

## Mini Review Article

# Risk of falls in chronic kidney disease

Konstantina Papakonstantinou<sup>1</sup>, Ioannis Sofianos<sup>2</sup>

<sup>1</sup>Department of Nephrology, Korgialeneio- Benakeio Hospital, Athens, Greece

<sup>2</sup>Department of Rheumatology, Asklepieio Voulas Hospital, Athens, Greece

### Abstract

Chronic Kidney Disease (CKD) is known to be an important risk factor for accidental, low-energy falls especially among elder individuals. The high incidence of falls is a major cause of morbidity and mortality with a substantial annual cost. Patients suffering from CKD are more prone to fall and develop fractures than the general population. Multiple risk factors have been identified and analyzed in order to explain this fact, such as drug combination, diabetes mellitus, orthostatic hypotension, vitamin D deficiency, sarcopenia and anemia, all very common in CKD. In this mini review of published evidence, we tried to search and present a complete aspect of the problem called 'Falls in Chronic Kidney Disease', focusing especially on the risk factors, discussing each one separately and its association with low- energy falls. Concluding, we discuss potential therapies and treatment goals based on the pathophysiology of CKD and accidental falls and propose new fields of investigation.

**Keywords:** Chronic kidney disease, Accidental falls, End stage renal disease, Hemodialysis

## Introduction

It is estimated that approximately one third of the general population beyond the age of 65 years suffers from at least one fall every year<sup>1-3</sup> whereas half of them falls repeatedly<sup>3,4</sup>. This percentage increases to 35% after the age of 75 years<sup>4</sup>. Falls and their complications are the fifth leading cause of death in the developed world<sup>5</sup> with substantial cost<sup>6</sup>. More specifically in the United States the total cost of the fall-related fractures exceeds \$US10 billions<sup>7</sup>. Patients on hemodialysis are on greater risk of falling and fall- related complications<sup>3,8</sup>. Moreover, they have a three to four times greater risk for hip fractures compared to the general population<sup>8,9</sup>. The morbidity and mortality are higher in the hemodialysis population<sup>6</sup> and in peritoneal dialysis patients as well<sup>10</sup>.

### Definition of the fall

In order to evaluate the incidence and complications of a fall it is important to determine the exact definition of this term. There are differences between the definition of a fall given by health care providers and seniors. More specifically, seniors focus on the consequences of the fall and associate the loss of balance to the incidence, whereas health care providers talk about the fall event itself<sup>11</sup>. Both groups tend to include in the definition only injurious events with the risk of disregarding non-injurious falls. Thus, it is recommended that a definition of a fall is provided to patients when asked if they have fallen or not<sup>11</sup>.

## Fall-related injuries

According to a prospective cohort study that included hemodialysis patients, the proportion of falls that needed medical attention was 19%, with the majority of injuries being minor (bruises and lacerations). A 7% of the patients experienced head injuries, with loss of consciousness, a 4% sustained fractures and 4% died due to an injury produced by the fall<sup>2</sup>. Moreover, except physical injuries, falls and disequilibrium can lead to 'fear of falling' which further restricts every day activities<sup>8,12</sup>, leads to depression<sup>12</sup> and reduces physical exercise such as walking<sup>13</sup>.

## Fall risk

The risk of falling is multifactorial. Although previously divided into two categories<sup>8</sup> - intrinsic and extrinsic risk factors- the most recent literature broadly classifies them into three categories: intrinsic, extrinsic and exposure to

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**Corresponding author:** Konstantina Papakonstantinou, Bironos 37, Athens, Greece

**E-mail:** Konstantina.smad@gmail.com

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risk<sup>14</sup>. Table 1 shows the most important intrinsic risk factors. Women fall more frequently than men and Caucasians more than Afro-Caribbeans<sup>14</sup>. The use of more than 4 medication categories and a variety of medical conditions such as CKD, diabetes and depression are common among fallers<sup>14</sup>. Moreover, impaired mobility, muscle atrophy and vitamin D deficiency are important risk factors for accidental falls<sup>14</sup>.

Extrinsic are the environmental factors that may have impact on the fall incidence. These include poor lighting, stairs, slippery floor, inappropriate clothing and others<sup>8,14</sup>. Studies of risk exposure have revealed that either lack of activity or excessive physical activity can cause falls, fact that shows the complex relationship between falls and risk<sup>14</sup>.

End- Stage Renal Disease patients form a special category that not only may have similar intrinsic and extrinsic risk factors for falls with the general population, but also usually have many comorbidities, as well as special skeletal, hematological and endocrine abnormalities that expose them to a greater risk of falls and fractures<sup>12,15</sup>.

More specifically, vitamin D deficiency<sup>8</sup>, post-hemodialysis postural hypotension<sup>8</sup>, diabetic neuropathy, sarcopenia<sup>16,17</sup>, polypharmacy<sup>18,19</sup> have been proved to be important risk factors for the increased fall incidence of the CKD and HD population. The most important causes of accidental falls in renal disease are revised in Table 2. Onwards, we will try to briefly analyze them according to the most recent studies and publications.

### Use of drugs

Polypharmacy is no longer considered an independent risk factor for falls in the elders, however the type of medication used may increase the risk of falling<sup>19</sup>. As a high number of drugs per person are prescribed, omissions could occur which cause higher proportion of hospitalization<sup>19</sup>.

In a meta-analysis the impact of nine classes of medications was studied (antihypertensives, diuretics,  $\beta$ -blockers, sedatives/hypnotics, neuroleptics/antipsychotics, antidepressants, benzodiazepines, narcotic analgesics, NSAIDs) in elderly persons. The results revealed that elderly individuals were more prone to fall when prescribed antidepressants, benzodiazepines or sedatives and hypnotics<sup>5</sup>.

A retrospective case- control study conducted in hospitalized, CKD patients, found that this population experienced more falls when treated with antidepressant or anticonvulsant drugs. Additionally, medications for dementia have been implicated as a risk factor for falls. It is shown that patients suffering from dementia have higher falling risk<sup>19</sup>. The association of CKD with cognitive impairment and dementia has been suggested in cross- sectional and longitudinal studies<sup>20</sup>.

Another reason for the increased risk of falls in HD patients receiving many drugs is that hemodialysis itself, fluid balance disturbance and increased uremic toxins can change the pharmacokinetics of certain medications leading to interactions and side-effects<sup>21</sup>.

1.	History of falls
2.	Advanced Age
3.	Gender (women>men)
4.	Ethnicity
5.	Medicines
6.	Medical Conditions
7.	Impaired Mobility
8.	Sedentary behavior
9.	Psychological Status
10.	Nutritional Deficiency
11.	Impaired Cognition
12.	Visual Impairment
13.	Foot Problems

**Table 1.** Falls associated intrinsic risk factors. (Retrieved from Todd C. et al. 2004)<sup>14</sup>.

1.	Use of drugs
2.	Dementia
3.	Diabetes Mellitus
4.	Postural Hypotension
5.	Vitamin D Deficiency
6.	Sarcopenia
7.	Anemi

**Table 2.** Etiology of most important CKD associated falls.

Several criteria have been proposed in order to identify the Potentially Inappropriate Medications (PIMs) in elderly Hemodialysis Patients. A recently published study that used the STOPP criteria was able to identify a large number of PIMs in the hemodialysis population (the most prevalent being proton-pump inhibitors)<sup>21</sup>.

This fact makes us think that we can always revise our patients' medications so as to find and reduce those of them not appropriate.

### Diabetes mellitus

Diabetes is the leading cause of chronic kidney disease and the prevalence of diabetic nephropathy is steadily increasing from 1988 through 2008<sup>22</sup>.

Both high and low values of HbA1c can cause falls in diabetic patients<sup>23,24</sup>. It has been proved that achieving values of HbA1c  $\leq 6\%$  with insulin treatment increases the risk of falls as a result of hypoglycemic episodes<sup>23</sup>. On the other hand, a significant relationship exists between poor

glycemic control (values of HbA1c > 7%) and risk of falls. This is due to complications of diabetes such as peripheral neuropathy and visual impairment<sup>24</sup>.

Equally important is the special type of hypoglycemia that occurs in HD sessions affecting more often diabetic HD patients. This is the intradialytic hypoglycemia, which affects more often the diabetic renal patients, especially those who have achieved a better glycemic control<sup>25</sup>.

### Orthostatic hypotension (OH)

The relationship between orthostatic hypotension (decrease of 20 mmHg in systolic blood pressure or decrease of 10 mmHg in diastolic blood pressure from supine to standing position) and falls is not certain<sup>26,27</sup>.

Various studies have managed to show that orthostatic hypotension is a risk factor for falls. More specifically, the results of a longitudinal cohort study indicated that sustained orthostatic hypotension was an independent risk factor for future, unexplained and injurious falls<sup>27</sup>. In a prospective study of 844 elderly nursing home residents, OH was an independent risk factor for recurrent falls<sup>26</sup>.

Autonomic nervous system dysfunction has been also proved to lead to orthostatic and generalized hypotension<sup>28</sup>.

Again hemodialysis patients are a population with special characteristics and more reasons to suffer from episodes of postural hypotension and consequently more falls.

Hemodialysis patients have increased prevalence for both orthostatic hypotension and autonomic nervous system dysfunction<sup>28,29</sup>. OH is usually caused by the nature of HD treatment itself<sup>28</sup> (rapid fluid exchange) or by a possible underestimation of hemodialysis dry weight<sup>30</sup>. Moreover, autonomic dysfunction due to uremia, diabetes and amyloidosis is also common in dialysis-dependent patients and a risk factor for falls<sup>28,29</sup>.

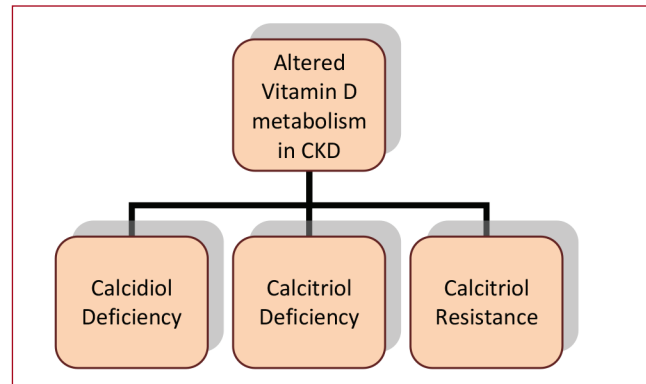
A better dry weight calculation, as well as a better diabetes and uremia control could be of significance in minimizing hypotensive episodes in this patient group.

### Vitamin D deficiency

Vitamin D is a fat-soluble secosteroid which plays a central role in calcium and phosphate metabolism. The effect of vitamin D on muscle strength, bone and falls has been studied in general population as well as in CKD patients and the results are discussed in this section.

Vitamin D deficiency is associated with muscle pain, myopathy<sup>31</sup> and reduction of the muscle strength<sup>32</sup>. Supplementation and correction of vitamin D deficiency can improve the strength of quadriceps muscle and thus reduce the incidence of the falls that are associated with mortality<sup>33</sup>. Moreover Vitamin D is essential for bone growth and higher bone density<sup>34</sup>.

The effect of vitamin D on falls has been studied in a meta-analysis which came to the conclusion that the supplementation of vitamin D reduces the risk of falls among ambulatory or institutionalized older individuals by more



**Figure 1.** The changes in vitamin D in chronic kidney disease.

than 20%<sup>35</sup>. The effect on muscles perhaps is due to de novo protein synthesis<sup>35</sup>. The combination with calcium may be of significance in reducing the risk of falls<sup>33,35</sup>.

Figure 1 shows the changes in vitamin D in Chronic Kidney Disease.

Chronic kidney disease can cause endocrine and mineral metabolism abnormalities even in early stages. Deficiency of 1,25 dihydroxyvitamin D [ $1,25(\text{OH})_2\text{D}_3$ ] due to hypohydroxylation of  $25(\text{OH})\text{D}_3$  by kidney 1  $\alpha$ -hydroxylase is one of them.  $1, 25(\text{OH})_2\text{D}_3$  (calcitriol) leads to hyperparathyroidism (HPTH) and parathyroid gland hyperplasia in CKD and ESRD patients<sup>36</sup>. Low levels of active vitamin D lead to impaired binding in the vitamin D receptor (VDR). The loss of VDR in the parathyroid glands is causing resistance to the action of calcitriol<sup>37</sup>.

CKD is also characterized by lower calcidiol, with reduced sun exposure, reduced skin production and loss of vitamin D binding protein (DBP) being the main reasons for these changes<sup>37</sup>.

Vitamin D deficiency is defined as a serum  $25(\text{OH})\text{D}$  level <20 ng/ml and insufficiency as between 21-29 ng/ml<sup>38</sup>. The optimal range remains controversial<sup>38</sup>. Among other consequences, low levels of vitamin D in chronic kidney disease and ESRD cause high bone turnover<sup>39</sup>, muscle weakness, higher risk of falls<sup>40</sup> and high mortality risk<sup>41,42</sup>.

The KDOQI guidelines recommend the administration of ergocalciferol and cholecalciferol to patients with CKD stage 3 to 4 if calcidiol levels are below 30 ng/ml<sup>43</sup> but further investigation is needed in order to identify the optimal levels of vitamin D, the appropriate regimen, dose and route of administration<sup>35</sup>.

### Sarcopenia

The term sarcopenia was coined by Irwin Rosenberg<sup>17</sup>. Derives from Greek 'sarx' that means flesh and 'penia' that means poverty. Sarcopenia is a component of the frailty syndrome, recognized by increased vulnerability as a result of age decline and compromised function across multiple

physiologic systems<sup>36</sup>. In its first definition sarcopenia was described as the muscle mass loss that occurs with advancing age<sup>16</sup>. Nowadays the definition has expanded to include muscle function and strength as well because in the elders the loss of muscle mass is only one reason for the loss of muscle strength among others, along with muscle atrophy and denervation of the muscle fibers<sup>16</sup>.

A healthy adult is losing 1% of muscle mass every year while CKD patients begin to do so in an earlier age<sup>44</sup>. Predisposing factors for this difference have to do either with kidney disease itself (metabolic acidosis, uremic toxins, mitochondrial dysfunction, inflammation, malnutrition, insulin resistance, increased ubiquitination, vitamin D deficiency, higher PTH levels<sup>38</sup>, physical inactivity<sup>15,17</sup>, calcium-phosphate disorders and proteinuria<sup>44</sup>) or with the inflammatory process following HD ( proinflammatory cytokines, oxidative stress)<sup>38,44,45</sup>. There is evidence that sarcopenia is associated with accidental falls: In a meta-analysis and systematic review of the health outcomes of sarcopenia it was shown that sarcopenic subjects were at a higher risk of accidental falls, fractures, hospitalization and longer hospital stay compared with non-sarcopenic subjects<sup>16</sup>. Moreover, loss of lean body mass weight is known to cause frequent falls and their complications<sup>46</sup>. It is therefore easy to understand that sarcopenia in CKD is of importance in CKD associated fall pathology but more research is needed focusing on this special population.

### Anemia

The World Health Organization (WHO) defines anemia as a hemoglobin (Hb) <12 g/dl in females and <13 g/dl in males<sup>40</sup>. Anemia in chronic kidney disease patients was described 170 years ago by Richard Bright<sup>41</sup>. Now we know that anemia is a common feature of CKD and affects almost all patients with stage 5 CKD<sup>42</sup>. The development of anemia in CKD is multifactorial related to lower levels of erythropoietin, inhibition of erythropoiesis by uremic toxins, disordered iron homeostasis and erythrocyte survival<sup>43</sup>.

The association between anemia and the risk of falls is ambiguous. There are studies that relate falls to anemia and others that do not come to this conclusion. For instance, two studies in older adults - hospitalized or in the community-managed to show an important link between anemia and accidental falls<sup>47,48</sup>. On the other hand, this independent association has not been always proved<sup>49</sup>, which makes it a promising field for further investigation.

### Discussion

In this mini review we tried to collect information about accidental, low-energy falls in chronic kidney disease population using published evidence. According to our investigation falling is a major clinical problem in elders, thus not only an important issue in every day clinical practice but also a big economic burden for the health system of a country. Chronic kidney disease and End Stage Renal Disease

patients have a higher risk of falls, fall-related fractures, hospitalization and mortality.

These patients are prone to falls and their complications for many reasons. Kidney disease is associated with hormonal, bone and hematologic abnormalities. The excessive use of drugs in this patient category, especially that of antidepressants and hypnotics, as well as the higher incidence of diseases such as dementia are some of them. Moreover the complications of diabetes mellitus (i.e. diabetic neuropathy) are a major risk factor, keeping in mind that diabetes is the first cause of ESRD.

Accidental falls due to postural hypotension are common in HD, especially when dry- weight is underestimated.

Many studies concentrate on the importance of vitamin D and its relation with falls. The results of these studies conclude that vitamin D deficiency, - a very common complication of CKD- and secondary hyperparathyroidism can result in muscle weakness and injurious falls and that treatment of patients with CrCl <65 ml/min with alfacacicol can reduce the risk of falls and number of fallers<sup>50</sup>.

It is also of great interest the investigation of anemia and sarcopenia of CKD and their possible relation with falls. More studies need to be done in order to have safe conclusions, but better control of the CKD abnormalities (such as metabolic acidosis, anemia) and muscle strength exercises seem to be reasonable solutions to this problem. Pharmacologic interventions that inhibit muscle wasting are in trials and research is needed in CKD population.

Moreover, progressive kidney disease is accompanied by an unhealthy lifestyle. It is estimated that for every month of hemodialysis the physical activity decreases by 3, 4%<sup>51</sup>. It has been shown that certain type of exercise on non- hemodialysis days is an interesting rehabilitation method for HD patients, providing a chance of better quality of life and lesser falls<sup>52</sup>.

For some of the issues mentioned above, the evidence is controversial and further studies are needed in order to get to safe results and conclusions. Recognizing the most important risk factors for accidental falls is necessary in order to find the appropriate prevention measures and therapies.

One limitation of our research is that there is little evidence concerning chronic kidney disease patients Stages 1-4. The majority of researches on accidental falls are performed in HD population. This observation leads us to the conclusion that more studies should be done focusing on patients on less severe stages of CKD as well as renal transplant patients, so that we can have a better understanding of the problem.

### Conclusion

Falls are extremely common among hemodialysis patients. Fall prevention has been found to be possible through review of the medications, orthostasis prevention, muscle strengthening, better glycemic control and vitamin D deficiency treatment. Further research is needed for the improvement of methods to prevent accidental falls as well as in order to include patients with less severe kidney disease.



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