The genetic polymorphism of diabetic nephropathy

Ricardo Moreno[1], Fernando Luiz Affo Fonseca[1], Vitor E. Valenti[2], Ana M. Antonio[2], Fernando H. Sousa[3], Luiz Carlos de Abreu[1]

[1] School of Medicine of ABC, Santo André, SP, Brazil,
[2] Faculty of Sciences and Technology, UNESP, SP, Brazil,
[3] Faculty of Sciences, UNESP, SP, Brazil.

Abstract

Introduction: The Diabetic Nephropathy (DN) affects approximately 40% of patients diagnosed with DM is associated with increased mortality from cardiovascular phenomena and is considered the main cause of Chronic Renal Failure (CRF) in patients dialectics.

Methods: Searches were performed on Medline, SciELO, Lilacs and Cochrane databases using the crossing between the key-words: "genetic polymorphism" and "diabetic nephropathy".

Results: The selected studies indicated that diabetic nephropathy is the leading cause of chronic renal failure, which significantly reduces the life expectancy of diabetics. Currently, some factors may have connection with DN. They are: genetic predisposition based on family history, hypertension, and cardiovascular events, quality of glycemic control and lipid levels and blood pressure and smoking.

Conclusion: Studies constants are essential to add new elements in the literature for the definition (s) of factor (s) gene (s) specific (s) of diabetic nephropathy.

Key words: Diabetic Nephropathies, Polymorphism, Genetic.

Introduction

The Diabetic Nephropathy (DN) affects approximately 40% of patients diagnosed with diabetes mellitus (DM) and it is associated with increased mortality from cardiovascular disorders. It is considered the main cause of Chronic Renal Failure (CRF) [1]. A review [2] cited it as responsible for 45% of cases of CRF on dialysis in the United States, 36% in Germany, 32% in Japan 15-25% and in several other European countries, apart from Australia. In Brazil and Latin America in general [3], about 15% of dialysis patients are diabetics.

Most diabetic patients with CRF are evolving with type 2 DM (DM-2) [4]. This finding takes on greater importance because of the prevalence of DM-2 is increasing in the world, according to the World Health Organization. There is also a higher incidence due to the global epidemic of obesity in developed and developing countries. More than 50% of global glomeruloesclerosis have clinical or pathological evidence that attribute diabetic sclerosis nephropathy [4].

The importance of ND is not only due to its high prevalence, but also because DM patients with proteinuria present a relative risk of premature death than not diabetic population [5]. In contrast, no diabetic nephropathy patients have twice the rate observed in non diabetics [5-6].

According to a sense of the Brazilian Society of Nephrology, the prevalence of CKD is 390 dialysis patients per million population, with about 73,600 in Brazil in dialysis patients. Although no systematic epidemiological studies in Brazil, it is estimated that DM is responsible for approximately 18% of dialysis patients in Brazil. There was an increase in the prevalence of CRF on dialysis secondary to ND in the last two decades. Studies [7-8] also estimate that 20- 45% of diabetic patients develop ND 10 to 15 years.

The World Health Organization estimates that up to 2025 there will be an increase in the prevalence of DM in the world, reaching a number of 300 million people. In developing countries, like Brazil, the increase is 170%. This increase, coupled with the increase in life expectancy of the general population can generate a significantly greater amount of patients with ND and dialysis [9].

Metabolic syndrome brought about by DM alone is enough to generate the glomerular lesions observed in ND. It is worth noting that these injuries can be prevented or have their intensity greatly diminished by the mere taking of blood glucose levels close to normal, always taking into

account the duration and intensity of treatment with insulin [10]. The interesting thing is that such renal lesions are reversed when an affected kidney is transplanted into an animal not diabetic [11].

In view of the above consideration, in this study we described the genetic polymorphism of diabetic nephropathy through a literature review.

Method

Search strategy and selection

The revisions were made between September 2012 and January 2013. The Medline (via PubMed), Lilacs, Scielo and Cochrane databases were searched using the following subject keywords: "genetic polymorphism" and "diabetic nephropathy". These words were defined by the Medical Subject Headings (MeSH).

The studies were selected by a reviewer and supervised by a senior reviewer. Based on the titles and abstracts, we excluded manuscripts not clearly related to the subject of the review. Thereafter, all the selected titles and abstracts were submitted to a final evaluation, which considered the inclusion criteria, and its reference lists independently checked to identify studies of possible relevance that were not found in the electronic search.

We excluded studies that presented no abstract or full text in English between 2000 and 2012 and literature reviews. As inclusion criteria we considered clinical trials and basic studies that investigated the effects of auditory stimulation on the ANS.

Results

The electronic search yielded a total of 898 references. Among these references the first elimination resulted in the exclusion of 837 titles and abstracts, which were not clearly related to the subject of review. The titles of the remaining 61 abstracts were submitted to a final evaluation that took into account the inclusion criteria. After the final exclusion of studies that did not investigate the SSCS, we finished the review with five references. The investigation of the reference lists confirmed the absence of relevant documents. Summaries of the main studies analyzed were selected.

Discussion

Diabetic nephropathy is the leading cause of chronic renal failure, especially in developed and developing countries, which significantly reduces the life expectancy of diabetics [12]. The DN gains importance as both the incidence of DM-2 is increasing and the beginning of its development has been increasingly early [12-13].

The prevalence of DM-2 is ten times greater than the DM-1, then it is observed by a greater prevalence of NA to CRF dialysis secondary to DM-2, both in foreign literature as national [14-15]. It is known that diabetic dialysis patients have lower survival rates than non-diabetics, which stems from an atherogenic vascular involvement that develops in a more accelerated [16].

A prospective cohort study followed 1853 dialysis patients with end-stage renal disease, 281 of these had ND as the main cause of dialysis, 107 had diabetes as a comorbid condition and 1465 did not have diabetes. The Dutch study of 2011 patients followed until they undergo the transplant or die, and the last outcome was common to 787 patients. Compared with nondiabetic patients, the risk of death was higher in both groups of patients, both those with ND as the main cause of dialysis (HR: 1.9) as those with diabetes as a comorbid condition (HR: 1.7) [17].

Coronel et al. in Madrid in Spain followed patients for at least 2 months of peritoneal dialysis for 25 years [18]. The study involved 118 diabetic patients of whom 66 had DM1 and 52 had DM2, and 117 patients who did not have diabetes. Number of hospitalizations and the same time were higher in diabetic patients than non-diabetic patients and there was no difference between patients with DM1 and DM2. Admissions due to cardiovascular problems were more common in patients with DM2. Mortality was 22% among those who did not have diabetes and 48% among carriers of the disease and in the last group mortality was higher in patients with T2DM.

In summary, many polymorphisms have been the subject of study, without having found what would be a specific marker. A supposed future identification of one or more factors that can define a direct genetic susceptibility to diabetic nephropathy allows patients at higher risk to be targets of intensive therapies or preventive interventions.

Unlike knowledge about genetic factors involved in ND, currently some nongenetic factors are recognized and clearly defined as its connection with the ND. It may be included genetic predisposition based on family history (patients in first degree) of hypertension and cardiovascular events, quality of glycemic control and lipid and blood pressure levels, besides smoking [19-20].

Among these factors it is included hypertension, its prevalence is approximately two times higher in diabetic patients compared to the normal population [21]. This relationship is conditioned to the fact that hypertension has a predictive factor for developing diabetes, but there is also a close relationship between hypertension and the development of ND. The prevalence of hypertension increases in ND concurrently with the severity and progress of IRC [22].

Katayama et al. [23] in a prospective 8-year follow-up also established a relationship between ND and rates of microalbuminuria. The Japanese study involving 1558 patients with DM2, showed progression of nephropathy in 74 patients. The rate of patients who progressed to ND was higher in patients with low microalbuminuria when compared to patients with microalbuminuria normal.

Faced with uncertainty about the genetic polymorphism of Diabetic Nephropathy, both in patients with DM-1 and DM-2, the correction of non-genetic factors associated with disease becomes key strategy for reduce prevalence and delayed clinical progression of the disease already established. Speak up on glycemic control, lipid and blood pressure, essentially.

Some studies have been done only in a particular country, which could characterize something typical of a certain ethnic group or population, restricted to their own cultures, having only a potentially regional applicability. Increasingly looking at isolated studies, what would be the main genetic factor of relevance, and several polymorphisms have been cited as involved in the pathophysiology of ND. Addressing genes in other populations previously studied in some research centers might create greater truthfulness of direct relationship, or lack thereof, of the genetic polymorphism in question with ND, excluding the obstacle of dealing with a polymorphism restricted to regional or an ethnicity or race.

Showing the influence of regional ethnic customs of a given population, cultural habits and even local genetic tendencies, compared to two recent studies in the literature regarding the main cause of kidney failure. The first, in 2012, conducted in the city of Jenin, Palestine, involved 84 patients with CRF, who were followed for 1 year. The study pointed to the DM as a cause of renal failure in 33.32% of patients [24]. The second study, in 2011, developed in Siri Lanka, followed 200 patients with chronic kidney disease for 3 months. Diabetes is the leading cause of CKD in 88.44% of patients [25].

Two distinct populations of one of the Middle East and other Asian continent, in presenting such a discrepancy in the pathogenesis of CKD, indicate the need to take into account the influence of regional factors in local studies. Also, there is the need for global multicenter studies evaluating genetic and non genetic factors common to different populations, to determine the precise pathogenesis of ND [26, 27].

Conclusion

The study of genes provides a wide researchers, the raw material, which is increasingly encouraged to go to search for new factors and new discoveries. Polymorphism of Diabetic Nephropathy not show different about this wide variety of new discoveries and constant studies are essential to the definition (s) of factor (s) gene (s) specific (s) of Diabetic Nephropathy.

Acknowledgements

This manuscript received financial support from UNESP. The funding body provided financial support to make all procedures and in the decision to submit the manuscript for publication.

References

1. *Gross JL, Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention and treatment. Diabetes Care 2005; 28: 164-76.*

2. *Locatelli F, Pozzoni P, Vecchio LD. Renal replacement therapy in patients with diabetes and end-stage renal disease. J Am Soc Nephrol 2004; 15: S25-9.*

3. *Oliveira MB, Romão JE, Zatz R. End-stage renal disease in Brazil: epidemiology, prevention and treatment. Kidney Int 2005; 68: S82-6.*

4. *Tervaert TW, Mooyaart AL, Amann K, et al. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol 2010; 21: 556–563.*

5. *Borch-Johnsen K, Andersen PK, Deckert T. The effect of proteinuria on relative mortality in type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1985; 28: 590-6.*

6. *Dorman JS, Laporte RE, Kuller LH, Cruickshanks KJ, Orchard JJ, Wagner DK, et al. The Pittsburgh insulin-dependent diabetes mellitus (IDDM) morbity and mortality study. Diabetes 1984; 33: 271-6.*

7. *Murussi M, Baglio P, Gross JL, Silveiro SP. Risk factors for microalbuminuria and macroalbuminuria in type 2 diabetic patients. Diabetes Care 2002; 25: 1101-3. Complications Study II. Diabetes 1990; 39: 1116-24.*

8. *Klein R, Klein BE, Moss SE, Cruickshanks KJ. Ten-year incidence of gross proteinuria in people with diabetes. Diabetes 1995; 44: 916-23.*

9. *Kinh H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care 1998; 21: 1414-31.*

10. *Rash R. Prevention of diabetic glomerulopathy in streptozotocin diabetic rats. Albumin excretion. Diabetologia 1980; 8: 413-6.*

11. *Lee CS, Mauer SM, Brown DM, Sutherland DE, Michael AF, Najarian JS. Renal transplantation in diabetes mellitus in the rat. J Exp Med 1974; 149: 793-800.*

12. *U.S.R.D.S. United States Renal Data System Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: 2002; 296–322.*

13. *Jones CAKA, Rogus J, Xue JL, Collins A, Warram JH. Epidemic of endstage renal disease in people with diabetes in the United States population: Do we know the cause? Kidney Int 2005; 67: 1684–1691.*

14. *American Diabetes Association: Standard of Medical Care in Diabetes-2008. Diabetes Care 2008; 31: S12-S54*

15. *Bruno RM, Gross JL. Prognostic factors in Brazilian diabetic patients starting dialysis. A 3.6-year follow-up study. J Diabetes Complications 2000; 14: 266-71.*

16. *Luke RG. Chronic renal failure – a vasculopathic state. N Engl J Med 1998; 339: 841-3.*

17. *Schroijen MA, Dekkers OM, Grootendorst DC, Noordzij M, Romijn JA, et al. NECOSAD Study Group. BMC Nephrol. 2011; 12: 69.52.*

18. *Coronel F, Cigarrán S, Herrero JA. Morbimortalidad en pacientes diabéticos en diálisis peritoneal. Experiencia de 25 años en un solo centro Nefrologia 2010; 30: 626-632.*

19. *Perneger TV, Brancati FL, Whelton PK, Klag MJ. End-stage renal disease attributable to diabetes mellitus. Ann Intern Med 1994; 121: 912-8.*

20. *Gaede P, Vedel P, Parving H-H, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomized study. Lancet 1999; 353: 617-22.*

21. *Epstein M, Sowers J. Diabetes mellitus and hypertension. Hypertension 1992; 19: 403-418.*

22. *Bakris G, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. Am J Kidney Dis 2000; 36: 646-661.*

23. *Katayama S, Moriya T, Tanaka S, Tanaka S, Yajima Y, et al. Japan Diabetes Complications Study Group. Diabetologia. 2011; 54: 1025-31.*

24. *Abumwais JQ. Etiology of chronic renal failure in Jenin district, Palestine. Saudi J Kidney Dis Transpl 2012; 23: 158-61.*

25. *Wijewickrama ES, Weerasinghe D, Sumathipala PS, Horadagoda C, Lanarolle RD, Sheriff RM. Epidemiology of chronic kidney disease in a Sri Lankan population: Experience of a tertiary care center. Saudi J Kidney Dis Transpl 2011; 22: 1289-93.*

26. *Ibanes AS, Cabral M, Abreu LC, Valenti VE, Gascon TM, et al. Effects of autohemotherapy on hematological responses in Wistar female rats Autohemotherapy in rats. HealthMED 2013; 7: 1256-1261.*

27. *Bucioli AS, Abreu LC, Valenti VE, Vannucchi H. Vitamin e and carnitine suplementation effects on blood glucose levels in young rats submitted to exhaustive exercise stress. HealthMed 2012; 6: 136-139.*

Corresponding Author
Fernando L. A. Fonseca,
School of Medicine of ABC,
Santo Andre,
Brazil,
E-mail: fon_fonseca@yahoo.com.br