].

2. The IGF–IGFBP–IGFBP–rP superfamily

IGF-I, IGF-II, their high-affinity binding proteins (IGFBP-1 to -6), low affinity IGFBP related peptides (IGFBP-rP1 to -4), and IGFBP proteases comprise a complex system which exerts fundamental regulation on growth and carbohydrate metabolism. IGFs exert their mitogenic actions primarily via the type 1 IGF receptors (IGF-1R), heterotetrameric tyrosine kinases on the cell surface. IGFBPs represent the largest family of proteins that bind IGFs with high affinity and specificity. Cellular actions are determined by the level of free, unbound IGF ligand.

Levels of free IGFs in a system are determined by rates of IGF production, IGF clearance, and degree of