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ORIGINAL ARTICLES

Nailfold capillaroscopy and microvascular involvement in Diabetes Mellitus

Capilaroscopia de leito ungueal e envolvimento microvascular em Diabetes Mellitus

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Abstract

Objective: to study the relationship between microvascular lesions of Diabetes Mellitus and alterations in the nailfold capillaroscopy.

Subjects and Methods: cross-sectional study including 140 individuals (70 with Diabetes Mellitus and 70 controls). Epidemiological and clinical variables were collected from patient's charts. Fundus ophthalmoscopy, nailfold capillaroscopy, analysis of microalbuminuria and renal clearance as well as fasting glycaemia and HbA1c values were studied simultaneously.

Results: capillary density was reduced, and vascular dilatation was increased in Diabetes Mellitus patients when compared to controls (both with p<0.0001). In diabetic individuals the number of dermal papillary capillaries/mm^3 correlated negatively with microalbuminuria (p=0.02), patient's age (p=0.03), values of HbA1c (p=0.03). Patients with diabetic retinopathy and using antiplatelet agents had lower capillary density (p<0.0001 and 0.04 respectively). Capillary dilatation was associated with disease duration (p=0.04).

Conclusion: microvascular disease in Diabetes Mellitus is reflected in nailfold capillaroscopy. Decreased capillary density, increased number of ectasias and increased presence of avascular areas were observed in patients with diabetes when compared to controls. In the present study, capillary density correlated/ associate with age, retinopathy, use of antiplatelet medication, HbA1c, microalbuminuria and diabetes duration. Ectasias or dilatations were related to retinopathy, glomerular filtration rate and longer disease duration.

Keywords: diabetes mellitus, microcirculation, diabetic retinopathy, microscopic angioscopy.

Resumo

Objetivo: estudar a relação entre lesões microvasculares do Diabetes Mellitus e alterações na capilaroscopia ungueal.

Sujeitos e Métodos: estudo transversal incluindo 140 indivíduos (70 com Diabetes Mellitus e 70 controles). Variáveis epidemiológicas e clínicas foram coletadas dos prontuários dos pacientes. A oftalmoscopia de fundo, capilaroscopia ungueal, análise de microalbuminúria e depuração renal, bem como glicemia de jejum e valores de HbA1c foram estudados simultaneamente.

Resultados: a densidade capilar foi reduzida e a dilatação vascular aumentada em pacientes com Diabetes Mellitus quando comparados aos controles (ambos com p <0,0001). Em indivíduos diabéticos, o número de capilares papilares dérmicos/ mm3 correlacionou-se negativamente com microalbuminúria (p = 0,02), idade do paciente (p = 0,03), valores de HbA1c (p = 0,03). Pacientes com retinopatia diabética e em uso de antiagregante plaquetário apresentaram menor densidade capilar (p <0,0001 e 0,04 respectivamente). A dilatação capilar foi associada ao tempo de doença (p = 0,04).

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Conclusão: a doença microvascular no Diabetes Mellitus reflete-se na capilaroscopia ungueal. Diminuição da densidade capilar, aumento do número de ectasias e aumento da presença de áreas avasculares foram observados em pacientes com diabetes quando comparados aos controles. No presente estudo, a densidade capilar se correlacionou/ se associou com idade, retinopatia, uso de antiagregante plaquetário, HbA1c, microalbuminúria e tempo de diabetes. Ectasias ou dilatações foram relacionadas à retinopatia, à taxa de filtração glomerular e a maior duração da doença.

Palavras-chave: diabetes mellitus, microcirculação, retinopatia diabética, angioscopia microscópica.

Abbreviations: DM, Diabetes Mellitus; NC, nailfold capillaroscopy; GFR, glomerular filtration rate; HbA1c, hemoglobin A1c; NV, normal value.

Introduction

Microvascular lesions are the hallmark of Diabetes Mellitus (DM), contributing to patient's morbidity and mortality. Eye and kidney damage are well known DM complications that mirror this kind of involvement (1, 2). Flow disturbances in skin microcirculation may precede development of typical diabetic complications (3).

Nailfold capillaroscopy (NC) is widely used to study vascular lesions in rheumatic diseases such as scleroderma and dermatomyositis (4). Due to its low cost and being easy to execute, the use of this instrument in other clinical situations with microcirculation's damage such as DM has been suggested (5). However, studies in NC application in this context are few and this method is not well known in the medical community. Nevertheless, this exam may offer an easy way to evaluate DM complications. According to Shikama et al. (6) NC is able to predict diabetic retinopathy independent of traditional risk factors. Another study, by Schoina et al. (7) in diabetic chronic kidney disease, showed that NC reflects microcirculatory structural and the functional impairment of this organ. These points illustrate the advantages of NC in the evaluation of DM patients.

NC is achieved by looking through the epidermis at the nailfold bed. The main pathological findings are decrease in capillaries density and changes in capillary dimensions. It can be done with videocapillaroscopy instruments, with a biomicroscope, with an ophthalmoscope or even with a dermatoscope (8).

Herein we proposed to study NC in diabetic patients and its associations with retinal and kidney complications.

Methods

This is a cross-sectional study approved by the local Committee of Ethics in Research number number 6895.934016.8117.3.0000.0103. All participants signed consent.

One hundred and forty individuals (70 with DM and 70 controls) were invited to participate. This is a convenience sample that includes all DM patients that came for regular consultations for the period of six months in a single Endocrinology Unit and that agreed to participate in the study. To be included, patients should be older than 18 years of age and have DM type 1 or type 2 diagnosed according to the American Diabetes Association guidelines (9) as follows: HbA1c≥6.5%; fasting glycemia ≥126 mg/dL and/or 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test.

Patients with systemic rheumatic diseases or recent injuries on the fingers were excluded. Patient's companions, paired for age and gender, were used as controls. Patients' charts were reviewed for epidemiological and clinical data (gender, age, tobacco exposure, auto declared ethnic background, diabetes type, comorbidities and treatment).

Evaluated laboratory data included fasting glycaemia, HbA1c, creatinine and microalbuminuria. At our institution, fasting glycaemia is measured by enzymatic analysis (normal values (NV)= 60-99 mg/dL); HbA1c is measured by high-performance liquid chromatography HPLC (NV< 5.7%; diabetes > 6.5%); creatinine is measured by colorimetric analysis method (NV for men <50 years: 0.84-1.25 mg/dL; men> 50 years old: 0.81-1.44 mg/dL; women: 0.66-1.09 mg/dL); and microalbuminuria is measured by immunoturbidimetry (NV<20mg/g of creatinine). Glomerular filtration rate (GFR) was

calculated according to the CKD-EPI equation (10).

A single examiner, blind for NC results, performed fundus ophthalmoscopy, using Pocket Scope Welch Allyn 12820® with 15-fold increase. The following findings were taken into account for diagnosis of diabetic retinopathy: micro aneurysms, soft and hard exudates, hemorrhages and macular edema (11).

A single examiner, also blind to clinical and ophthalmoscopic findings, performed NC using a Coleman® stereomicroscope with 10-fold increase. To perform NC, a drop of immersion oil was added in each nailfold from 2nd to 5th digits of both hands. Capillary count and morphologic alterations were reported. The capillary density was measured by manual count/mm3; less than 7/mm was considered abnormal (12). For statistical purposes, mean values obtained in all examined fingers were used. A capillary was considered to be dilated when the afferent, efferent and transition loops were enlarged from up to 4 to 9 times the normal. Mega capillaries were considered if they were enlarged 10 times or more (13). Avascular areas or focal deletion was defined as the absence of two or more successive capillaries (12, 13).

Frequency tables and contingency tables were created. Distribution was judged by Shapiro-Wilk's test. Chi-squared and Fisher's tests were used to compare nominal and categorical data. Mann-Whitney U and unpaired t-tests were used to compare numerical data. Spearman's test was used for correlations between number of capillaries and laboratory data, disease duration and age. A p value of 0.05 was considered significant. All tests were calculated with Graph Pad Prism 6.0 software.

Results

The main characteristics of DM studied sample are on **Table 1** that shows that most of the patients were Caucasian females with type 2 DM; more than half of the sample used oral hypoglycemic drugs and insulin.

TABLE 1 – Description of epidemiological, clinical and laboratory data of 70 patients with diabetes mellitus.

PARAMETERS	n	%
Female gender	42	60
Auto declared ethnic background		
Caucasians	46	65.7
Afro descendants	24	34.2
Type 2 Diabetes Mellitus	66	94.2
Disease duration years -median	10	2-34
Oral hypoglycemic use	53	75.7
Use of insulin	48	68.5
Obesity*	12	17.1
Arterial hypertension	54	77.1
Dyslipidemia	36	51.4
Diabetic retinopathy	27	38.5
Laboratory data	median	Range
Fasting blood glucose,	126.4	63.2 - 423.0
HbA1c (%)	8.1	5.8 - 15.0
Microalbuminuria (mg/day)	37.45	1.6 - 235.0
Serum creatinine (mg/dL)	0.98	0.7 - 3.1
Glomerular filtration rate (mL/min)	62.0±21.07	18.0 – 124.4

HbA1c, glycated hemoglobin. * defined as body mass index > 30 Kg/m^2.

Pairing data and comparison of NC findings between DM patients and controls are on **Table 2**. In this table is possible to note that DM patients had more alterations than controls in all studied parameters of NC. Mega capillaries were not found neither in patients nor in controls.

TABLE 2 – Pairing data and comparison of nailfold capillaroscopy findings between diabetes mellitus patients and controls.

Parameters	DM n = 70	CONTROLS n = 70	P
Gender (male/female)	28/42	20/50	0.15*
Age (years), median (IQR)	62.0 (50.7-70.0)	57.0 (48.0-66.0)	0.12†
Capillaries density (n/mm), median (IQR)	6.12 (5.5-7.0)	7.12 (7.0-7.4)	< 0.0001†
Patients with alterations in capillaries density, n (%)	52 (74.2)	13 (18.5)	< 0.0001*
Patients with capillaries dilation, n (%)	32 (45.7)	4 (5.7)	< 0.0001‡
Patients with avascular area, n (%)	22 (31.4)	6 (8.5)	0.0005*

DM, diabetes mellitus. IQR, interquartile range. * chi squared test; † Mann Whitney test; ‡ Fisher test.

The comparison of capillary density according to the studied clinical and treatment parameters is on **Table 3** that shows that patients using antiplatelet agents and those with retinopathy had lower capillary density than those without. In addition, negative correlations of capillary density with age, HbA1c, microalbuminuria and disease duration were observed.

TABLE 3 – Comparison and correlation studies of capillary density (n/mm) according to clinical, laboratory and treatment parameters.

	Patients with capillary loss	Patients without capillary loss	P
Comparison studies, median (IQR)			
Arterial hypertension	6.0 (5.5-6.5)	6.1 (5.5-7.0)	0.43†
Dyslipidemia	6.1 (5.6-6.5)	6.1 (5.3-7.0)	0.79†
Obesity	5.9 (5.4-6.5)	6.1(5.6-7.0)	0.36†
Insulin use	6.1 (5.5-7.0)	5.9 (5.4-6.4)	0.22†
Oral hypoglycemic use	6.1 (5.6-6.8)	5.70 (5.1-7.0)	0.51†
Antiplatelet agents use	5.7 (5.5-6.3)	6.5 (5.6-7.0)	0.04†
Diabetic retinopathy	5.6 (5.4-6.0)	6.3 (6.0-7.0)	< 0.0001†
Correlation studies˙	Spearman Rho	95%CI	
Age (years)	-0.24	-0.46 to -0.007	0.03
Fasting glycaemia (mg/dL)	-0.11	-0.34 to 0.13	0.36
HbA1c (%)	-0.24	-0.46 to-0.007	0.03
Serum creatinine (mg/dL)	-0.07	-0.31 to 0.18	0.52
Microalbuminuria	-0.37	-0.63 to -0.04	0.02
Glomerular filtration rate (mL/min)	0.17	-0.07 to 0.39	0.15
Disease duration (years)	-0.59	-0.72 to -0.40	0.0001

CI=confidence interval. IQR, interquartile range. ˙Spearman test; † Mann Whitney test.

The study of capillary dilatation showed the results in **Table 4.** An association of capillary dilatation with disease duration and capillary density was seen as well as a trend towards association with retinopathy and GFR.

TABLE 4 – Comparative studies of patients with diabetes mellitus presenting with and without capillary dilatation at nailfold capillaroscopy

Parameter	With dilatation (n=32)	Without dilatation (n=38)	P
Age (years), median (IQR)	62.0 (51.7-71.5)	61.5 (50.2-69.2)	0.57 *
Insulin use, n (%)	21 (65.6)	27 (71.0)	0.12†
Oral hypoglycemic use, n (%)	22 (68.7)	31 (81.5)	0.21†
Antiplatelet agents use, n (%)	15 (46.8)	18 (47.3)	0.96‡
Diabetic retinopathy, n (%)	16 (50.0)	11 (28.9)	0.07†
HbA1c (mg/dL), median (IQR)	8.3 (7.2-8.7)	7.65 (6.8-8.6)	0.15*
Microalbuminuria (mg/day), median (IQR)	38.2 (1.6–236.0)	436.7(4.1-195.8)	0.69*
Glomerular filtration rate (mL/min), mean±SD	57.0±20.3	66.2±21.0	0.06‡
Disease duration (years), median (IQR)	11.3 (7.0-20.0)	10.0 (5.0-15.0)	0.04*
Capillary density (n/mm), mean±SD	5.8±0.68	6.4±0.8	0.0007‡

n=number; IQR= interquartile range; SD=standard deviation. *Mann Whitney test; †chi-squared test; ‡ unpaired t test.

Discussion

The present study showed that DM patients have lower capillary density and more capillary dilatation and avascular areas than controls. The capillary density correlated with age, retinopathy, antiplatelet medication use, HbA1c, microalbuminuria and diabetes duration. Ectasias or dilatations were related to retinopathy, GFR and longer disease duration.

Other authors found the same capillaroscopic changes (1, 11, 14-16) that we did. Kaminska-Winciorek et al. (2) detected that the levels of HbA1c influenced the capillaroscopic findings, mainly the number of vessels, similarly to our results. In this context, it would be interesting to know if the glycemic control would revert such alterations. It is possible that the effects of hyperglycaemia on hyperfibrinogenaemia changing plasma viscosity and its hemorheological variables (16, 17) could play a role in such alterations. Increase in plasma fibrinogen and viscosity attenuates the vasodilatation in blood vessels from periphery (18).

The association of capillary loss and presence of morphologic alterations (dilatations) in NC with retinopathy has also been described (8). Diabetic retinopathy is an important cause of blindness and may evolve without symptoms until it has reached a very advanced state (19). Therefore, NC could point to its presence, allowing the clinicians to adopt preventive measures.

While the association with low capillary density is easily understood by the ischemic changes in microcirculation (20, 21), the appearance of dilatation in the loops is less clear. We noted an inverse relationship between capillary density and the presence of dilatations. Meyer et al. (22) described the ecstatic alterations as a reaction to tissue ischemia caused by local capillary loss. Hypoxia is a key regulator of VEGF (vascular endothelial growth factor) induced ocular neovascularization (23) and we can hypothesize that the same mechanism is seen in the nailfold. If this proves to be right, the presence of dilatations at NC could be a surrogate to proliferative

changes in the retina. However, more studies are needed in this context.

We also detect that capillary loss was associated with microalbuminuria but not with changes in GFR; capillary dilatation did not associate with microalbuminuria but a trend towards association with loss of GFR was seen. A cross-sectional study with 866 patients by Martens et al. (24), found lower capillary density of the skin microcirculation to be independently associated with the presence of albuminuria as in the present study. Microalbuminuria is an early sign of diabetic nephropathy appearing first than proteinuria and decline in GFR (25). Nevertheless, diabetic glomerulosclerosis is multifactorial: intraglomerular hypertension, ischemic injury, increased VEGF and TGF-beta expressions (26, 27) and alterations in renal bone morphogenetic protein-7 levels (28) are some of the players. This multifactorial aspects of the pathophysiologic mechanisms of diabetic kidney injury may explain why the NC associations with microalbuminuria and GFR were dissociated. It is worthwhile to note that some authors found dissociation between loss of GFR and albuminuria (29). The widespread use of angiotensin-converting inhibitors and angiotensin II receptor blockers as anti-proteinuric agents may also have affected these findings (30).

Another important point is the relation between disease duration and the appearance of capillary alterations. In this study, it was demonstrated that patients with prolonged duration of disease presented more alterations when compared to those with less time of disease, which is compatible with the literature. Other researchers also emphasize the progressive development of capillaroscopic alterations mainly in patients with more than 10 years of disease (15, 22).

An unexpected finding was the association of capillary loss with the use of anti-platelet agents. We do not have an explanation for this but it is reasonable to think that these are patients with more severe vascular damage and the relation could be with the indication of these drugs rather than with the drug itself.

The present study has limitations: one of them is its cross-sectional design. Prospective studies are welcome to analyze possible changes in NC pattern according to diabetes control. The other is that we did not quantify the retinal changes in these patients, using just a yes/no option. We also did not study DM type-1 and DM type-2 apart, as our sample of DM type-1 patients was quite small. However, it has the merit to highlight the existence of NC changes in DM and its relationship with microvascular damage. NC is a cheap exam and it is performed without difficulties; it also can be easily repeated. As a proper retinal evaluation requires pupillary dilatation (not always welcome by the patients) and following nephropathy with microalbuminuria and GFR determinations have considerable costs, it would be interesting to stimulate the NC's widespread use.

Concluding, decreased capillary density, increased number of ectasias and increased presence of avascular areas were observed in patients with DM when compared to controls. In the present study, capillary density correlated/associate with age, retinopathy, use of antiplatelet medication, HbA1c, microalbuminuria and diabetes duration. Ectasias or dilatations were related to retinopathy, GFR and longer disease duration.

References

1. Maldonado G, Guerrero R, Paredes C, Ríos C. Nailfold capillaroscopy in diabetes mellitus. Microvasc Res. 2017;112:41-6. https://doi.org/10.1016/j.mvr.2017.03.001

2. Oliveira ACR., Mendes BB, de Alcântara KC. Neutrophil/lymphocyte and platelet/lymphocyte ratios in diabetic patients with or without renal dysfunction. Scientia Medica. 2018;28(3):ID30376. https://doi.org/10.15448/1980-6108.2018.3.30376

3. Lambova SN. Nailfold Capillaroscopy – Practical Implications for Rheumatology Practice. Curr Rheumatol Rev. 2020;16(2):79-83. https://doi.org/10.2174/1573397116022004150834444

4. Hsu PC, Liao P-Y, Chang H-H, Chiang JY, Huang Y-C, Lo L-C. Nailfold capillary abnormalities are associated with type 2 diabetes progression and correlated with peripheral neuropathy. Medicine. 2016;95(52):e5714. https://doi.org/10.1097/MD.0000000000005714

5. Lambova SN, Muller-Ladner U. Nailfold capillaroscopy within and beyond the scope of connective tissue diseases. Curr Rheumatol Rev. 2018;14(1):12-21. https://doi.org/10.2174/1573397113666170615093600

6. Shikama M, Sonoda N, Morimoto A, Suga S, Tajima T, Kozawa J, et al. Association of crossing capillaries in the finger nailfold with diabetic retinopathy in type 2 diabetes mellitus. J Diabetes Investig. 2021;12(6):1007-14. https://doi.org/10.1111/jdi.13444

7. Schoina M, Loutradis C, Theodorakopoulou M, Dimitroulas T, Triantafillidou E, Doumas M, et al. The presence of diabetes mellitus further impairs structural and functional capillary density in patients with chronic kidney disease. Microcirculation. 2021;28(2):e12665. https://doi.org/10.1111/micc.12665

8. Rajaei A, Dehghan P, Farahan Z. Nailfold capillaroscopy findings in diabetic patients (A pilot cross-sectional study). Open Journal of Pathology. 2015;5:65-72. https://doi.org/10.4236/ojpathology.2015.52010

9. American Diabetes Association. Standards of medical care in diabetes 2011. Diabetes Care. 2011;34:S11-61. https://doi.org/10.2337/dc11-S011

10. Warnock DG. Estimated glomerular filtration rate: fit for what purpose? Nephron. 2016;134:43-9. https://doi.org/10.1159/000444062

11. Kollias AN, Ulbig MW Diabetic Retinopathy: Early Diagnosis and Effective Treatment Dtsch Arztebl Int. 2010;107:75-83. https://doi.org/10.3238/arztebl.2010.0075

12. Kayser C, Andrade LEC. Importance of the nailfold capillaroscopy in the investigation of Raynaud's phenomenon and scleroderma-spectrum syndromes. Rev Bras Reumatol. 2004;44:46-52. https://doi.org/10.1016/j.rbr.2014.09.003

13. Tavakol ME, Fatemi A, Karbalaie A, Emrani Z, Erlandsson B_E. Nailfold capillaroscopy in rheumatic diseases: Which parameters should be evaluated? Biomed Res Int. 2015; 2015:974530. https://doi.org/10.1155/2015/974530

14. Ciaffi J, Ajasllari N, Mancarella L, Brusi V, Meliconi R, Ursini F. Nailfold capillaroscopy in common non-rheumatic conditions: A systematic review and applications for clinical practice. Microvasc Res. 2020;131:104036. https://doi.org/10.1016/j.mvr.2020.104036

15. Uyar S, Balkarlı A, Erol MK, Yeşil B, Tokuç A, Durmaz D, et al. Assessment of the relationship between diabetic retinopathy and nailfold capillaries in type 2 diabetics with a noninvasive method: nailfold videocapillaroscopy. J Diabetes Res. 2016; 2016:7592402. https://doi.org/10.1155/2016/7592402

16. Cicco G, Cicco S. Hemorheological aspects in microvasculature of several pathologies. Adv Exp Med Biol. 2007; 599:7-15. https://doi.org/10.1007/978-0-387-71764-7_2

17. Reid HL, Vigilance J, Wright-Pascoe RA, Choo-Kang E. The influence of persistent hyperglycaemia on hyperfibrinogenaemia and hyperviscosity in diabetes mellitus. West Indian Med J. 2000;49:281-4.

18. Vigilance J, Reid HL. Glycaemic control influences peripheral blood flow and haemorheological variables in patients with diabetes mellitus. Clin Hemorheol Microcirc. 2005;33:337-46.

19. Mozetic V, Daou JP, Martimbianco ALC, Riera R. What do Cochrane systematic reviews say about diabetic retinopathy? Sao Paulo Med J. 2017;135(1):79-87. https://doi.org/10.1590/1516-3180.2016.0356040117

20. Richardson D, Schwartz R, Hyde G. Effects of ischemia on capillary density and flow velocity in nailfolds of human toes Microvasc Res. 1985;30:80-7. https://doi.org/10.1016/0026-2862(85)90040-8

21. Herrick AL, Moore TL, Murray AK, Whildby N, Manning JB, Bhushan M, Vail A. Nailfold capillary abnormalities are associated with anti-centromere antibody and severity of digital ischaemia, Rheumatology. 2010;9:1776-82. https://doi.org/10.1093/rheumatology/keq139

22. Meyer MF, Pfohl M, Schatz H. Assessment of diabetic alterations of microcirculation by means of capillaroscopy and laser-Doppler anemometry. Med Klin (Munich). 2001;96:71-7. https://doi.org/10.1007/pl00002181

23. Campochiaro PA. Molecular pathogenesis of retinal and choroidal vascular diseases.Prog Retin Eye Res. 2015;49:67-81. https://doi.org/10.1016/j.preteyeres.2015.06.002

24. Martens RJH, Henry RMA, Houben AJHM, Van der Kallen CJH, Kroon AA, Schalkwijk CG, et al. Capillary rarefaction associates with albuminuria: The Maastricht study. J Am Soc Nephrol. 2016;27:3748-57. https://doi.org/10.1681/ASN.2015111219

25. Persson F, Rossing P. Diagnosis of diabetic kidney disease: state of the art and future perspective. Kidney Int Suppl. 2018;8:2-7. https://doi.org/10.1016/j.kisu.2017.10.003

26. Wolf G, Ziyadeh FN. Molecular mechanisms of diabetic renal hypertrophy. Kidney Int 1999;56:393-405. https://doi.org/10.1046/j.1523-1755.1999.00590.x

27. Hohenstein B, Hausknecht B, Boehmer K, Riess R, Brekken RA, Hugo CPM. Local VEGF activity but not VEGF expression is tightly regulated during diabetic nephropathy in man. Kidney Int. 2006;69:1654-61. https://doi.org/10.1038/sj.ki.5000294

28. Wang S, Caestecker M, Kopp J, Mitu G, Lapage J, Hirschberg R. Renal bone morphogenetic protein-7 protects against diabetic nephropathy. J Am Soc Nephrol. 2006;17:2504-12. https://doi.org/10.1681/ASN.2006030278

29. Thomas M, Macisaac R, Jerums G, Weekes A, Moran J, Shaw J et al. Nonalbuminuric renal impairment in type 2 diabetic patients and in the general population (National evaluation of the frequency of renal impairment co-existing with NIDDM. Diabetes Care. 2009;32:1497-502. https://doi.org/10.2337/dc08-2186.

30. Wang K, Hu J, Luo T, Wang Y, Yang S, Qing H, et al. Effects of angiotensin-converting enzyme inhibitors and angiotensin ii receptor blockers on all-cause mortality and renal outcomes in patients with diabetes and albuminuria: a systematic review and meta-analysis. Kidney Blood Press Res. 2018;43(3):768-79. https://doi.org/10.1159/000489913

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