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Relationship of serum zinc with high-impact clinical–metabolic profiles in Mexican population

Relación del zinc sérico con perfiles clínico-metabólicos de alto impacto en población mexicana

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ABSTRACT

Background: Zinc is related to the regulation of the different metabolic processes that are associated with diseases. **Objective:** To determine the relationship of serum Zn (S-Zn) with the high-impact clinical–metabolic profiles. **Methods:** In 191 subjects, we set the high-impact clinical–metabolic profiles and principal diagnostic parameters by principal component analysis of diagnostic parameters. S-Zn levels were measured by atomic absorption spectrophotometry. **Results:** Three high-impact clinical–metabolic profiles were determined with a cumulative variance of 52.4%. The ZnS levels were related to two profiles, "Impaired insulin action and obesity" (Profile 1), and "Impaired glycemia and middle age" (Profile 2). Profile (1) Significantly lower ZnS levels in subjects with insulin resistance (IR) when compared to subjects without IR ($p = 0.014$), significantly lower ZnS levels in subjects with abdominal obesity compared to subjects without abdominal obesity ($p = 0.006$) and, a negative and significant correlation of ZnS levels with HOMA2-IR ($p = 0.037$). Profile (2) Significantly lower ZnS levels in subjects with diabetes compared to subjects without diabetes ($p < 0.001$) and, a negative and significant correlation of ZnS levels with fasting glucose ($p = 0.032$) and HbA1c ($p < 0.028$). **Conclusions:** The decrease in zinc levels could be relationship to the presence of high-impact clinical metabolic profiles regardless of age, total fat, and gender.

Keywords: Zinc. Clinical–metabolic profile. HOMA-IR. HbA1c.

RESUMEN

Antecedentes: El zinc (Zn) está relacionado con la regulación de diferentes procesos metabólicos asociados a algunas enfermedades. **Objetivo:** Determinar la relación del Zn sérico (ZnS) con los perfiles clínico-metabólicos de alto impacto. **Métodos:** En 191 sujetos, determinamos los perfiles clínico-metabólicos de alto impacto y los parámetros diagnósticos mediante análisis de componentes principales (PCA). Los niveles de S-Zn se midieron por espectrofotometría de absorción atómica. **Resultados:** Se determinaron tres perfiles clínico-metabólicos de alto impacto con una varianza acumulada del 52.4%. Los niveles de ZnS se relacionaron con dos perfiles: «desórdenes de la acción de la insulina y obesidad» (perfil 1) y «desórdenes de la glucemia y edad media» (perfil 2). Perfil 1: niveles significativamente más bajos de ZnS en sujetos con resistencia a la insulina cuando fueron comparados con sujetos sin resistencia a la insulina ($p = 0.014$), niveles significativamente más bajos en sujetos con obesidad abdominal en comparación con sujetos sin obesidad abdominal ($p = 0.006$) y una correlación negativa y significativa de los niveles de ZnS con HOMA2-IR ($p = 0.037$). Perfil 2: niveles de ZnS significativamente más bajos en sujetos con diabetes en comparación con sujetos sin diabetes ($p < 0.001$) y una correlación negativa y significativa de los niveles de ZnS con glucosa de ayuno ($p = 0.032$) y HbA1c ($p < 0.028$). **Conclusiones:** La disminución de los niveles de Zn podría estar relacionada con la presencia de perfiles clínico-metabólicos de alto impacto independientemente de la edad, el porcentaje de grasa y el sexo.

Palabras clave: Zinc. Perfil clínico-metabólico. HOMA-IR. HbA1c.

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INTRODUCTION

Zinc (Zn) is a micronutrient associated with the regulation of different metabolic processes[1], and the decrease in serum is associated with diabetes (DT), poor glycemic control, insulin resistance (IR), hypertension (HT), and nephropathy[2-4]. In addition, Zn supplementation reduces blood lipids, helping to reduce cardiovascular risk in patients with chronic kidney disease[5,6]. However, the association of serum Zn (S-Zn) levels with clinical-metabolic diseases is complex; thus, studies are needed to aid in elucidating this association[7,8].

On the other hand, over the years, in adult Mexican population, the prevalence of obesity, DT, hypertriglyceridemia (HTGC), hypercholesterolemia (HCT), and HT has increased; moreover, during the SARS-CoV-2 virus (COVID-19) pandemic, and Mexico came to be the second highest country in fatality rates (5.7%) and in which HT, DT, and obesity were the main associated comorbidities (44.1%, 36.7%, and 20.8%, respectively)[9]. Nevertheless, to the best of our knowledge, the clinical-metabolic profiles with the greatest impact on the Mexican population and their relationship with S-Zn have not been reported.

Therefore, considering that the evaluation of the state of health and of the adjustment of methodologies for its approach constitute a challenge and that it is imperative to elucidate the complex relationship between clinical-metabolic disorders and Zn, the present study aims to determine the relationship of S-Zn with high-impact clinical–metabolic profiles present in Mexican population. This will contribute to the implementation of new treatment strategies with the consequent decrease in the prevalence of the clinical-metabolic pathologies that affect the population.

METHODS

We designed a cross-sectional study, in a population of 191 Mexican subjects from central Mexico, 18-60 years of age, men and non-pregnant women, apparently healthy, subjects with the previous diagnosis of cardiovascular, renal, inflammatory, hepatic or chronic diseaseswere excluded from the study as well as those who consumed vitamin supplements in the last year, with incomplete clinical history, under pharmacological treatment, dependent on alcohol and/or cigarettes; Subjects with hypertension, obesity, or dyslipidemia were not excluded from the study.

The study was conducted following the guidelines of the Declaration of Helsinki. The participants provided their written informed consent. The results are part of Protocol 552, approved by the Research Committee of the Faculty of Medicine, Benemérita Universidad Autónoma de Puebla, Mexico. Subjects with alcohol dependence and/or steroid use in the last year, a previous diagnosis of liver, kidney, and/or inflammatory disease, and cigarette dependence were excluded from the study.

A standardized history of each study participant was taken, which included the diagnostic parameters: gender, weight, height, percentage of total fat (TF), waist circumference (WC), systolic (SBP) and diastolic (DBP) blood pressure, and the cigarette and alcohol consumer questionnaires. Body mass index (BMI) was calculated using the Quetelet Index (weight (kg)/height in m^2).

After fasting for 12 h, blood samples were obtained from the subjects through venipuncture to later determine the diagnostic parameters. Fasting glucose (FG), HbA1c, insulin, triglycerides (TGC), total cholesterol (TC), low density lipoproteins (cLDL), high density lipoproteins (cHDL), urea, creatinine, uric acid, and blood urea nitrogen (BUN) using the periodic endpoint method according to the conventional laboratory protocols of the Puebla University Hospital, measured using the Architect System equipment (Architect I 2000 SR; Abbott Laboratories).

IR, insulin sensitivity (%S), and beta-cell function (%B) were quantified by the homeostatic model assessment (HOMA) employing the HOMA2© calculator[10]. S-Zn levels were measured by atomic absorption spectrophotometry (Perkin Elmer equipment), the assay detection limit was 0.010 μmol/L, and values of 10.4-18.4 μmol/L were considered normal.

According to the human life cycle, young adults were defined by an age of 25-44 years, and middle-aged adults were aged 45-60[11]; clinical-metabolic disorders

Table 1. Characterization with the diagnostic parameters of the clinical-metabolic alterations

Diagnostic parameter	n = 191	Normal value	Diagnostic parameter	n = 191	Normal value
Age (years)	41.6 ± 13.6	-	HOMA2-%S	74.5 ± 45.4	< 173.45
BMI (kg/m^2)	27.4 ± 4.47	< 25	HOMA2-%B	130.8 ± 79.1	< 60.0
WC (cm)	95.8 ± 11.0	< 80 women < 90 men	TGC (mg/dL)	214.9 ± 133.1	< 150
TF (%)	28.3 ± 13.1	< 25 men < 32 women	TC (mg/dL)	199.3 ± 37.6	< 200
SBP (mmHg)	116.3 ± 17.7	< 130	cLDL (mg/dl)	126.9 ± 33.2	< 130
DBP (mmHg)	76.5 ± 10.5	< 85	cHDL (mg/dL)	45.0 ± 11.8	< 40
FG (mg/dL)	108.7 ± 49.2	< 126	Urea (mg/dL)	29.1 ± 8.01	14.9-38.5
Hb1Ac (%)	6.5 ± 1.54	< 6.5	Creatinine (mg/dL)	0.88 ± 0.19	0.7-1.3
Insulin (mU/mL)	16.2 ± 13.2	< 11.25	Uric acid (mg/dL)	5.13 ± 1.47	2.4-7
HOMA2-IR	4.64 ± 5.28	< 2.0	BUN (mg/dL)	13.6 ± 3.75	9-23

Data are presented as mean ± SD (standard deviations).
BMI: body mass index; WC: waist circumference; TF: total fat; SBP: systolic blood pressure; DBP: diastolic blood pressure; FG: fasting glucose; HbA1c: glycosylated hemoglobin; HOMA2-IR: insulin resistance; HOMA2-S: insulin sensitivity; HOMA2-B: beta cell function; TGC: triglycerides; TC: total cholesterol; cLDL: low density cholesterol; cHDL: high density cholesterol; BUN: ureic nitrogen.

were defined as follows: overweight/obesity (Ov/Ob) by BMI of ≥ 25.0 kg/m^2; abdominal obesity (Ab/Ob) by WC > 90.0 cm for men and > 80.0 cm for women; high TF by TF ≥ 25% for men and ≥ 32% for women; systolic arterial hypertension by SBP ≥130 mmHg, and diastolic arterial hypertension (DAH) by DBP ≥ 85 mmHg, or the report of antihypertensive intake; hyperglycemia by GF of ≥ 126.0 mg/dL; diabetes (DT) by HbA1c ≥ 6.5%; hyperinsulinemia by insulin > 11.25 μU/mL[12]; RI by HOMA-IR ≥ 2.0[13]; beta-cell hypofunction by HOMA-%B > 60.0%; insulin hyposensitivity by HOMA-%S of ≤ 173.45, according to the method of Modan et al.[14] (values greater than the 75 profile: normal beta cell function and adequate sensitivity, values below the 75th percentile represented a beta cell function deficit and hyposensitivity); HCT by TC ≥ 200 mg/dL, high cLDL, by cLDL levels ≥ 130 mg/dL and low cHDL by cHDL levels ≤ 40 mg/dL for men and women[15] and HTGC by TGC of ≥ 150 mg/dL). Impaired renal function was defined as a glomerular filtration rate of < 90 mL/min/m^2, and high creatinine was > 1.3 mg/dL.

The high-impact clinical–metabolic profiles were obtained using the component of the principal component analysis (PCA) of diagnostic parameters. Each PCA was defined as clinical–metabolic profiles, and those with a variance of > 10% as high-impact clinical–metabolic profiles, and diagnostic parameters with absolute values of > 0.500 were defined as principal diagnostic parameters. Normality was tested using the Kolmogorov–Smirnov test. Comparison of S-Zn levels was carried out between the absence or presence of clinical-metabolic disorders using the Student's t test. The relationship of S-Zn with high-impact clinical–metabolic profiles was by the correlation (Pearson or Spearman as appropriate) between S-Zn and the principal of diagnostic parameters. The statistical software program SPSS (Statistical Package for the Social Science) version 23 was used, and a p value of 0.05 was considered statistically significant.

RESULTS

One-hundred and ninety-one Mexican subjects participated in this study, volunteers, and 58% were women and 42% men. Table 1 summarize the characterization of the diagnostic parameters of clinical-metabolic disorders. In addition, 81% of the study participants reported a family history of type

2 diabetes, 47% smoked cigarettes (28% with moderate and 19% with high consumption), and 56% consumed alcohol.

Seven clinical–metabolic profiles were obtained by PCA with a total cumulative variance of 80.52%, a sample adequacy of 0.552, and a sphericity test of $p < 0.001$; the first three components correspond to the high-impact clinical–metabolic profiles, with a cumulated variance of 52.4% (Fig. 1 and Table S1). Profile 1: "Impaired insulin action and obesity" with an individual variance of 23.38%, "Profile 2: "Impaired glycemia and middle age" with an individual variance of 15.96%, and Profile 3: "Impaired renal function" with an individual variance of 13.10%.

The clinical-metabolic disorders found were classified into high-impact clinical–metabolic profiles according to the principal diagnostic parameters (prevalence is presented in parentheses); Profile 1: IR (61%), insulin hyposensitivity (76%), hyperinsulinemia (56%), Ov/Ob (72%), Ab/Ob (78%) and DAH (32%); Profile 2: beta cell hypofunction (75%), elevated TF (74%), hyperglycemia (35%) and diabetes (23%); in addition, it was estimated that 39% of the participants belong to the group of middle-aged adults; Profile 3: impaired renal function (28%) and elevated creatinine (2%).

Regarding Zn, 87% of the population presented normal levels, with a mean concentration of 13.80 ± 2.87 μmol/L. The comparison of S-Zn levels between the presence and absence of clinical-metabolic disorders by high-impact clinical-metabolic profiles are presented at Table 2. In addition, men have higher S-Zn levels than women (14.35 ± 2.96 vs. 13.40 ± 2.75, $p = 0.024$), and no significant differences were found between relatives and non-family members with diabetes, with and without smoking, and with and without alcohol consumption (14.31 ± 3.07, 13.69 ± 2.82, $p < 0.245$; 13.73 ± 2.97, 13.88 ± 2.78, $p < 0.768$, and 13.45 ± 2.93, 14.08 ± 2.82, $p < 0.350$, respectively).

In addition to the latter, S-Zn levels are significantly correlated with principal diagnostic parameters (Table 3). Profile 1) HOMA2-IR ($p = 0.035$) and HOMA2-%S ($p = 0.038$); Profile 2) HOMA2-B ($p = 0.008$), age ($p < 0.001$), TF ($p = 0.046$), FG ($p < 0.001$), and HbA1c ($p < 0.001$), and Profile 3) creatinine ($p = 0.019$). After adjusting for age, TF, and gender, the negative correlation remained significant with HOMA2-IR ($p = 0.037$), FG ($p = 0.032$), and HbA1c ($p < 0.028$).

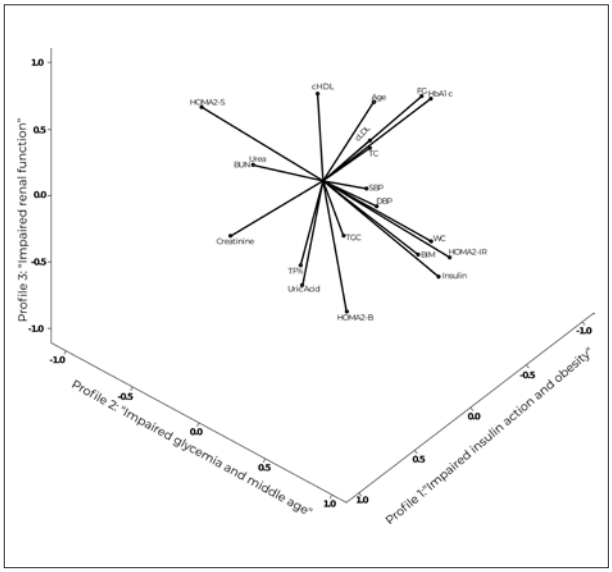

Figure 1. Clinical–metabolic profiles of diagnostic parameters by principal component analysis. The coordinates of each diagnostic parameter indicate the value that they quantitatively have by weight for each main component. The larger the value, the more the variable contributes to that component. Accumulated variance of 80.52%. Profile 1: 23.38%; Profile 2: 15.9%, and Profile 3: 13.10%. Sample adequacy of 0.552 and sphericity test of $p = 0.000$. S-Zn: serum zinc; BMI: body mass index; TF: total fat; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; FG: fasting glucose; HbA1c; HOMA-IR: insulin resistance; HOMA2-B: beta cell function; HOMA2-S: insulin sensitivity; BUN: blood urea nitrogen; TC: total cholesterol; cHDL high density lipoproteins, cLDL: low density lipoproteins, TGC: triglycerides.

Power analysis was satisfactory in both cases, without adjustment, with 1-β of 0.57, and 0.95, 0.99, respectively, and Type 2 error (β) of 0.43, 0.05, 0.01, respectively, and with adjusted 1-β of 0.58, 0.60, and 0.63, respectively, and Type 2 error (β) of 0.42. 0.40, and 0.37, respectively.

DISCUSSION

The present work reports that S-Zn levels are associated with high-impact clinical–metabolic profiles; is based on a negative and significant correlation of S-Zn levels with HOMA2-IR, FG, and HbA1c, even after adjusting for age, TF, and gender.

Table 2. Serum zinc levels and high-impact clinical–metabolic profiles

Clinical metabolic alterations	With/Without clinical metabolic alteration	S-Zn (mmol/L)	p
Profile 1: "Impaired insulin action and obesity"			
Insulin resistance	With (n = 116)	14.3 ± 2.86	0.014
	Without (n = 75)	13.3 ± 2.80	
Insulin hyposensitivity	With (n = 146)	14.4 ± 2.83	0.11
	Without (n = 45)	13.6 ± 2.87	
Hyperinsulinemia	With (n = 107)	14.2 ± 3.19	0.08
	Without (n = 84)	13.4 ± 2.56	
Ov/Ob	With (n = 137)	13.9 ± 3.09	0.83
	Without (n = 54)	13.8 ± 2.75	
Ab/Ob	With (n = 149)	14.8 ± 3.36	0.006
	Without (n = 42)	13.5 ± 2.65	
DAH	With (n = 61)	13.8 ± 2.95	0.78
	Without (n = 130)	13.6 ± 2.08	
Profile 2: "Impaired glycemia and middle age"			
Beta cell hypofunction	With (n = 143)	13.9 ± 2.32	0.62
	Without (n = 48)	13.7 ± 3.04	
Middle aged adults	With (n = 74)	12.7 ± 3.17	< 0.001
	Without (n = 117)	14.5 ± 2.51	
% Elevated TF	With (n = 142)	12.4 ± 3.07	< 0.001
	Without (n = 49)	14.2 ± 2.66	
Hyperglycemia	With (n = 67)	14.8 ± 2.37	0.36
	Without (n = 124)	14.3 ± 2.43	
Diabetes	With (n = 44)	14.3 ± 2.46	< 0.001
	Without (n = 147)	12.4 ± 3.35	
Profile 3: "Impaired renal function"			
Altered renal function	With (n = 17)	13.8 ± 2.82	0.54
	Without (n = 174)	13.6 ± 3.01	
High creatinine	With (n = 4)	13.8 ± 2.88	0.16
	Without (n = 187)	11.8 ± 2.83	

Student *t* test.
S-Zn: serum zinc; Ov/Ob: overweight/obesity; Ab/Ob: abdominal obesity; TF: total fat; DAH: diastolic arterial hypertension.

Initially through PCA, the interaction between diagnostic parameters of metabolic disorders allowed established three high impact clinical-metabolic profiles in the study population, "Impaired insulin action and obesity", "Impaired glycemia and middle age", and "Impaired renal function" a consequence of a high prevalence of obesity, IR, hyperglycemia, and alterations of renal function present in the Mexican population. It is noteworthy that the prevalence of clinical-metabolic disorders reported in this

Table 3. Correlation of serum zinc levels with principal diagnostic parameters by high-impact clinical–metabolic profiles

Profile	DDP	CC	p	CC*	p
Profile 1 "Impaired insulin action and obesity"	HOMA2-IR‡	−0.155	0.035	−0.157	0.037
	HOMA2-S‡	0.153	0.038	0.111	0.14
	WC**	−0.118	0.10	−0.047	0.53
	BMI‡	0.037	0.61	−0.008	0.91
Profile 2 "Impaired glycemia and middle age"	HOMA2-B‡	0.195	0.008	0.04	0.59
	Age**	−0.379	< 0.001	-	-
	%TF‡	0.145	0.046	-	-
	FG‡	−0.348	< 0.001	−0.161	0.032
	HbA1c‡	−0.26	< 0.001	0.161	0.028
Profile 3 "Impaired renal function:	Creatinine‡	0.17	0.019	0.061	0.42

CC: correlation coefficient; DDP: principal diagnostic parameters.
*Adjusting for age, %TF, and gender.
**Pearson correlation.
‡Spearman correlation.
The variables are presented in descending order according to the absolute value obtained in the PCA. BMI: body mass index; TF: total fat; WC: waist circumference; FG: fasting glucose; HbA1c: glycosylated hemoglobin; HOMA2-IR: insulin resistance; HOMA2-β: beta cell function; HOMA2-S: insulin sensitivity.

study is not surprising, because various surveys have shown their progressive increase over the years, in Mexico[9].

Later, it was established that S-Zn plays a relevant role in the pathophysiology of two of the high impact profiles, "Impaired insulin action and obesity, "Impaired glycemia and middle age"; because a decrease in zinc levels is observed in subjects with clinical-metabolic disorders associated with each profile and because the S-Zn levels correlate in a negative and significant way with the increase in the serum levels of principal diagnostic parameters of these profile, even after adjusting for age, TF, and gender.

Specifically, we determined that S-ZN plays a key role in the presence of "Impaired insulin action and obesity" profile, due to its decrease in states of IR, hyperinsulinemia, and overweight/obesity, and that it correlated negative and significant with IR determined by HOMA2-IR, even after adjusting for age, TF, and gender. This association of S-ZN with IR is previously reported in the population with prediabetes by Kant et al.[16] who established that, after adjusting for multiple confounding variables, IR is associated with low levels of S-ZN (CI: −0.007 - −0.0002, p = 0.04).

We also determined that S-ZN plays an important role in the presence of "Impaired glycemia and middle age" profile; due to its reduction in the presence of diabetes, and to the negative and significant correlation of zinc with FG and with HbA1c, even after adjusting for age and FT; several studies support our finding for example, Sanghani et al.[17] reported that, in patients with diabetes with and without complications, Zn and HbA1c are negatively correlated (r = −0.505, p < 0.01; r = −0.62.6, p < 0.01), and Grădinaru et al.[2] proposed that Zn is a biomarker of the persistence of hypoglycemia, due to its antiglycation action, an action proposed because Zn negatively correlates with advanced glycosylation end products (advanced glycation end-products [AGE]; *r* = −0.454, p < 0.02) and because the Glucose/Zn ratio correlates positively with AGE (*r* = 0.767, p < 0.001).

To the best of our knowledge, this is the first study that determines the high-impact clinical–metabolic profiles of the Mexican population and their relationship with Zn with statistical satisfaction. The results presented in this study show that the decrease in S-ZN levels is associated with the presence of high-impact clinical–metabolic profiles in the Mexican population.

According to earlier studies, the elevation in this micronutrient in serum is relationship to the increase in the insulin signaling pathway[18,19] as well as with the decrease in fasting glucose and hemoglobin glycation[2]. In this context, Hassan et al.[20] reported that Zn supplementation (25 mg) for 12 weeks, in patients with diabetes, decreases HbA1c levels when compared to the group that received the placebo ($p = 0.0008$). Therefore, the implementation of new treatment strategies based on Zn supplementation could contribute to the decrease in the prevalence of high-impact clinical–metabolic profiles, increasing the quality of life of the Mexican population.

However, because our study population presented average of S-ZN levels in normal and because the relationship of zinc with the biochemical parameters studied here can be modified in the presence of other alterations such as anemia, the intake of foods rich in Zinc, and the polymorphisms related to the capture and function of this micronutrient, it is necessary to carry out studies to determine the relationships demonstrated in this study with a population with low levels of S-ZN, in another type of population with zinc supplementation and/or with other pathological states that could play a significant role in this relationship. Furthermore, this study is cross-sectional, and it has limitations; therefore, studies that determine causality would be necessary to reinforce our findings.

Taking into consideration all the above, we can conclude that the S-Zn levels influences the presence of high-impact clinical–metabolic profiles in the Mexican population because Its decrease is related to the increase of HOMA2-IR, FG, and Hb1Ac, principal diagnostic parameters involved in the pathophysiology of clinical-metabolic disorders of high prevalence in the in Mexican population such as IR, obesity, and diabetes.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL DISCLOSURES

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

SUPPLEMENTARY DATA

Supplementary data are available at DOI: 10.24875/RME.22000041. These data are provided by the

corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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