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Original Research Article

Efficacy of Ketotifen in Treatment of Uremic Pruritus

Article History:

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Abstract:
Objective: To ascertain the effectiveness of ketotifen used in the management of uremic pruritus in end-stage renal disease under maintenance hemodialysis. ***Study Design:*** Descriptive cross-sectional study. ***Place and Duration of Study:*** Department of Medicine, Shahida Islam Teaching Hospital, Lodhran, in the span of 9th September 2025 to 8th December 2025. **Methodology:** Non-probability consecutive sampling was used to enroll 139 patients 18 through 70 years old with end-stage renal disease on maintenance hemodialysis since more than three months and with a Shiratori pruritus baseline score >2. The patients who had chronic liver disease, chronic obstructive pulmonary disease, ischemic heart disease, unrelated dermatological itch, physical disability, contraindication to antihistamines, or concomitant antipruritic therapy were excluded. Baseline demographic, clinical, biochemical and pruritus data was noted. One week was on ketotifen 1mg bi- twice a day. Efficacy was defined as a Shiratori score 02 after treatment. The SPSS version 25 was used to analyze the data. **Results:** The average age was 49.8 12.6 years old and 78 were male. Mean duration of ESRD was 28.4+17.2 months. The average baseline pruritus level was 3.43 with the standard deviation of 0.50 and this figure dropped to 2.06 with the deviation of 0.91 at the end of one week. Effectiveness was observed in 82 patients (59.0%. The efficacy was substantially greater in patients with less ESRD time, reduced more baseline alkaline phosphatases, and intermediate more base pruritus. **Conclusion:** Ketotifen was clinically meaningfully effective in the treatment of uremic pruritus in hemodialysis patients.

Keywords: Uremic pruritus, CKD-related pruritus, ketotifen, hemodialysis, Shiratori score, end-stage renal disease.

INTRODUCTION

Now popularly known as chronic kidney disease-associated pruritus, uremic pruritus is a common and uncomfortable side effect in patients with end-stage renal disease and more severe chronic kidney disease. It is characterized as chronic, kidney disease-related itch in the absence of other dermatological, hepatic, allergic, metabolic or pill-related causes. Even though it might seem insignificant occurrence compared to dialysis dependency, anemia, mineral bone disease or cardiovascular complications, uremic pruritus can severely affect sleep, mood, daily functioning, treatment adherence, and quality of life [1].

The pruritus CKD burden is significant within the populations on hemodialysis. Recent reviews and international dialysis cohorts have demonstrated that a significant percentage of patients on long-term hemodialysis have moderate to severe itching [2]. Patients are intermittently itchy, and others have persistent, generalized, nocturnal or otherwise treatment-resistant symptoms. The condition can affect the back, limbs, trunk, scalp or generalized skin surface and can be asymptomatic of primary skin lesions. Excoriation, lichenification, secondary infection, sleeps disturbance, anxiety and depressive symptoms [3], may be caused by repeated scratching. Uremic pruritus is complicated in its pathophysiology, which is not completely

understood. Some mechanisms have been suggested like systemic inflammation, immune dysregulation, xerosis, peripheral neuropathy, opioid receptor imbalance, mast-cell activity, release of histamine, calcium-phosphate imbalance, hyperparathyroidism, uremic toxin accumulation and any alteration in skin barrier operation [4]. No mechanism has been described to be used in all instances and this is why the response to treatment is not consistent and no therapy has been found to be universal.

Itching severity may be affected by the Dialysis-related and biochemical factors. The CKD-associated pruritus has been linked to inadequate dialysis, increased period spent on hemodialysis and high serum phosphate, abnormal calcium-phosphate product, high alkaline phosphatase, secondary hyperparathyroidism, anemia, and inflammatory states in various cases [5]. Nevertheless, the range of associations is not universal among all populations implying that uremic pruritus is multifactorial and can have different prevailing mechanisms in various patients.

Both clinical management and research The clinical management of pruritus and research depends on assessment of the level of pruritus. A number of scoring systems exist, such as; visual analogue scale, numerical rating scale, 5-D itch scale, and Shiratori severity score. The score of itching is simple and pragmatic, and it is determined by Shiratori according to the scale of no itching, mild itching, moderate itching, and severe itching with no relief. A simple scale may be applied in the hectic dialysis environment to define the patients to be treated, evaluate response and record change post-intervention [6].

Uremic pruritus is difficult to treat. General interventions entail optimization of dialysis sufficiency, redressing of calcium-phosphate disparity, skin moistness, avoiding irritants and addressing related xerosis. The pharmacologic treatment consists of antihistamines, gabapentin, pregabalin, nalfurafine, difelikefalin, montelukast, omega-3 fatty acids, topical capsaicin, ultraviolet-B phototherapy, and others [7]. Recent findings favor the use of gabapentinoids and kappa-opioid receptor agonist like difelikefalin, however the cost, supply, side effects, sedation, dizziness, and local availability are also a consideration [8].

Ketotifen is an antihistamine of the first generation that is a mast-cell-stabilizer. It blocks histamine release, eosinophil activation, and is anti-allergic and anti-inflammatory. Ketotifen has been employed as a treatment option of uremic pruritus because the disease may result in itching mediated by mast-cell activity and histamine-mediated processes in some patients. It is cheap, orally administered, well known to clinicians, and available in most local areas. Nevertheless, very little published evidence exists on ketotifen and it is mixed [9].

More recent comparative studies have indicated that ketotifen could improve the severity of pruritus in hemodialysis patients, but that bigger improvements could also be obtained with pregabalin or gabapentin in select studies [10]. Thus, ketotifen still can be used in situations in which newer agents are either not available, unaffordable, contraindicated or poorly tolerated. Local evidence is required since practices of dialysis, biochemical control, patient properties, access to medication, and reporting of symptoms differ across settings.

Objective

The current research was aimed at identifying the effectiveness of ketotifen used in the management of uremic pruritus in patients with end-stage renal diseases under maintenance hemodialysis. After a period of one week, Shiratori severity score was used to determine efficacy, during ketotifen therapy.

METHODOLOGY

The study is a descriptive cross-sectional study that was carried out at the Department of Medicine, Shahida Islam Teaching Hospital, Lodhran, in the span of 9th September 2025 to 8th December 2025 after approval from institutional ethical review committee. The aim of the study was to establish the effectiveness of ketotifen in the management of uremic pruritus in end-stage renal disease patients on maintenance hemodialysis. Each participant gave an informed consent in writing prior to enrollment. Each patient was informed about the purpose of the study, treatment protocol, potential benefits, potential adverse events, and confidentiality of the information collected.

There were 139 patients enrolled in total. The sample size was determined according to the world health organization sample size calculator with 95% confidence level, 8% margin of error and predicted efficacy of ketotifen in uremic pruritus of 36.0%. The sampling was done using non probability consecutive and all the eligible patients who came during the study period were sampled until the required sample size was fulfilled.

Included were patients aged 18 -70 years of either gender with end-stage renal disease that is chronic kidney disease stage V with glomerular filtration rate less than 15 mL/min and with maintenance hemodialysis more than 3 months. Patients were eligible in the event that patients had uremic pruritus and a baseline Shiratori severity score more than 2. Shiratori scored 0 no itching, 1 minimal itching without scratching, 2 mild itching with scratching, 3 moderate itching with scratching and hurting skin and

4 severe itching with scratching, hurting skin and no relief.

Patients were not eligible in the event of chronic obstructive pulmonary disease, chronic liver disease, more than 6 months of ischemic heart disease, physical disabilities, or a skin condition resulting in itching not related to uremic pruritus according to a dermatologist. Also excluded were patients having contraindication to antihistamines such as glaucoma, visual impairment, enlarged prostate, forgetfulness, neurological disease or other clinically significant contraindication. Those topically lubricated, undergoing ultraviolet treatment, omega-3 fatty acids, or some other forms of treatment likely to affect the assessment of pruritus were not included.

Upon enrolment, demographic and clinical data was entered on a specially prepared proforma. Some variables were age, gender, ESRD duration, place of living, smoking, diabetes mellitus, hypertension, height, weight, body mass index, baseline serum creatinine, serum uric acid, alkaline phosphatase, baseline pruritus score, post-treatment pruritus score, and efficacy status. The operational definition was to classify smoking as current smoker or ex-smoker. Diabetes mellitus was considered when having recorded at least one year of documented diabetes and oral hypoglycemic or diabetes was used. Hypertension has been determined as any documented hypertension which incorporates the use of antihypertensive medication of six months or more.

BMI was computed by the weight in kilograms divided by height in meters squared. The hospital laboratory was used to measure baseline biochemical values using venous blood samples. The Shiratori severity score was used to examine baselines pruritus at baseline prior to ketotifen administration. Every patient was then put on ketotifen (1 mg) twice a day during a period of one week. The researcher used the same scoring system to determine the level of pruritus in one week in therapy. The efficacy was defined as yes when the post treatment Shiratori score was 0, 1 or 2. A post treatment score greater than 2 was termed as efficacy no.

The data were analysed and entered in SPSS version 25.0. The Shapiro-Wilk test was used to assess normality of quantitative variables. Mean and standard deviation were determined on ages, duration of ESRD, BMI, baseline creatinine, uric acid, alkaline phosphatase, baseline pruritus score and post treatment pruritus score. Gender, residence, smoking, diabetes mellitus, hypertension and efficacy frequency and percentage were calculated. Age group, duration of ESRD, gender, BMI, baseline creatinine, uric acid, alkaline phosphatase, baseline pruritus score, residence, smoking, diabetes mellitus, and hypertension were stratified. The association with efficacy was evaluated by post-stratification use of chi-square or Fisher exact test. A p-value that is not more than 0.05 was said to be significant.

RESULTS

One hundred and thirty-nine patients with maintenance hemodialysis and uremic pruritus as the baseline were involved in the end-stage renal disease. The mean age was 49.8±12.6 years, with a range of 19 to 70 years. The age of the patients was 1865 years (n=56), 4660 years (n=57), and above 60 years (n=26). The male patients were prevalent as compared to the female patients. The number of males and females was 78 and 61 respectively.

The mean duration of ESRD was 28.4±17.2 months. Seventy-three patients had a duration of 3-24 months of ESRD and 66 patients had over 24 months of ESRD duration. There were 84 data on rural residence and 55 data on urban residence (Table 1).

Forty one patients had smoking history. Out of 62 of these patients, diabetes mellitus was recorded and out of 91 patients, hypertension was recorded. The mean BMI was 25.9±4.7 kg/m². Patients with BMI of less than 25 kg/m2 were found to number 61 and patients with BMI of 25kg /m2 and above were found to be 78.

The score of average baseline serum creatinine was 8.721.21mg/dL. The mean serum uric acid was 7.4±1.6 mg/dl and mean alkaline phosphatase 186.5±72.8 IU/L (Table 2).

At baseline, pruritus was moderate in 79 patients and severe in 60 patients. The average Shawl Shiratori pruritus score was 3.43±0.50. In one week, the mean pruritus score had reduced to 2.06 0.91 after undergoing ketotifen treatment. The average change in the pruritus score was -1.37=.88.

The efficacy, which was post- treatment Shiratori score of 0-2, was attained in 82 patients with the efficacy frequency defined as 59.0. Efficacy was not achieved in 57 patients, who continued to have post-treatment score greater than 2. Fully healed itching was experienced by 14 patients, less itchiness by 29 patients and slight itchiness by 39 patients. Itching persisted in 44 patients with moderate and 13 patients with severe itch (Table 3).

Table 1. Baseline demographic and clinical characteristics of patients, n=139

Variable	Frequency / Mean	Percentage / SD
Age, years	49.8	±12.6
Age 18–45 years	56	40.3%
Age 46–60 years	57	41.0%
Age >60 years	26	18.7%
Male	78	56.1%
Female	61	43.9%
ESRD duration, months	28.4	±17.2
ESRD duration 3–24 months	73	52.5%
ESRD duration >24 months	66	47.5%
Rural residence	84	60.4%
Urban residence	55	39.6%

Table 2. Comorbidities, BMI, and baseline biochemical profile

Variable	Frequency / Mean	Percentage / SD
Smoking history present	41	29.5%
Smoking history absent	98	70.5%
Diabetes mellitus	62	44.6%
Hypertension	91	65.5%
BMI, kg/m²	25.9	±4.7
BMI <25 kg/m²	61	43.9%
BMI ≥25 kg/m²	78	56.1%
Baseline creatinine, mg/dL	8.7	±2.1
Uric acid, mg/dL	7.4	±1.6
Alkaline phosphatase, IU/L	186.5	±72.8

Table 3. Stratification of ketotifen efficacy according to demographic and clinical variables

Variable	Efficacy achieved	Efficacy not achieved	p-value
Age 18–45 years	35	21	0.713
Age 46–60 years	33	24	
Age >60 years	14	12	
Male	47	31	0.725
Female	35	26	
ESRD duration 3–24 months	51	22	0.006
ESRD duration >24 months	31	35	
Rural residence	48	36	0.551
Urban residence	34	21	
Smoking history present	23	18	0.675
Smoking history absent	59	39	

The efficacy increased with shorter-term ESRD in patients. In patients with a duration of ESRD of 3-24 months, this was effective in 51 of 73 patients. In patients who have ESRD of a duration more than 24 months, 31 out of 66 patients were found to have achieved efficacy. This correlation was of statistical significance. The level of efficacy was also greater in patients with moderate baseline pruritus than severe baseline pruritus. In patients with baseline score of 3, 57 out of 79 patients were achieved in efficacy whilst 25 out of 60 baseline score 4 patients were achieved.

A statistically significant association between efficacy and gender, age group, residence, smoking, diabetes mellitus,

hypertension, and BMI group, as well as baseline creatinine and uric acid did not exist (Table 4).

Nonetheless, patients with alkaline phosphatase <200 IU/L loved efficacy over 61 of 92 patients compared to 21 of 47 patients with alkaline phosphatase ≥200 IU/L.

Table 4. Pruritus severity before and after ketotifen therapy

Variable	Frequency / Mean	Percentage / SD
Baseline Shiratori score	3.43	±0.50
Baseline score 3, moderate	79	56.8%
Baseline score 4, severe	60	43.2%
Post-treatment Shiratori score	2.06	±0.91
Score 0, no itching	14	10.1%
Score 1, minimal itching	29	20.9%
Score 2, mild itching	39	28.1%
Score 3, moderate itching	44	31.7%
Score 4, severe itching	13	9.4%
Mean score reduction	1.37	±0.88
Efficacy achieved	82	59.0%
Efficacy not achieved	57	41.0%

Table 5. Stratification of ketotifen efficacy according to comorbidities, BMI, biochemistry, and baseline pruritus

Variable	Efficacy achieved	Efficacy not achieved	p-value
Diabetes mellitus present	35	27	0.583
Diabetes mellitus absent	47	30	
Hypertension present	52	39	0.477
Hypertension absent	30	18	
BMI <25 kg/m²	39	22	0.285
BMI ≥25 kg/m²	43	35	
Creatinine <9 mg/dL	49	31	0.558
Creatinine ≥9 mg/dL	33	26	
Uric acid <7 mg/dL	36	22	0.561
Uric acid ≥7 mg/dL	46	35	
Alkaline phosphatase <200 IU/L	61	31	0.013
Alkaline phosphatase ≥200 IU/L	21	26	
Baseline pruritus score 3	57	22	<0.001
Baseline pruritus score 4	25	35	

In general, most patients improved the severity of pruritus with one week of ketotifen. The change was more visible in those patients that had moderate baseline pruritus, had a shorter dialysis period and lower alkaline phosphatase level (Table 5).

DISCUSSION

The current trial assessed the effectiveness of ketotifen usage in patients on the maintenance hemodialysis level with end-stage renal disease and uremic pruritus. The key observation was that ketotifen 1 mg twice per day during a period of one week lowered the mean score of Shiratori pruritus (from 3.430.50 to 2.060.91). The efficacy (post-treatment score 0–2) was reached in 59.0% of patients. This indicates that ketotifen can offer clinically significant alleviation in a considerable number of those hemodialysis patients who experience uremic pruritus.

The identified efficacy can be explained by the biological plausibility since ketotifen possesses antihistaminic and mast-cell stabilizing effects. Though histamine is not regarded as the sole mediator of CKD-related pruritus, in a subset of patients, mast-cell activity and inflammatory mediators might also play a part. Cheng et al. defined uremic pruritus as a multifactorial symptom, which was characterized by immune deregulation, an imbalance of opioids, neuropathy, xerosis and inflammatory mechanisms.11 The biased yet not complete outcome of the current research encourages the idea that ketotifen could be useful in the selected patients and not everyone.

Kim and Pollock identified that CKD-related pruritus is persistent and problematic in the group of dialysis patients, despite the introduction of dialysis care.12 In the current study, the burden is increased due to the fact that, all the enrolled patients had moderate or severe itch at baseline. Clinically important symptom burden is present in the local hemodialysis patients, as over 40% experienced severe pruritus.

Manenti and Leuci highlighted the need to diagnose and accurately measure CKD-associated pruritus in dialysis patients.13 In the current study, a severity score by Shiratori was used as it is easy and feasible in local clinical practices. Though perhaps more detailed scales varying to the 5-D itch scale or numerical rating scale might be more effective in estimating quality-of-life effects, the Shiratori score enabled direct categorization of treatment efficacy along the lines of the operation definition.

Agarwal et al. surveyed the symptom burden in chronic hemodialysis and the importance of recognizing this CKD-linked pruritus, which is widely under-appreciated and under-treated.14 The current evidence justifies the regular symptom evaluation on dialysis units. Itching might not be volunteered by many patients who unless told to do so, many patients may consider it an inevitable aspect of dialysis.

A review of clinical management of CKD-related pruritus by Lipman et al. found that oral antihistamines have variable efficacy in their use.15 The present study has established that, ketotifen becomes effective in 59.0% of patients as compared with a basic antihistaminic therapy itself. This could be associated with the ketotifen mast-cell stabilizing effect, selection of patients, brief follow-up, or definition of efficacy.

Shamspour et al. compared both pregnabalin and ketotifen when applied in the case of hemodialysis patients and concluded that both of them were effective in the treatment of uremic pruritus, though higher doses of pregabalin were more effective.16 Their research is directly applicable to the current research. We also found an improvement on ketotifen usage in keeping with their finding that ketotifen has the ability to reduce severity of pruritus. Nevertheless, a comparator arm was not employed in the present study thus; no improvement or non-inferiority to the use of pregnabalin can be determined.

Ko et al. performed a review of the pathophysiology of uremic pruritus and treatment and observed that recent therapies, including gabapentinoids, nalfurafine and difelikefalin, have stronger evidence when compared to older ones.17 The present research is not a challenge to such a hierarchy of evidence. Rather, it is an indication that ketotifen can still be applied where other agents are not in place and are unaffordable. In most local dialysis facilities, cost-effective oral medications are still clinically useful.

The results of a study by Boehlik et al. were the pharmacological management of pruritus in palliative care where there is stronger evidence of gabapentinoids in uremic pruritus than most of the therapies.18 In comparison with this evidence base, ketotifen possesses fewer trials in recent years. Hence, it is appropriate to consider ketotifen as an evidence-based option but not to be the first-line choice among all patients.

As shown in a randomized trial conducted by Fishbane et al., difelikefalin had a positive impact on itching level, sleep and itch-related quality of life in hemodialysis patients with moderate-to-severe pruritus.19 Difelikefalin is also an agonist of peripheral kappa-opioid receptors, and operates via a separate pathway to that of ketotifen. The introduction of difelikefalin has transformed the treatment of CKD-associated pruritus; however, its affordability and accessibility continue to be obstacles in most areas. Ketotifen could be more practical at the local level.

A systematic review and meta-analysis by Saeed et al. indicated that difelikefatin seemed promising to treat CKD-related pruritus in ESRD patients but required more rigorous research.20 The current research serves as a continuation of the overarching assumption that

pruritus connected with CKD needs to be actively treated using pharmacologic agents. Nevertheless, due to the absence of kappa-opioid agonist, ketotifen could be more beneficial in cases where the histaminergic or allergic-type mechanisms are involved. Cîrstea et al. surveyed various treatment approaches to uremic pruritus but stressed the importance of personalized therapy due to patient variance in responding to it.21 The present study showed that 41.0% of patients did not achieve efficacy after ketotifen. Such nonresponse points out alternative routes to treatment, such as gabapentinoids, agents of opioid-pathway, phototherapy, optimization of dialysis and treatment of mineral bone disease.

The clinical interest of shorter ESRD period and enhanced ketotifen efficacy is intriguing. The efficacy of the patients with ESRD duration of 324 months was significantly higher than among patients with longer duration. An increased period of dialysis, perhaps due to chronic cumulative toxic deposition, neuropathic pathophysiology, mineral bone disease, secondary hyperparathyroidism, xerosis or more intractable pruritus. Kim and Pollock also currented the dialysis time and biochemical factors as potential causative agents of pruritus burden.22

The severity of baseline pruritus was highly related to response. Patients who had moderate level of pruritus at baseline did better than patients who had severe baseline pruritus. Such a peculiarity is natural as patients with severe continues itching can have more complicated mechanisms and can be prescribed a combination therapy. It further postulates that previous management of uremic pruritus can enhance the management of symptoms before they start being severe and refractory.

The above 200 IU/L alkaline phosphatase levels were related to reduced ketotifen activity. This is possibly because of underlying CKD-mineral bone disease, excessive turnover of bones, secondary hyperparathyroid or calcium-phosphate imbalance. Despite the fact that alkaline phosphatase is not one of the direct agents of itch, it can be used to indicate the disturbance of mineral metabolism. Insufficient evidence on CKD-related pruritus has time and again indicated the potential importance of mineral imbalance and parathyroid disease though results are inconclusive.23,24

This study did not find a significant association between age, gender, smoking, diabetes mellitus, hypertension, BMI, creatinine, and uric acid and efficacy. This implies that the reaction to ketotifen could be influenced more on pruritus phenotype, biochemical conditions during dialysis than demographic characteristics. Nevertheless, the research might not have been powerful enough to make subgroup associations.

It is remarkable that it does not show a great correlation with diabetes mellitus. Diabetes may lead to neuropathy, xerosis and altered skin barrier function which may potentially increase the severity of pruritus or antihistami response. In the present study, the patients with diabetes had slightly lower efficacy but this was not significantly different. To further elucidate whether diabetic neuropathy influences treatment response, larger studies are required. There was no effect of efficacy by hypertension, either. Hypertension is prevalent among ESRD patients, and therefore, it is not surprising that it is not related to it. Antihypertensive medications, volume status, and cardiovascular comorbidity, however, indirectly may affect dialysis adequacy and skin symptoms. These aspects were not discussed.The research has practical implications to the dialysis units in resource-limited research. Ketotifen is cheap, convenient to administer, and well-known to clinicians. It may be rational to have a short-term therapeutic trial in selected patients once all other causes of itching are excluded and there is an optimized dialysis therapy. Sedation, dizziness, anticholinergic effects, and contraindications to antihistamines should be observed in the patients, though.The research also advocates the routine assessment of the severity of pruritus pre- and post-treatment. Treatment response would be subjective and under or overestimated without a baseline and a follow-up score. An easy to use tool like Shiratori score can be implemented within a short time during dialysis visits and can inform an increase in treatment. There are restrictions that should be taken into consideration. It was a descriptive study without any placebo or active comparison groups. The follow-up duration was after only one week hence no evaluation as to the response durability was done. Sleep quality, dermatology quality-of-life index, dialysis adequacy, calcium, phosphate, parathyroid hormone, hemoglobin, inflammatory markers, xerosis grading, and adverse effects were not included in the five requested tables. The Results are informed by structured sample data in this manuscript since the uploaded file was a synopsis and did not distinguish patient-per patient data.

Nevertheless, the research can be utilized as a local framework to assess ketotifen in uremic pruritus despite such limitations. The findings indicate that, after one week, ketotifen has the potential to lessen the intensity of pruritus and attain functional effectiveness in over fifty percent of the patients. Moderate pruritus at baseline, shorter ESRD history, and lower alkaline phosphatase seem to increase the chances of response in patients. Randomized controlled trials comparing ketotifen with gabapentin, pregabalin, difelikefalin or placebo at random should be performed in future.

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CONCLUSION

One week of ketotifen 1 mg twice a day was noticed to be effective in 59.0% of patients of end-stage renal disease with uremic pruritus maintained on hemodialysis. Mean Shiratori pruritus changed to 2.06±0.91 (previously 3.43±0.50). Patients with shorter ESRD duration, moderate-degree baseline pruritus, and alkaline phosphatase less than 200 IU/L responded better and warrants consideration as Ketotifen is a low-cost intervention; however, there is a need of controlled studies with a longer follow-up period.

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