Research Article

Effect of Zinc Supplementation on Renal and Sexual Function of Men with Diabetic Nephropathy and Impotence, a Randomized Double-Blind Cross Over Clinical Trial

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ABSTRACT

Background: Free radical generation and oxidative stress has been hypothesized to be underlying pathogenesis of diabetic complications like nephropathy and erectal dysfunction. Zinc can reduce lipid per-oxidation and improves endothelial functions.

Objectives: In this study, we evaluated the effects of Zinc supplementation on the renal and sexual function of men with Type 2 diabetes.

Methods: The study registry code (www.irct.ir) IRCT138806091179N3.

Fifty adult type 2 diabetic men with diabetic nephropathy and erectal dysfunction were enrolled in double-blind, randomized trial. Twenty-five patients received 30 mg Zinc-sulfate per day and the remaining subjects received placebo for three months. Body mass index, Fasting Plasma Glucose (FPG), (BMI), Blood Pressure (BP), HbA1C, lipid profiles, level of Creatinine (Cr), testosterone hormone and zinc concentrations were measured at base and end of study. Albumin/Creatinine Ratio (ACR) and Glumerular Filtration Rate (GFR) were calculated for all the participants. Sexual dysfunction was determined with International Index for Erectile Dysfunction questionnaire (IIEF-5).

Results: Slight non-significant reduction versus a minimal non-significant increase in mean of ACR was seen with Zinc supplementation and placebo respectively (-3.7 ± 17.1 µg/mg vs. 2.8 ± 21.4 µg/mg; P= 0.130. Additionally Zinc supplementation had no effect on GFR and also erectile dysfunction of diabetic patients. However, significant improvement in FPG, HbA1c, total cholesterol and HDL-cholesterol concentration were seen with zinc supplementation (p:0.03).

Conclusion: The results suggest that albuminuria, GFR and erectile function of men with type 2 DM cannot be affected by Zinc supplementation in dose of 30mg/day. More investigations with large population are needed.

INTRODUCTION

A major cause of morbidity and mortality in the patients with documented diabetes mellitus is diabetic nephropathy [1,2]. In both diabetes type I and II, the clinical course of pathological changes in the kidney, and the risk of nephropathy development are quite similar [3]. Tight control of blood glucose level reduces the risk of diabetic nephropathy and other complications [4,5]. Renal function decline has been relation with age, sex, the initial GFR, initial Urinary Albumin Excretion rate (UAE), glucose level and blood pressure [6,7]. Endothelial dysfunction and changes in vascular permeability are considered as the first steps of diabetic nephropathy. Additionally

renal microvascular changes may be accompanied by other microvascular complications of DM like retinopathy, neuropathy and sexual dysfunction.

On the other hand, it has been reported that near half of men with type 2 diabetes over age 65 suffer from erectile dysfunction [8]. Duration of diabetes, poor glycemic control, higher Body Mass Index (BMI), smokers and those with other diabetes micro or macrovascular complications like nephropathy are other risk factors of erectile dysfunction.

Erectile dysfunction in diabetic men may be result of neuropathy, endothelial dysfunction and smooth-muscle changes which can be all together the harmful effects of free radicals and lack of antioxidants [9].

Free radical generation and oxidative stress due to increased production of plasma free radical and decreased antioxidant defense has been hypothesized to be underlying pathogenesis of diabetic complications [10-12]. Free radicals are considered to play key roles in hyperglycemia [13] hyperinsulinemia and/or insulin resistance [14].

Thereupon, it is assumed that antioxidant supplement therapies such as vitamin E, vitamin C, Chromium and zinc, reduce lipid per-oxidation and improve insulin-glucose imbalance and endothelial function. To address the current deficient knowledge of zinc supplementation effect on albuminuria and erectile dysfunction of men with diabetes mellitus this study was designed.

MATERIALS AND METHOD

Study population

We designed a double- blind, cross over clinical trial to evaluate the efficacy of zinc supplements on renal function, albuminuria and erectile dysfunction of men with type 2 DM. The participants were randomly selected from the patients introduced to diabetes clinic at vali-e-Asr hospital, as a referral academic university hospital in Zanjan.

Fifty men with type 2 DM whose albuminuria has been detected newly by two times measurement of 24-h urinary albumin excretion was enrolled in this study. Albuminuria more than 30 mg/24h in double checking and reconfirmation with ACR>=30µg/mg in the absence of other causes of albuminuria defined as diabetic nephropathy in this study. Coexistence of erectile dysfunction, using international index of erectile function -5 (IIEF-5), made the patients eligible for this study.

All the subjects with history of any forms of supplement therapy in the previous six months and those who suffered from active urinary tract infection based on urinary analysis test were excluded .We also excluded all the patients with Glomerular Filtration Rate (GFR) less than 30mL/min, or other causes of micro-albuminuria and hypogonadism , acute or chronic inflammation or active liver disease . Patients who are not satisfied to participate or not to pursue a regular observe or medication allergies happened for them, were excluded from the study.

Participants were informed about this study and assigned an informed consent. All experiments were performed in compliance with the relevant laws and institutional guidelines, and Zanjan Metabolic Research Center committee approved the study. Also, this clinical trial was registered in Iran registry of clinical trial (IRCT code: IRCT138806091179N3).

Measurements

Before and at the end of first and second phase of the study, the measurements were done. We recorded demographic, anthropometric and clinical information of patients. Blood pressure was measured by a mercury barometer after 10 min resting in sitting position; weight was measured with minimum dress by Seca scale and accuracy of 0.1kg. Height of the subjects and Body Mass Index (BMI) were calculated by standard methods.

All the subjects had laboratory measurements including FPG, HbA1C, lipid profile (total cholesterol,HDL-c, LDL-c and triglyceride), serum creatinine (Cr), serum zinc and testosterone level and also Albumin to Creatinine Ratio (ACR) at the first and after the end of first and second phase of the study. ACR and mean of them in two different urine samples were reported as final ACR result at the two stages of the study.

The entire laboratory tests were run in one laboratory center and all assays were unchanged during the project. Creatinine was measured by Jaff method formula and glomerular filtration rate by using Cockcroft_gault formula; it is GFR= ([140-age (years)] ×Weight (kg)/72×Pcr) ×0.085.

HemoglobinA1c levels were calculated by using Ione exchange method by DS5 device set. Lipid levels were measured by the colorimetric enzymatic method and by Cubas Mira, auto analyzer. Urine Albumin was measured by using Binding Site kits (UK). The inter-assay CV of the kit was 4.1% for higher

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levels of albumin and 3.1% for lower levels of it. Intra-assay CV for the kit was 2.6% for upper and lower levels of albumin. Sensitivity of zinc kit was detected 3µmol/L and normal zinc ranges from 4.1 up to 4.16µmol/L.

International Index of Erectile Function -5 (IIEF-5) was used to detect erectile function of the subjects. IIEF-5 is a sexual function questionnaire contains 15 questions with 5 or 6 choices. Score between 0-5 awards to each of the items. Impairment of erectile function was evaluated by six questions of fifteen with a maximum score of 30 and score of 20 or less than is defined a documented erectile dysfunction.

Study protocol

A randomized two- phase, double blind study was assigned. At first, participants were categorized randomly and equally into two zinc-experimental and placebo-control groups and received zinc or placebo for a three- month period. Then they were undergone 1 month (4 weeks) of wash out period. Finally, reverse placebo or zinc intervention was conducted as second phase for additional three months. Any documented side effects of the medications were recorded.

Twenty-five men in experimental group received one capsule of zinc –sulfate per day containing 30 mg elemental zinc (made by Iran_Al-havi Company) for 3months. The other twenty-five subjects in control group received placebo in similar designed to zinc capsules. List of medications were checked by a blind third physician. Patients were explained to continue their previous drugs with the same dose throughout the study. To ensure the drug taking, patients were asked to have two controlling visits during the study and bring their medication cartridge. In every visit, subjects were reevaluated for their blood pressure, weight, BMI and the side effects of patent's medication.

Statistical analysis

Data are reported as mean (± SD). The results of patient's groups were compared by using Student t tests for quantitative independent variables and Chi square test for qualitative one. The changes of variables in one group were evaluated by Paired T test. We applied mann_Witney Test and Wilcoxon Signed Ranks test to evaluate nonparametric data. Log transformation was done for ACR to change it to a normal distributed variable. We emitted confounding variables with multivariate linear regression analysis.

To determine the normal distribution of variables, Komogorov_Sminrnov test was used. Analysis was done by SPSS version 22. Significant different was defined as P is less than 0.05.

RESULTS

A total of 50 men enrolled in the study. Eight patients (4 patients in each group) were excluded from the study including 3 people with incorrect use of prescribed medication, 2 patients with refusing follow-up and 2 subjects with no consent to continue their treatment. One patient was withdrawn from the experimental group because of GI complications. Finally, forty two individuals completed the study (21 subjects in experimental-zinc group and 21 in control- placebo group). No significant differences between the two groups were found in the study population and their clinical characteristics. Basal characteristics of the two groups are illustrated in Table 1a, b.

All of participants had normal serum concentrations of Zinc and have remained in the normal range after treatment of Zinc supplements. No significant difference was found for serum Zinc concentrations between the groups at baseline and after the intervention (Figure1). No zinc toxicity was reported after zinc supplementation.

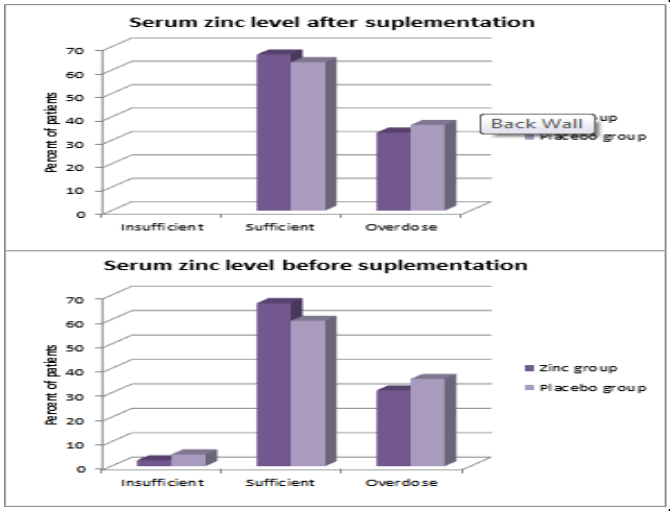

Figure1: Serum zinc level before and after zinc supplementation in both experimental and placebo group.

RENAL PARAMETER

No significant changes were seen in the GFR of the participants with Zinc supplementation. According to Table 2, although GFR showed slight decrease (-0.02 ml/min) and mild elevation (+0.88ml/min) in the experimental and placebo groups

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respectively, these changes seen were not significant (P: 0.569, P: 0.418).

Table 1a: clinical and biomedical characteristics of diabetes subjects in zinc-placebo groups before and after first 3 months intervention.

Variable	First 3-month intervention			
	Before		After	
	Zinc-group N=21	Placebo-group N=21	Zinc-group N=21	Placebo-group N=21
BMI (kg/m²)	26.9±2.5	27.5±3.3	---	---
SBP (mmHg)	138±3.15	134.1±15.3	136.2±11.9	135±13
DBP (mmHg)	85.7±3.7	82±3.7	85.2±4.7	84.5±6.1
FBS (mg/dL)	140.2±47	162.8±56.4	112±22.3	131.2±31.5
HbA1C (%)	8.9±0.8	8.8±1.5	7.7±0.6	8.2±1
Cholesterol (mg/dL)	172.7±34.6	186.9±32.5	167.7±29.8	182.3±27.5
TG (mg/dL)	171.9±73.1	211.9±108.6	172±67.3	196.9±74.4
HDL (mg/dL)	38.7±1.4	39.6±1.4	39.7±2.4	39.8±2.2
LDL (mg/dL)	102.2±28.8	104.9±30.5	95.6±26.8	103.1±26.2
ACR (µg/mg)	170.1235.1	186.1±276.9	170.7±23.7	186.1±257.5
GFR (mL/min)	39.8±8.8	43.3±17.3	39.5±8.8	44.7±14.2
Zn (µg/dL)	102.5±22.4	97.9±25	100±17.2	103±26.5
IIEF-5 Score	13.9±5.7	13.4±6.4	13.9±5.7	12.6±6.3
Testosterone (nm/dL)	9.2±2.3	9.7±2.1	9.1±4.4	8.9±2.3

*-p value is <0.05 and statistically significant. We did not find any significant difference in none of variables within 2 groups' comparison in 2 phase of intervention.

Table 1b: clinical and biomedical characteristics of diabetes subjects in zinc-placebo groups before and after second 3months intervention.

Variable	Second 3-month intervention			
	Before		After	
	Zinc-group N=21	Placebo-group N=21	Zinc-group N=21	Placebo-group N=21
BMI (kg/m²)	27.4±1.3	27±2.6	---	
SBP (mmHg)	138.1±15.3	137.9±12.4	134±10.7	139.1±16.6
DBP (mmHg)	83.8±1.7	85.9±6.8	82.2±6.6	85.8±6.6
FBS (mg/dL)	133.5±21.3	110.9±29.2	118.9±17.8	*115.6±16.8
HbA1C (%)	8±0.8	7.6±0.5	7.7±0.5	*7.4±0.3
Cholesterol (mg/dL)	174.3±28.7	169.2±30.4	171±32.5	165.9±31
TG (mg/dL)	185.5±59.9	173.7±54.4	181.6±62.2	171.1±49.5
HDL (mg/dL)	38.1±3.6	38.5±2.3	39.3±2.2	39.5±1.7
LDL (mg/dL)	99.1±27.7	95.9±27.8	95.4±29.6	92.2±27.9
ACR (µg/mg)	185±253.2	175.4±235.8	177±246.9	180.9±236.1
GFR (mL/min)	44.5±13.6	39.3±8.5	44.7±13.8	39.6±8.9
Zn (µg/dL)	98.9±14.9	99.9±12.3	104.6±21.9	100±11.2
IIEF-5 Score	13.8±6.3	13.9±5.7	13.8±6.3	13.9±5.7
Testosterone (nm/dL)	8.7±1.4	8.2±1.5	8.3±1.1	8.3±1.7

*-p value is <0.05 and statistically significant.

Mean of Albumin-Creatinine Ratio (ACR) was not different in both groups before the intervention. At the end of trial, a non significant reduction in ACR was seen in the experimental group. Mean of changes of ACR was not significantly different between experimental and control groups (-3.7 µg/mg decrement Vs 2.8µg/mg increment respectively, p: 0.13) (Table 2).

METABOLIC PARAMETERS

Mean duration of DM confirmation for both zinc and placebo groups was 10.5 and 10.9 years old respectively. Fasting Blood Glucose (FPG) did not differ between the two groups before intervention. After complement of 3 months of the intervention, FPG decreased 21.2 mg/dl (P<0.0001) with zinc supplementation. This considerable decrease was approved with significant reduction of HbA1C level (0.3 %; p<0.0001) (Table 3).

Table 2: mean of variation in clinical and biomedical parameters of total diabetes subjects after complete zinc supplementation therapy based on type of intervention.

Variable	Type of intervention		CI95%	P value
	Zinc (mean of variation)	Placebo (Mean of variation)		
SBP (mmHg)	8.7±-1.6	11.1.±1.1	-1.6_7.1	0.49
DBP (mmHg)	6.9±-0.9	5.5±0.7	-4.4_1	0.28
FBS (mg/dL)	32.5±-2.21	36.7±-13.9	-22.5_8	0.34
HbA1C (%)	0.4±-0.3	0.5±-0.4	-0.1_0.3	0.47
Cholesterol (mg/dL)	12±-1.4	11.2±-4	-2.5_4.9	0.94
TG (mg/dL)	27.7±-1.8	27.1±-8.8	-4.8_18.9	0.57
HDL (mg/dL)	2.2±1.1	2.2±0.5	-0.4_1.6	0.21
LDL (mg/dL)	12.1±-1.5	11/5±2.7	-5.7_2.8	0.36
ACR (µg/mg)	17.1±-3.7	21.4±2.8	-2_14.9	0.13
GFR (mL/min)	3.15±-0.02	6.44±0.88	-1.35_3.34	0.94
Zn (µg/dL)	18.5±1.6	14.1±1.5	-2.7_2.7	0.86
IIEF-5 Score	0	0.16±0.3	-0.03_0.08	0.32
Testosterone (nm/dL)	1.5±-0.2	1.6±-0.4	-0.5_0.9	0.57

*-p value is <0.05 and statistically significant.

Lipid profile was not different between the two groups at baseline. But, after 3 months of zinc supplementation, total cholesterol and LDL-c concentrations reduced significantly (-4.1mg/dL and -5.1mg/dL; P: 0.031 and P: 0.01 respectively). Also HDL level elevated remarkably after receiving three months of zinc supplement (P: 0.002) (Table 3). Other metabolic parameters including BMI, SBP and DBP did not show any significant changes with the intervention.

SEXUAL PARAMETERS

No significant changes were seen for serum testosterone concentrations with Zinc supplements (Table 1).

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Assessments of erectile dysfunction by IIEF-5 before the intervention demonstrated score 13.9 for zinc-experimental group and score 13.4 for placebo-control group. However, statistically significant improvements of erectile dysfunction were not presented in the groups after the intervention (Table 1).

Table 3: mean of variation in clinical and biomedical parameters of total diabetes subjects in after zinc supplementation based on time of measurement.

Variable	Time of Measurement		Mean of variation	CI95%	P value
	Before zinc supplementation	After zinc supplementation			
SBP (mmHg)	136.7±15	135.1±11.2	-1.6	-4.4_1.1	0.24
DBP (mmHg)	84.8±7.5	83.7±5.9	-0.9	-3.2_1.2	0.36
FBS (mg/dL)	136.8±35.9	115.6±20.2	* -21.2	-31.5_-10.9	0.0001>*
HbA1C (%)	8±0.8	7.7±0.6	* -0.3	-0.4_-0.2	0.0001>*
Cholesterol (mg/dL)	173.5±31.4	169.4±30.8	*-4.1	-7.9_-0.4	0.031*
TG (mg/dL)	178.7±66.4	176.9±64.4	-1.8	-10.4_6.9	0.68
HDL (mg/dL)	38.4±3.8	39.5±2.3	* 1.1	0.4_1.8	0.002*
LDL (mg/dL)	100.6±27.9	95.5±28	* -5.1	-8.9_-1.3	0.01*
ACR (µg/mg)	177.5±241.4	173.2±236	-3.7	-9_1.6	0.22
GFR (mL/min)	42.13±11.56	42.11±11.71	-0.02	-1.21_1.16	0.96
Zn (µg/dL)	100.7±18.9	102.3±19.6	1.6	-4.1_7.4	0.57
IIEF-5 Score	13.9±5.92	13.9±92.5	0	---	---
Testosterone (nm/dL)	8.9±1.9	8.7±1.9	-0.2	-0.7_0.3	0.39

*-p value is <0.05 and statistically significant.

DISCUSSION

Our clinical research investigated effect of zinc supplementation on albuminuria and sexual (erectile) dysfunction of men with DM. We didn't find any significant changes of GFR, ACR and erectile function of the subjects after seven months of follow up and with a cross over design for the Zinc supplementation and placebo. Although total ACR and GFR were decreased slightly during zinc supplementation in comparison to pre-treatment, it was not remarkable.

It is assumed that diabetic complications including nephropathy, retinopathy or erectile dysfunction are induced by production of plasma free radicals; hyperglycemia hyperinsulinemia and/or insulin resistance [10-14]. Impaired metabolism of several trace elements, like copper, zinc, manganese, and magnesium were shown to have association with impaired insulin secretion, insulin resistance, and glucose tolerance in experimental trials of animals and humans [15-23].

Several mechanisms are hypothesized for anti-oxidative effect of zinc in diabetes. Zinc maintains integrity of Cu-Zn -SOD structure [24, 25]. This complex provides protection against immune-mediated free-radical attack in the islet cells of pancreas [26]. Protection of sulfhydryl groups against oxidation, prevention in production of the free radical in the Haber Weiss cycle by competing with transition metals [27], inhibition of proteins oxidation is supposed to be the other mechanisms [28]. Zinc also plays a role as a cofactor for caspases [29] and enzymes of nucleic acid catabolism. Also, Zinc trace is supposed to reserve in cellular death by apoptosis [30].

Our results did not reveal zinc insufficiency in the studied patients. Without causing zinc toxicity, we evaluated the anti-oxidant effect of zinc supplements on complication of diabetes. GFR and Albumin/Creatinine Ratio (ACR) were not reduced significantly in our study with 30 mg/d of Zinc supplementation .This findings are not consistent with results of some studies in which the urinary albumin excretion ratio had declined in diabetic participants who had received 30 mg zinc and magnesium [31] or zinc and melatonin for three months [32] or zinc supplement alone for 3 months [33]. However, in consistent with our results; a systematic review did not confirm a role of zinc supplementation in the prevention of type 2 diabetes [34]. All of the participants in our study were Zinc sufficient. That might be deduced that zinc supplement for diabetic patients with normal zinc levels is not generally beneficial.

Diabetes as an important metabolic disorder is associated with erectile dysfunction with pathology of vascular and/or neurological damage [35]. Diabetic patients with poor control of diabetes as well as metabolic syndrome also have recorded more dysfunction of gonadal system, reduced libido and retrograde ejaculation [36].

Zinc has effect on different aspects of mammalian reproduction systems. Testicular disruption, poor semen parameters and spermatogenesis are found in males with documented zinc deficiency [37]. Zinc therapy improved sexual competence of male rats' model in Dissanayake and his colleagues' study. They found that this effect is dose dependent and an increase in testosterone level was reported after zinc therapy and considered as a beneficial mechanism of the intervention. However, elevated levels of prolactin was detected in this

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model could be considered as a responsible factor for the reduced libido [38].

All the participants in our study have suffered from erectile dysfunction according to score obtained by International Index of Erectile Function (IIEF-5) questionnaire. Nevertheless, in our study, zinc administration had no significant effect on any aspects of sexual function. Plasma basal testosterone level was also unaltered by zinc administration. These results are in the line with few previous studies in this field [39,40]. Absence of Zinc deficiency in the study population or low-dose zinc supplementation may be causes of the mentioned results. We followed our patients for three months in each phases of the study that may be not enough to see clinical improvements in impotence.

Our investigation showed that FPG and HbA1c have been modulated significantly after zinc supplementation. Contrary, there are some reports of no significant changes of FPG with zinc intake [31,32,35]. However; reduction in HbA1c was reported with zinc administration in one another study [33]. In that study, Zinc supplementation reduced HbA1c without any effect on fast plasma glucose and they have concluded that this may be due to the effect of zinc on post prandial plasma glucose concentration.

We found a significant fall in total cholesterol, LDL-c, and triglyceride concentration and also an elevation in HDL-c level after three months of zinc supplement therapy. Similar to our study, Gunasekara study showed that treatment with multivitamin-mineral with or without zinc supplement can reduce serum TG and LDL-c and increase HDL-c concentrations [36]. These observations have emphasized with a group of poor diabetes control patients who were supplemented with zinc and melatonin for a duration of three months [37,38]. However, in all of these studies co-administration of zinc with other materials like melatonin or vitamins make some confusion about the main cause of changes in lipid profile reported by them. Our results with administration of Zinc alone could be a confirmation of the effect of zinc on these metabolic components. Nevertheless, there are some studies and review reported zinc supplementation on lipid profile may delay the progression to and may beneficially have an influence on lipid profile in the patients with type 2 diabetes mellitus especially young adults [39,40].

CONCLUSION

In conclusion although zinc supplementation could make some improvement in blood glucose and lipid concentrations no improvement in GFR, ACR and erectile function of the participants could be expected with 30mg/d of elemental zinc for at least three months of treatment in diabetic patients without zinc deficiency.

LIMITATION

It was better if participants with zinc deficiency were included in the study. Zinc supplement therapy is preferred in those with zinc insufficiency and could compare with normal ones. Also, it was better that if our intervention was designed with longer duration of follow up to achieve a more complete assessment.

DECLARATION/CONFLICT OF INTEREST

This study was a residency thesis and has been supported financially by Zanjan University of Medical Sciences and registered in Iranian registry of clinical trials (www.irct.ir) with this code: IRCT138806091179N3. The authors declare that they have no conflict of interest. All material and data are available if needed to review. With the submission of this manuscript, I would like to undertake the responsibility that the above mentioned manuscript has not been published totally or partly, accepted for publication or under editorial review for publication elsewhere.

All authors confirmed manuscript and are informed about journal submission. Our study does not involve any human or animal research. We also have no copyright holder to republish previously published material, from the patient or legal guardian for publication of recognizable photographs, and/or from no specific person named in the Acknowledgments

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