Brief Review

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

Katherine Carranza\textsuperscript{a}, Dolores Veron\textsuperscript{b}, Alicia Cercado\textsuperscript{c}, Noemi Bautista\textsuperscript{c}, Wilson Pozo\textsuperscript{d}, Alda Tufro\textsuperscript{e}, Delma Veron\textsuperscript{c}

\textsuperscript{a} School of Medicine, School of Medical Sciences, Universidad de Guayaquil [University of Guayaquil]. Guayaquil, Guayas (Ecuador)
\textsuperscript{b} School of Social Work, School of Law and Social Sciences, Universidad Nacional de Córdoba [National University of Córdoba], Córdoba (Argentina)
\textsuperscript{c} School of Health Sciences, Universidad Estatal de Milagro [State University of Milagro], Milagro, Guayas (Ecuador)
\textsuperscript{d} School of Natural Sciences, Universidad de Guayaquil, Guayaquil. Guayas (Ecuador)
\textsuperscript{e} Department of Paediatrics, School of Medicine, Yale University, New Haven, Connecticut (USA)

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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VEGF-A, VEGF
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* Corresponding author.
Delma Veron, School of Health Sciences, Universidad Estatal de Milagro, Ciudadela Universitaria, UNEMI, Kilómetro 1 ½ Via KM 26., 091050, Milagro, Guayas, Ecuador. Tel.: (593) 46038456
E-mail: delveron@gmail.com; proyectond@hotmail.com

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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 insulinoresistencia. 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.

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### Issue relevance

The prevalence of diabetes mellitus has increased worldwide since the last century. In adults aged between 20 and 79 years of age, its prevalence reaches 8%. 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. 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. In Spain, a diabetes prevalence rate of 13.8% was reported, while 6.0% had not yet been diagnosed. 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%. In addition, 45.5% of individuals with diabetes will not be diagnosed with the disease.

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. Moreover, native populations are particularly vulnerable due to the change in lifestyle, marginalisation and lower exposure to health care systems. In Ecuador, the prevalence of diabetes is 6%, and in 2010 it was the second cause of mortality. 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 (Figure 1).

Kidney disease caused by diabetes is called diabetic nephropathy (DN). About 30% of patients with diabetes develop DN. Such disease is the main cause of chronic kidney disease (CKD) and of admission to dialysis. 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. 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. In Ecuador, the prevalence of patients who received renal function replacement therapy in 2010 was 406 individuals per one million inhabitants. 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). 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),
with type 2 diabetes was 24.9% after a ten-year follow-up,
one study, the prevalence of microalbuminuria in patients
hyperglycaemia, hypertension (HTN), dyslipidaemia, age over
sixty-five years, male gender, smoking habit, family history and
Hispanic or Afro-American origin. Familial clustering was
reported in populations with different ancestors, especially
in Pima Indians and Afro-Americans. Mooyaart et al. found
24 genetic variations associated with DN. Epigenetic mech-
anisms were also implied. For example, chronic hypergly-
caemia, without altering the nucleotide sequence, may
modify DNA or methylate histones associated with DNA.
However, the significance of these findings on the develop-
ment of DN has not been determined yet.

Many factors were implied in DN pathophysiology, such as:
glucose, glucose receptors, VEGF-A, NO, reactive oxygen
species (ROS), transforming growth factor beta (TGF-Beta),
RAAS, kinin-kallikrein system, mammalian target of rapa-
mycin, inflammation, tumour necrosis factor alpha, adipo-
nectin, advanced glycation end products and receptors
thereof, mitochondrial oxidative stress and micro-
RNA.

From the pathologic point of view, type 1 and type 2 dia-
betes induce common kidney lesions. These lesions were
characterised in type 1 diabetes and type 2 diabetes, the
kidney histology and course have special features, associ-
ated with comorbidities such as HTN, vascular diseases,
ageing and obesity. Five years after diabetes diagnosis,
there is hyperfiltration, microalbuminuria, glomerulomegaly,
glomerular basal membrane (GBM) thickening and alteration
of podocytes. Subsequently, the extracellular matrix (ECM)
is deposited in the mesangium. Approximately ten years later,
proteinuria and HTN are evident, and GF becomes progres-
sively impaired. Within a period of 20 to 25 years, scle-
rosis is advanced, there is tubulointerstitial fibrosis and CKD
progresses to end-stage phases.

Meanwhile, the glomeruli, tubules, interstitium and renal
arteries are modified by the diabetic environment. Glomerular
changes involve the glomerular filtration barrier (GBF), ECM,
and the main cells composing it (podocytes, endothelial cells
and mesangial cells). In addition, it prevents the
abnormal passage of plasma protein based on size and load,
and its alteration was associated with proteinuria.

The GBF is composed of podocytes, GBM, and the endothelium
(Figure 2). Podocytes are markedly differentiated epithelial
cells, with a large cell body, and primary and secondary
extensions connected by slit diaphragms (SD). The SD
is permeable to water and small solutes, but it is selective to
large molecule passage, which is a key factor in GBF perme-
ability. Moreover, it is composed of a protein complex, where
neprhin plays an important role. On the apical side,
podocytes float within the urinary space, while on the baso-
lateral side, they make contact with the GBM. Podocyte cyto-
skeleton proteins are related to GBM proteins through
integrins and dystroglycans. The GBM is mainly com-
posed of proteins, such as collagen IV and laminins. The
fenestrated endothelium, covered by glycocalyx, is the inner
most layer of the GBF. Diabetes alters the three layers
that make up the GBF. Among the early changes, neoangio-
genesis in the glomerular vascular pole and loss of endothel-
ilial fenestrations have been described. The GBM shows
an increased thickness due to protein exchange alter-
ations. In podocytes, flattening, hypertrophy,

**Figure 1** – In Ecuador, mortality caused by diabetes mellitus
was higher in the provinces of Guayas, Los Ríos and Manabí,
located on the Pacific coast. Map shows the mortality rate
due to diabetes mellitus (deaths/100,000 individuals per year,
INEC, Instituto Nacional de Estadísticas y Censos – National
Institute of Statistics and Census of Ecuador, 2011). This figure
is part of a figure originally published by Neira-Mosquera et
al., with minor modifications (authorised reproduction).
VEGF-A is a potent angiogenic factor related to normal and pathological angiogenesis. It promotes the proliferation, differentiation and migration of endothelial cells; it induces vasodilation and increases vascular permeability. It plays an important role in kidney development; in the adult kidney, it is secreted by podocytes and is essential for the maintenance of the GFB. It acts through tyrosine-kinase receptors, which are known as VEGF receptor 1 and 2 (VEGFR1 and 2). VEGFR2 is expressed in endothelial cells and podocytes; it is related to the most important signals of VEGF-A. Two co-receptors called neuropilins 1 and 2 amplify the VEGFR2 signal.

There is evidence that glucose directly and indirectly stimulates VEGF-A expression in podocytes through angiotensin II and TGF-Beta. Glucose plays a very important role in DN pathophysiogenesis. Glycaemic control reduces DN progression and induces reversion of proteinuria and advanced histological lesions. In a 30-year follow-up study, protein-

### Table 1 – Glomerular pathways with therapeutic potential for DN

<table>
<thead>
<tr>
<th>Stimulated pathways</th>
<th>Inhibited pathways</th>
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<tbody>
<tr>
<td>TGF-Beta</td>
<td>eNOS</td>
</tr>
<tr>
<td>CTGF</td>
<td>VEGFR2 activity</td>
</tr>
<tr>
<td>VEGF-A</td>
<td>Nephrin</td>
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<tr>
<td>Angiopoietin 2</td>
<td>Angiopoietin 1</td>
</tr>
</tbody>
</table>

**Legend:** TGF-Beta (transforming growth factor), CTGF (connective tissue growth factor), VEGF-A (vascular endothelial growth factor), eNOS (endothelial nitric oxide synthase)
uria, GF and HTN showed an improvement in patients with type 1 diabetes when there was better glycaemic control28. With a higher control of hyperglycaemia, GBM has shown less thickening29. Histological changes of advanced DN reverted 10 years after pancreas transplantation30. Haraguchi et al. were able to revert nephrotic-range proteinuria and histological lesions compatible with advanced DN after five years of intensive treatment of hyperglycaemia31. Treatment with bariatric surgeries administered to patients with type 2 diabetes and obesity improved GF and proteinuria, which was related to weight loss and decreased hyperglycaemia32. Hypertension and obesity improved GF and proteinuria, which was prevented mesangial build-up and kidney function impairment19,20. These antibodies represent a therapeutic hope for prevention of hyperfiltration, GBM thickening and glomerulosclerosis through the VEGF and podocyte apotosis15,19,20. In contrast, the increase in VEGF expression and it correlated with proteinuria33. Contrarily, in the diabetes context, VEGF-A has not been observed to be a good marker of glomerular expression or DN severity. Urine and systemic VEGF-A levels were high in diabetic mice with and without glomerular VEGF overexpression34. Probably, within the diabetes context, urinary excretion of VEGF-A reflects systemic levels, while hiding VEGF glomerular changes34. In short, these experiments suggest that glomerular VEGF-A is a determining factor in DN, that VEGF overexpression in podocytes is dangerous, and that glucose directly and indirectly stimulates the VEGF-A signalling cascade in podocytes. In diabetes, urinary and systemic VEGF-A did not correlate with either glomerular VEGF expression or with the severity of glomerular lesions, which brings into question the use of VEGF-A as a DN biomarker.

Glomerular VEGF-A reduction was shown to generate GFB lesions, proteinuria and kidney failure in animals and humans42,43. Transgenic mice with silencing of VEGF-A in podocytes showed AKF, alteration of the three GFB layers and reduced integrin expression42. Some patients treated with anti-VEGF-A antibodies showed proteinuria, endothelial lesions and thrombotic microangiopathy42. This evidence suggests that VEGF-A released by podocytes is important for the maintenance of the function and the glomerular structure in the adult kidney. Whether glomerular VEGF-A expression control improves DN has not yet been determined, but there is evidence that shows contradictory results. Administration of anti-VEGF-A antibodies improved DN in rodents44. In experiments conducted in mice, endostatin and tumstatin prevented the development of DN due to a decrease in VEGF-A and angiopoietin 236. In contrast, diabetic mice with gene deletion of VEGF-A in podocytes showed proteinuria and severe diffuse glomerulosclerosis associated with endothelial injury and apoptosis42. The evidence described herein suggests that close monitoring of glomerular VEGF-A levels in diabetes is required in order to avoid adding new lesions or worsening DN. Monitoring glomerular VEGF-A expression within very close margins may have a therapeutic potential, but the optimal concentrations and the right moment to perform such manipulation have not yet been defined.

Glomerular VEGF-A modifications in DN

Starting from early DN stages, systemic and renal VEGF-A are elevated in humans and mice, VEGF-A has been associated with neangiogenesis15,21,22. RAAS, VEGF-A and nephrinuria were seen to be involved in this process15,19,20,22,33-38. Cultured podocytes and endothelial cells increased VEGF-A and VEGFR2 expression in response to the increase in glucose39-41. We showed that glomerular VEGF is a key factor for DN development and progress33-34. Normoglycaemic mice with VEGF overexpression in podocytes developed glomerulomegal, hyperfiltration, GBM thickening and podocyte lesion, which are changes similar to early DN33. In these transgenic mice, diabetes caused massive proteinuria, advanced nodular glomerulosclerosis and less nephrin expression34. Diabetic mice with no VEGF overexpression only showed mild diffuse glomerulosclerosis34. These experiments demonstrate that the increase in glomerular VEGF, irrespective of the diabetic environment, generates identical changes to the early DN and that increasing glomerular VEGF speeds up DN progress to more advanced stages. In the absence of diabetes, the urinary VEGF-A was reported to be a good marker of VEGF glomerular expression and it correlated with proteinuria33. Contrarily, in the diabetes context, VEGF-A has not been observed to be

VEGF-A relationships with insulin receptors, nephrin and ROS in DN

In DN, glomeruli with different lesion degrees coexist; VEGF-A expression and its signalling cascade have been related to glomerular changes32. In biopsies of patients with DN, there has been evidence of a higher VEGF expression in the glomeruli with lesions due to diabetes than in intact glomeruli37. However, VEGF-bound receptor expression was seen to be elevated in glomeruli with mild lesions and decreased in glomeruli with moderate or severe compromise37. A similar behaviour was observed with phosphorylation of serine/threonine protein kinase, a protein located in the VEGF signalling cascade, which suggested that other factors would modulate VEGF/VEGFR activity37. Podocytes express insulin receptors, whose activity depends on nephrin expression45,46. Insulin receptors are located in the SD, where podocytes express nephrin and
VEGFR2 and SHP-1. We have characterised the existing interaction between nephrin and VEGFR2. VEGF overexpression in podocytes was found to decrease nephrin expression and phosphorylation. In transgenic mice, this VEGF-A increase was disrupted by insulin resistance, anticipating the development of podocyte lesions secondary to insulin resistance. In patients with insulin resistance caused by diabetes and by other diseases, kidney alterations, such as hyperfiltration, proteinuria, modifications in FGB and mesangium were described. Jointly, these findings suggest that VEGF, nephrin and insulin receptor may be related to DN and insulin resistance, thus constituting glomerular pathways susceptible to being modified.

Furthermore, oxidative stress secondary to hyperglycaemia may modify glycocalyx, increase ROS and advanced glycation end products, and alter the endothelium. In addition, protein kinase C (PKC) glomerular activation was associated with mesangial expansion, GBM thickening, endothelial dysfunction, cytokine and TGF-Beta activation. Mima et al. described that hyperglycaemia alters nephrin phosphorylation in diabetic rats and cultured podocytes exposed to high concentrations of glucose. Nephrin phosphorylation interruption was attributed to a "glomerular VEGF resistance" status related to PKC activation. The VEGF signalling cascade in podocytes and endothelial cells was selectively inhibited by hyperglycaemia. The increase in glucose and diabetes would cause higher podocyte apoptosis and endothelial dysfunction, partly due to a higher activation of mitogen-activated protein kinase (PKCκ/p38) and SRC homology-2-domain-containing phosphatase-1 (SHP-1) overexpression. In addition, SHP-1 negatively regulates VEGFR2 and the insulin receptor.

Warren et al. showed that hyperglycaemia reduces endothelial VEGFR2 activity in diabetes. ROS generation caused by hyperglycaemia was observed to induce VEGFR2 activation and its subsequent breakdown, notwithstanding the VEGF-A. This would alter the normal response of endothelial cells to circulating VEGF-A due to lower receptor availability. By blocking ROS production with antioxidants, VEGFR2 availability and the lack of endothelial response to VEGF-A caused by hyperglycaemia were reverted. These results suggest that the increase in VEGF-A present from early stages of DN may be secondary to "VEGF-resistance" of the VEGFR2 caused by higher receptor breakdown in endothelial cells.

Jointly, these publications indicate that, in DN, VEGF overexpression in podocytes may be stimulated in an autocrine and paracrine way by a "VEGF-resistance" state. VEGF-A connections with oxidative stress at glomerular level may reconstitute pathways with therapeutic potential.

**Relationship between angiopoietins and VEGF-A in DN**

Angiopoietins, which are growth factors involved in angiogenesis, have been related to DN. Plasma levels of angiopoietin 2 are high in diabetic humans and mice, thus altering the angiopoietin-1/angiopoietin-2 ratio. Diabetic mice with lower angiopoietin 1 levels showed aberrant angiogenesis, hyperfiltration, glomerulomegaly and albuminuria, accompanied by VEGF-A and phosphorylated VEGFR2 overexpression. Alterations caused by reduced angiopoietin 1 were seen to be partially prevented by restoring its expression in podocytes of transgenic mice. These experiments show the importance of angiopoietins and their relationship with VEGF-A in DN pathophysiology. Modification of protein expression at the glomerular level (by manipulating the cells that produce these proteins) is a therapeutic alternative.

**VEGF-A and nitric oxide in DN**

VEGF-A stimulates NO production by means of endothelial NO synthase (eNOS) activation. The effects of VEGF-A on vasodilatation and on the vascular permeability increase are mediated by the increase in eNOS-dependent NO. Under normal conditions, VEGF-A induces eNOS activation and an increase in NO; this increase negatively regulates VEGF-A and CTGF, inhibiting ECM build-up. In diabetes, this relationship changes: the increase in VEGF-A coexists with lower eNOS activity, and there is VEGF-A and NO decoupling. Along the lines of this theory, enOS KO diabetic mice increased VEGF-A expression and developed severe DN. We showed that VEGF overexpression in podocytes of enOS KO mice, induced indistinguishable changes of the advanced DN. In the absence of diabetes, these transgenic mice developed proteinuria, kidney failure and nodular glomerulosclerosis. This evidence suggests that alterations in glomerular VEGF-A/eNOS relationship are critical and very dangerous, highlighting these events and their relationship with VEGF-A as treatment targets at the glomerular level.

Endothelial NO deficiency secondary to reduced eNOS activity may also associate insulin resistance mechanisms with endothelial dysfunction. Endothelial cells express insulin receptors. By means of eNOS activation, these receptors control vascular tone by inducing vasodilation. For example, in patients with diabetes there are alterations in eNOS activation, establishing a relationship between NO and endothelial insulin resistance. These findings suggest that VEGF-A and the glomerular NO/eNOS ratio may be implied in the insulin resistance status associated with prediabetes, diabetes and CKD.

**Conclusions**

Population studies reveal an increasing prevalence of type 2 diabetes worldwide, which suggests that DN will become an even more serious problem. It is imperative to look for alternatives for the diagnosis, prevention and treatment of DN. Going further in the study of molecular pathways with therapeutic potential, such as angiogenic factors, the glomerular VEGF resistance status, insulin resistance in podocytes, the VEGFR2/nephrin relationship, VEGF/insulin receptors/nephrin relationship, and the VEGF/NO-eNOS relationship, may provide solutions to the urgent problem of DN in the world.
Key concepts

1. Diabetes mellitus and CKD prevalence have increased in recent decades. The most frequent isolated cause of CKD is DN. Factors related to DN development are: age over 65, uncontrolled hyperglycaemia, hypertension, dyslipidaemia, male gender, smoking habit, family history, and Hispanic or Afro-American origin.

2. Glucose directly and indirectly stimulates VEGF-A cell expression. In DN, there is a systemic and glomerular increase in VEGF-A, but glomerular VEGF-A and the glomerular VEGF-A/NO-eNOS relationship are key factors in DN pathophysiology.

3. Endothelial cells and podocytes express insulin receptors. Nephrin is essential for the action of the insulin receptor in podocytes; its activation is related to VEGF-A. VEGFR2 and nephrin interact in podocytes. Insulin receptors, nephrin and VEGF-A receptors may be mechanistically related to DN and insulin resistance.

4. In DN, VEGF overexpression in podocytes may be stimulated in an autocrine and paracrine way by a “VEGF-resistance” status, in which PKC and ROS would be involved. VEGF-A connections to oxidative stress at the glomerular level may represent pathways with a therapeutic potential for DN.

5. Angiogenic factors, such as VEGF-A and angiopoietins, the relationship of VEGF receptor 2/nephrin, VEGF/insulin receptors/nephrin and the relationship of VEGF/NO-eNOS, VEGF-A/insulin receptors/nephrin, and VEGF/NO-eNOS, represent glomerular pathways that have a crucial significance and may be potential treatment targets for DN.

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