Review

The emerging concept of chronic kidney disease without clinical proteinuria in diabetic patients

J.-M. Halimi *

Service de Néphrologie-Immunologie clinique, Hôpital Bretonneau, CHU de Tours, EA 4245, université François-Rabelais, 2, boulevard Tonnellé, 37044 Tours cedex, France

Received 5 February 2012; received in revised form 28 March 2012; accepted 2 April 2012

Abstract

The natural history of diabetic nephropathy was defined in the 1980s on the basis of longitudinal studies undertaken in patients with type 1 and type 2 diabetes. However, an increasing number of studies have indicated that certain diabetic patients do not present with the same evolution as was then defined: for example, some often have significant initial deterioration of glomerular filtration rate whereas, in others, microalbuminuria is reduced spontaneously. Chronic kidney disease (CKD) may be accompanied, rather than preceded, by macroalbuminuria, or it may develop in patients with microalbuminuria or even in those with albuminuria levels that revert to normal. CKD can also develop in patients whose albuminuria levels remain normal. Progression to macroalbuminuria is, in fact, less frequent than regression to normoalbuminuria or no change in microalbuminuria status in diabetic patients with microalbuminuria, especially in type 1 diabetes. Some experience progressive deterioration of renal function due to diabetes without developing significant proteinuria: this is seen fairly frequently and can affect 50% of patients with renal insufficiency. Such cases are more often older patients treated with renin–angiotensin system blockers who usually have a history of cardiovascular disease. Evolution to end-stage renal disease is slower in this subgroup of patients, although histological analyses may show surprisingly advanced glomerular lesions. The main parameters of surveillance remain regular monitoring of glycaemia, and control of blood pressure and the evolution of initial albuminuria levels. Nevertheless, why some patients exhibit conventional diabetic nephropathy while others have slower declines in renal function associated with normal albuminuria levels or microalbuminuria is unclear. It is hoped that the new pathological classification of diabetic nephropathy will help in our understanding of these discrepancies.

© 2012 Elsevier Masson SAS. All rights reserved.

Keywords: Diabetes; Albuminuria; Chronic kidney disease; Renin-angiotensin system; Epidemiology; Review

Résumé

Néphropathie diabétique sans protéinurie: apparition d’un concept nouveau.

L’histoire naturelle de la néphropathie diabétique a été définie dans les années 1980 à partir d’études longitudinales menées chez des patients diabétiques de type 1 et de type 2. Cependant, des études de plus en plus nombreuses indiquent que certains patients diabétiques n’ont pas l’évolution naturelle telle qu’elle a été décrite dans les années 1980. Ils ont souvent une dégradation initiale de leur débit de filtration glomérulaire très importante; chez d’autres, la microalbuminurie peut régresser spontanément. Le développement d’une insuffisance rénale chronique (IRC) peut être accompagnée mais non précédée d’une macroalbuminurie et peut se développer chez un patient qui reste microalbuminurique ou qui peut régresser au stade de normoalbuminurie. L’IRC peut aussi se développer chez un patient initialement normoalbuminurique qui reste normoalbuminurique jusqu’à un stade avancé. Plus généralement, les patients diabétiques microalbuminuriques ont davantage de risque de régresser au stade de normoalbuminurie que de progresser au stade de macroalbuminurie. Certains développent une altération progressive de la fonction rénale dont la cause est bien le diabète sans développement d’une protéinurie importante: cela semble être une situation assez fréquente et peut atteindre 50 % des patients diabétiques en IRC. Ces patients sont souvent plus âgés, ont un diabète ancien et ont souvent un traitement qui comporte un bloqueur du système rénine-angiotensine et des antécédents cardiovasculaires. Leur vitesse d’évolution vers l’IRC terminale est plus faible.

Mots clés : Diabète ; Albuminurie ; Protéinurie ; Insuffisance rénale chronique ; Système rénine angiotensine ; Épidémiologie ; Revue générale

1. Introduction


Mots clés : Diabète ; Albuminurie ; Protéinurie ; Insuffisance rénale chronique ; Système rénine angiotensine ; Épidémiologie ; Revue générale

1. Introduction

The natural history of diabetic nephropathy was defined in the 1980s on the basis of longitudinal studies of patients with type 1 and type 2 diabetes. These studies identified stages in the evolution of diabetic nephropathy, and led to the development of strategies of detection and guidelines for use in clinical trials and the identification of therapeutic targets in such patients, and also influenced how the natural history of diabetic nephropathy was taught. Evidently, however, a minority of diabetic patients can develop renal disease other than diabetic nephropathy, as occurs in any individual. More disturbingly, a growing number of studies have indicated that many diabetic patients do not present with the natural evolution described in the 1980s, particularly in terms of the relationship between the development of urinary albumin excretion (UAE) and the glomerular filtration rate (GFR), with some developing a progressive deterioration of renal function that is indeed due to diabetes, but without an evolution unlike that described in the 1980s. Also, it was long considered that there were only a few such patients, but recent findings indicate that this is not the case and, thus, raises pathophysiological, nosological and practical questions regarding kidney surveillance and treatment.

2. The conventional natural history of diabetic nephropathy

Four major studies on the natural history of diabetic nephropathy were reported between 1982 and 1984 [1–4]. In these prospective studies, the authors evaluated the predictive value of microalbuminuria in relation to the development of proteinuria in patients with type 1 diabetes monitored for 6–14 years. The definition of microalbuminuria varied according to the studies, but generally corresponded to a UAE of 15–70 µg/min. Proteinuria was defined as a UAE > 150 µg/min or proteinuria > 0.5 g/day. These studies concluded that the mean risk of passing from the microalbuminuria stage to the proteinuria stage (as defined in these studies) was 86% (range: 75–100%) over the period of follow-up.

In 1989, Hasslacher et al. [5] reported that the evolution of diabetic nephropathy was comparable in both type 1 and type 2 diabetes: 50% of patients with either type of diabetes developed proteinuria after 25 years of evolution of the disease, and a little over 50% of the patients with proteinuria developed renal insufficiency (defined as serum creatinine > 14 mg/L) within 5 years.

Thus, the subsequent teaching regarding the natural history of diabetic nephropathy included five well-known successive stages (Table 1). The findings of the United Kingdom Prospective Diabetes Study (UKPDS) provided more precise information regarding the probability of passing from one stage to another in newly diagnosed patients [6]. However, two other significant findings were emphasized in that study. First, the risk of mortality increased in parallel with worsening of renal disease, and the risk was greater from the microalbuminuria stage onwards (and even greater at the renal insufficiency stage) than the risk of passing to the next stage of diabetic nephropathy. These findings emphasized what subsequent studies have since consistently confirmed: markers of renal disease are not specific to renal risk, but are also markers of the risk of mortality, often from cardiovascular causes. Second, the risk of passing directly from the stage of normoalbuminuria to the microalbuminuria stage or to renal insufficiency was low, but real (0.1% per annum), and there was also a risk of passing directly from the microalbuminuria stage to renal insufficiency (0.3% per year). However, as the numbers were low, the guidelines for teaching the natural history of diabetic nephropathy remained the same [7].

3. Chronic kidney disease (CKD) without clinical proteinuria in diabetic patients

Nevertheless, ever since, the edifice has begun to crack. First, the UKPDS also showed that the risk factors for developing microalbuminuria and renal insufficiency were not the same: some were shared (raised blood pressure, smoking, poor control of diabetes, history of cardiovascular disease), whereas some were specifically related to the development of microalbuminuria (male gender, increased waist size and/or triglyceride levels) and others were specifically related to the development of renal insufficiency (raised cholesterol levels, age, elevated initial albuminuria and serum creatinine levels; Table 2) [7].

A meta-analysis of studies published mostly in the 1990s [35] indicated that 26% of type 1 diabetes patients with initial microalbuminuria became normoalbuminuric during follow-up (mean duration: 6 years; range: 1–23 years); the respective figures were 44% in children and teenagers, and 18% in type 2 diabetes patients (follow-up duration: 2–10 years). In contrast, only 19% of type 1 diabetes patients became macroalbuminuric.
Risk factors of both microalbuminuria and CKD

- Elevated arterial pressure
- Poor glycemic control
- Smoking
- History of cardiovascular disease

Risk factors of CKD (but not microalbuminuria)

- Male gender
- Elevated waist circumference
- High triglyceride levels

Risk factors of microalbuminuria (but not CKD)

- Male gender
- Elevated waist circumference
- High triglyceride levels
- Advanced age
- High serum creatinine
- Abnormal urinary albumin excretion

**Table 2**

Specific risk factors of microalbuminuria and chronic kidney disease (CKD) in United Kingdom Prospective Diabetes Study (UKPDS).  

<table>
<thead>
<tr>
<th>1st author</th>
<th>Journal (reference)</th>
<th>Type</th>
<th>Patients with MA (n)</th>
<th>Follow-up (years)</th>
<th>Remission/regression (%)</th>
<th>Progression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tabaei</td>
<td>Diabetes Care 2001 [19]</td>
<td>Type 1/Type 2</td>
<td>16</td>
<td>7</td>
<td>56</td>
<td>11</td>
</tr>
<tr>
<td>Perkins</td>
<td>NEJM 2003 [20]</td>
<td>Type 1</td>
<td>386</td>
<td>8</td>
<td>58</td>
<td>19</td>
</tr>
<tr>
<td>Hovind</td>
<td>BMJ 2004 [21]</td>
<td>Type 1</td>
<td>79</td>
<td>7.5</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Gaede</td>
<td>NDT 2004 [22]</td>
<td>Type 2</td>
<td>151</td>
<td>7.8</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Araki</td>
<td>Diabetes 2005 [23]</td>
<td>Type 2</td>
<td>216</td>
<td>8</td>
<td>51</td>
<td>28</td>
</tr>
<tr>
<td>Steinke</td>
<td>Diabetes 2005 [24]</td>
<td>Type 1</td>
<td>22</td>
<td>5</td>
<td>64</td>
<td>NA</td>
</tr>
<tr>
<td>Yamada</td>
<td>Diabetes Care 2005 [26]</td>
<td>Type 2</td>
<td>94</td>
<td>8</td>
<td>21</td>
<td>17</td>
</tr>
</tbody>
</table>

**Table 3**

Evolution of microalbuminuria in type 1 and type 2 diabetic patients in longitudinal studies in the 2000s.

<table>
<thead>
<tr>
<th>1st author</th>
<th>Journal (reference)</th>
<th>Type</th>
<th>Patients with MA (n)</th>
<th>Follow-up (years)</th>
<th>Remission/regression (%)</th>
<th>Progression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tabaei</td>
<td>Diabetes Care 2001 [19]</td>
<td>Type 1/Type 2</td>
<td>16</td>
<td>7</td>
<td>56</td>
<td>11</td>
</tr>
<tr>
<td>Perkins</td>
<td>NEJM 2003 [20]</td>
<td>Type 1</td>
<td>386</td>
<td>8</td>
<td>58</td>
<td>19</td>
</tr>
<tr>
<td>Hovind</td>
<td>BMJ 2004 [21]</td>
<td>Type 1</td>
<td>79</td>
<td>7.5</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Gaede</td>
<td>NDT 2004 [22]</td>
<td>Type 2</td>
<td>151</td>
<td>7.8</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Araki</td>
<td>Diabetes 2005 [23]</td>
<td>Type 2</td>
<td>216</td>
<td>8</td>
<td>51</td>
<td>28</td>
</tr>
<tr>
<td>Steinke</td>
<td>Diabetes 2005 [24]</td>
<td>Type 1</td>
<td>22</td>
<td>5</td>
<td>64</td>
<td>NA</td>
</tr>
<tr>
<td>Yamada</td>
<td>Diabetes Care 2005 [26]</td>
<td>Type 2</td>
<td>94</td>
<td>8</td>
<td>21</td>
<td>17</td>
</tr>
</tbody>
</table>

MA: microalbuminuria; remission/regression: to normoalbuminuria during follow-up; progression: to macroalbuminuria during follow-up; NA: not applicable.

This suggests that such patients do not represent just a small number of exceptions, but are rather a frequent occurrence, even in type 1 diabetes patients (Table 4) [8,10,11,15,27–33].

### 3.1. Impact of modifiable factors on renal disease risk associated with low levels of albuminuria in diabetes

In the absence of clinical trials, there are only observational studies to estimate the effects of modifiable factors on the risk of renal disease in diabetic patients. Analysis of the available studies indicates that two elements remain associated with the development of renal insufficiency and the increase in UAE: blood pressure and glycaemia levels (Table 5) [8,10,11,19–26,28–33]. However, any association with inhibition of the renin–angiotensin system, total cholesterol levels, weight, the metabolic syndrome and smoking appears less clear in these observational studies (Table 5).

### 3.2. Initial albuminuria and its evolution remain major predictors of renal risk in diabetes even in the setting of diabetic nephropathy-associated pauciproteinuria

A recent study involving 569 patients with type 1 diabetes and microalbuminuria or normoalbuminuria monitored for 8–12 years analyzed the initial decrease in eGFR [8]. An initial decrease of >5% was observed only in the 301 patients with microalbuminuria, whereas it was the exception in the 268 patients with normal albuminuria levels. Among patients with microalbuminuria, the evolution of UAE was a good predictor of the initial decline in renal function, which occurred in 16% of patients who developed microalbuminuria, in 32.2% of those who continued to have microalbuminuria and in 67.7% of those who progressed to the macroalbuminuria stage [9].

Similar results were found in the Diabetes Control and Complications Trial (DCCT): patients who had an eGFR <60 mL/min and remained below the threshold more often had macroalbuminuria (61%) than those who had normal albuminuria levels (24%) or microalbuminuria (16%) [10]. In patients monitored for more than 20 years, the speed of deterioration of renal function was more rapid in patients with macroalbuminuria that in those with normal albuminuria or microalbuminuria levels [10]. Also, the risk of end-stage renal...
Table 4
Percentage of diabetic patients with chronic kidney disease (CKD) and normoalbuminuria or microalbuminuria in studies published in the 2000s.

<table>
<thead>
<tr>
<th>1st author</th>
<th>Journal (reference)</th>
<th>Type</th>
<th>Patients (n) with GFR &lt;60 mL/min (n)</th>
<th>% Nalb</th>
<th>% MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kramer</td>
<td>JAMA 2003 [27]</td>
<td>Type 2</td>
<td>171</td>
<td>35</td>
<td>37</td>
</tr>
<tr>
<td>Caramori</td>
<td>Diabetes Care 2004 [28]</td>
<td>Type 2</td>
<td>109</td>
<td>39</td>
<td>35</td>
</tr>
<tr>
<td>McIsaac</td>
<td>Diabetes 2006 [29]</td>
<td>Type 2</td>
<td>1132</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>Yokoyama</td>
<td>Nephrology Dialysis Transplantation 2009 [31]</td>
<td>Type 2</td>
<td>506</td>
<td>73</td>
<td>21</td>
</tr>
<tr>
<td>Molitch</td>
<td>Diabetes Care 2010 [10]</td>
<td>Type 1</td>
<td>89</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>Afghahi</td>
<td>Nephrology Dialysis Transplantation 2011 [32]</td>
<td>Type 2</td>
<td>407</td>
<td>71</td>
<td>21</td>
</tr>
<tr>
<td>Penno</td>
<td>Journal of Hypertension 2011 [33]</td>
<td>Type 2</td>
<td>2959</td>
<td>57</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>mean</td>
<td></td>
<td></td>
<td>50</td>
<td>31</td>
</tr>
</tbody>
</table>

CKD: chronic kidney disease; GFR: glomerular filtration rate; Nalb: normoalbuminuria; MA: microalbuminuria; NA: not applicable; Type: type 1 or type 2 diabetes mellitus.

Disease or death was greater in patients with macroalbuminuria than in patients with diabetes (mostly type 2) and normal albuminuria or microalbuminuria [11]. In the diabetes patients with microalbuminuria included in the Irbesartan Microalbuminuria in Type 2 Diabetic Subjects (IRMA 2) study, which compared the effects of two doses of irbesartan on UAE vs. the effects of a placebo, the long-term decrease in eGFR was greater in patients with initially low rates of albuminuria than in patients whose albuminuria levels remained low or increased. Of the patients whose UAE increased, the decrease in eGFR was greater in those in whom the reduction in systolic blood pressure was less than the median [12].

Thus, the predictive value of microalbuminuria is important in patients with a renal evolution corresponding to the natural history, and is of significant predictive value for renal risk, cardiovascular complications and mortality, even in those in whom the progression of renal involvement is not typical [35]. This indicates that UAE and its changes remain important.

Table 5
Significant associations between selected parameters and development of microalbuminuria or chronic kidney disease (CKD) in diabetic patients without clinical proteinuria in the 2000s.

<table>
<thead>
<tr>
<th>1st author</th>
<th>Journal (reference)</th>
<th>Arterial pressure</th>
<th>RAS blockade</th>
<th>HbA1c</th>
<th>Triglyceride levels</th>
<th>Cholesterol levels</th>
<th>Smoking</th>
<th>Body weight (or metabolic syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caramori</td>
<td>Diabetes Care 2004 [28]</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>McIsaac</td>
<td>Diabetes 2006 [29]</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Retnakaran</td>
<td>Nephrology Dialysis Transplantation 2009 [31]</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Parving</td>
<td>Kidney International 2006 [30]</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Yokoyama</td>
<td>Nephrology Dialysis Transplantation 2009 [31]</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Afgahi</td>
<td>Nephrology Dialysis Transplantation 2011 [32]</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Perkins</td>
<td>Kidney International 2010 [8]</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Molitch</td>
<td>Diabetes Care 2010 [10]</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Penno</td>
<td>Journal of Hypertension 2011 [33]</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>

CKD: chronic kidney disease; RAS: renin-angiotensin system.
prognostic factors for a deleterious renal outcome even in those without proteinuria, although the rate of renal function decline appears to be lower in this situation than in the proteinuric form of diabetic nephropathy [9,10].

3.3. Renal histology in diabetic patients with chronic kidney disease (CKD) and no clinical proteinuria

For more than 20 years, it was accepted that patients with type 1 diabetes without proteinuria or hypertension could still have glomerular lesions such as glomerulosclerosis [13] and that renal biopsy in patients with microalbuminuria could be normal, or show thickening of the basal glomerular membranes or more severe tubular, vascular or glomerular lesions [14]. Currently, however, histological lesions do not allow the differentiation of patients who continue to have low levels of proteinuria despite progressive deterioration of renal function. A recent study has shown that such patients may also have advanced glomerular lesions despite the absence of proteinuria [15]. However, the use of the recently published international histological classification of diabetic nephropathy may perhaps clarify the issue [16], although the use of renal biopsy in diabetic patients is usually restricted to those with unexplained rapid deterioration of renal function or suspected secondary renal disease. Whether renal biopsy will be more frequently proposed for diabetic patients with CKD and normoalbuminuria or microalbuminuria is unlikely.

3.4. Practical implications

Modalities of detection and surveillance of diabetes patients were defined following the description of the natural history of diabetic nephropathy. Yet, while the natural history of diabetic patients who continue to have low levels of proteinuria is different, the detection and surveillance measures for these patients do not differ, as serum creatinine and UAE levels remain key elements. On the other hand, interpretation of the onset of microalbuminuria in a diabetic patient is more subtle: it does not always indicate progression to diabetic nephropathy; and it also has a greater tendency to regress to the stage of normal proteinuria levels than evolve to macroalbuminuria. However, its evolution provides important information on the outcome of the eGFR in patients with type 1 and type 2 diabetes.

UAE is often used in clinical trials as a marker of renal and cardiovascular risk; however, it is not possible to identify whether the patient with raised UAE is at risk of developing ‘classical’ diabetic nephropathy, diabetic nephropathy without overt proteinuria or no nephropathy at all. Thus, the use of this parameter in clinical trials should be questioned and discussed as a subject of methodological reflection [17].

Although there have been no dedicated clinical trials, the current findings concerning the deleterious roles of certain parameters are in agreement: they indicate that poor control of glycaemia and increased blood pressure are major elements associated with the decline of renal function in diabetes patients. They indicate above all that initial albuminuria and its evolution should be measured and should probably be therapeutic targets. On the other hand, it is still not certain that renin-system inhibition is effective in terms of renal protection in such patients, and the association between renal disease and other parameters (such as high cholesterol, overweight, the metabolic syndrome and smoking) is not always clear in the studies so far. It would be of interest to evaluate whether there is activation of the intrarenal renin–angiotensin system in such patients, as has recently been demonstrated [18].

In addition, in a recent report of 15,775 type 2 diabetes patients, the eGFR was < 60 mL/min in 18.7% of patients; of these, 57% had normoalbuminuria and 31% had microalbuminuria (Table 4); more important, retinopathy was absent in 70% of patients with eGFR < 60 mL/min and in 50% of patients with eGFR < 30 mL/min. This observation has important clinical implications [33].

4. Conclusion

Observational studies have identified another natural history of diabetic nephropathy particularly in type 1 and type 2 diabetes patients. However, it is not clear why some patients develop the ‘classical’ diabetic nephropathy with significant proteinuria, while others have impaired renal function associated with very low levels of proteinuria that sometimes persist as late as end-stage renal disease. This phenomenon may be due to renal vascular disease, as the intrarenal resistive index is greater in patients with type 2 diabetes and decreased GFR (regardless of UAE levels) than in patients with normal GFR [36]. In addition, their rate of evolution to end-stage renal disease is slower. Such patients are more often older, their duration of diabetes is longer and they more often have a history of cardiovascular disease than the patients described in the 1980s [33]. Indeed, diabetes may be considered an additional risk factor for deterioration of renal function related to age [34], as histological analysis has shown advanced glomerular lesions in diabetic patients with CKD despite the absence of significant proteinuria. These patients have often received renin-system inhibitors, although this observation does not completely explain the low UAE associated with CKD [33]. Nevertheless, over and above the nosological and pathophysiological uncertainties, the essential elements of surveillance remain the same: surveillance of glycaemia; and the control of blood pressure and initial albuminuria, and its evolution.

A recent publication has indicated that the number of patients with diabetes and renal disease are increasing with time in the US: the prevalence of diabetic kidney disease in the US population was 2.2% in the Third National Health and Nutrition Examination Survey (NHANES III), 2.8% in NHANES 1999–2004, and 3.3% in NHANES 2005–2008: the prevalence of CKD likewise increased from 14.9% to 17.7%. However, at the same time, the prevalence of albuminuria decreased from 27.3% to 23.7%, suggesting that more and more diabetic patients are likely to develop non proteinuric renal disease in the future [37].
Disclosure of interest

The author declares that he has no conflict of interest concerning this article.

References


