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Brief Review

Cellular and molecular aspects of diabetic nephropathy; the role of VEGF-A

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ABSTRACT

The prevalence of diabetes mellitus increased during the last century and it is estimated that 45% of the patients are not diagnosed. In South America the prevalence of diabetes and chronic kidney disease (CKD) increased, with a great disparity among the countries with respect to access to dialysis. In Ecuador it is one of the main causes of mortality, principally in the provinces located on the coast of the Pacific Ocean. The greatest single cause of beginning dialysis is diabetic nephropathy (DN). Even using the best therapeutic options for DN, the residual risk of proteinuria and of terminal CKD remains high. In this review we indicate the importance of the problem globally and in our region. We analyse relevant cellular and molecular studies that illustrate the crucial significance of glomerular events in DN development and evolution and in insulin resistance. We include basic anatomical, pathophysiological and clinical concepts, with special attention to the role of angiogenic factors such as the vascular endothelial growth factor (VEGF-A) and their relationship to the insulin receptor, endothelial isoform of nitric oxide synthase (eNOS) and angiopoietins. We also propose various pathways that have therapeutic potential in our opinion. Greater in-depth study of VEGF-A and angiopoietins, the state of glomerular VEGF resistance, the relationship of VEGF receptor 2/nephrin, VEGF/insulin receptors/nephrin and the relationship of VEGF/eNOS-NO at glomerular level could provide solutions to the pressing world problem of DN and generate new treatment alternatives.

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Aspectos celulares y moleculares de la nefropatía diabética, rol del VEGF-A

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Angiopoietina
ROS
Riñón
Diabetes mellitus
Proteinuria
Sudamérica
Angiogénesis
Enfermedad renal crónica
Insulinorresistencia

RESUMEN

La prevalencia de diabetes mellitus aumentó en el último siglo y se estima que el 45% de los pacientes, no estarían diagnosticados. En Sudamérica la prevalencia de diabetes y de enfermedad renal crónica (ERC) incrementó, existiendo gran disparidad entre los países respecto al acceso a diálisis. En Ecuador es una de las principales causas de mortalidad, principalmente en las provincias ubicadas en la costa del océano Pacífico. La mayor causa aislada de ingreso a diálisis es la nefropatía diabética (ND). Aun utilizando las mejores opciones terapéuticas para la ND, el riesgo residual de proteinuria y de ERC terminal permanece elevado. En esta revisión describimos la importancia del problema en el mundo y en nuestra región. Analizamos estudios moleculares y celulares relevantes que indican la crucial importancia de eventos glomerulares en el desarrollo y en la evolución de la ND y en la insulinorresistencia. Incluimos conceptos anatómicos, fisiopatológicos y clínicos básicos, desarrollando especial énfasis en el rol de factores angiogénicos como el factor de crecimiento vascular endotelial (VEGF-A) y su relación con el receptor de insulina, la sintasa endotelial de óxido nítrico-óxido nítrico (eNOS) y las angiopoietinas. En el transcurso del texto proponemos diversas vías, que a nuestro entender tienen potencial terapéutico. Profundizar en el estudio del VEGF-A y las angiopoietinas, el estado de VEGF resistencia glomerular, la relación del receptor 2 de VEGF/nefrina, VEGF/receptores de insulina/nefrina, la relación VEGF/eNOS-ON a nivel glomerular podría aportar soluciones al acuciante problema de la ND en el mundo y generar nuevas alternativas de tratamiento.

Issue relevance

The prevalence of diabetes mellitus has increased worldwide since the last century[1]. In adults aged between 20 and 79 years of age, its prevalence reaches 8%[1]. Diabetes spreads through rich and poor countries, but it is prevalent in vulnerable groups and lower-income regions of the world. Territories showing the highest numbers of affected individuals are: China, India, the United States, Brazil and Russia[1]. This situation is associated with greater urbanisation, low socioeconomic level, inequality, increased life expectancy and population density, ethnic factors, nutrition, physical inactivity, and being overweight[1,2]. In Spain, a diabetes prevalence rate of 13.8% was reported, while 6.0% had not yet been diagnosed[3]. Recent estimates suggest that worldwide prevalence will have doubled by 2035, while in our region, South America and Central America, it will have increased to 9.8%[1,2]. In addition, 45.5% of individuals with diabetes will not be diagnosed with the disease[1,2].

In the urban population located on the coasts of our region, diabetes prevalence is higher than in the mountains or the jungle, and the same happens with people who move from the rural to the urban environment[1-2]. Moreover, native populations are particularly vulnerable due to the change in lifestyle, marginalisation and lower exposure to health care systems[2]. In Ecuador, the prevalence of diabetes is 6%, and in 2010 it was the second cause of mortality[2,4,5]. In the provinces of Guayas, Los Ríos and Manabí, located on the Pacific coast, the mortality rate due to diabetes and industrialised food consumption is higher; meanwhile, in the Amazon, natural food-based nutrition predominates and the rate is lower[6] (Figure 1).

Kidney disease caused by diabetes is called diabetic nephropathy (DN). About 30% of patients with diabetes develop DN[7,8]. Such disease is the main cause of chronic kidney disease (CKD) and of admission to dialysis[7-11]. The increase in adult diabetes has been recorded in the last few decades, and CKD affects 10% to 16% of adults, which constitutes a serious worldwide problem[7-11]. In South America, the prevalence of diabetes and end-stage CKD (ECKD) has increased in recent decades, and access to dialysis varies greatly among these countries[9-11]. In Ecuador, the prevalence of patients who received renal function replacement therapy in 2010 was 406 individuals per one million inhabitants[11]. On the other hand, the renin-angiotensin-aldosterone system (RAAS) inhibitors constitute the best therapeutic option for DN, but the residual risk of ECKD continues to be high and the association of these drugs was related to hyperkalemia and acute kidney failure (AKF)[12-13]. The search for new therapeutic alternatives is necessary.

Population studies raise awareness of the problem, while the knowledge generated in research laboratories expand our understanding of the biological events that occur in individuals. In this review, we will include anatomical and pathophysiological concepts that reveal the crucial importance of events occurring at the glomerular level. In addition, we will analyse the role played by the vascular endothelial growth factor (VEGF-A) and its relationships with nitric oxide (NO),