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Study of Inter-relatedness between Hepato-renal Indices and Essential Minerals during the Last Trimester of Pregnancy

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Authors' contributions

This work was carried out in collaboration among all authors. Author OTO designed the study, collected the data and processing, literature search, writing of first draft. Author RAO did the analysis or interpretation of data, literature search. Author GUJ did the data collection and literature search. Author AAI did the study concept, literature search, final draft. All authors read and approved the final manuscript.

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ABSTRACT

Purpose: Earlier on, it was reported that altered hepato-renal parameters and depletions of some nutrients co-existed at third trimester among the study participants. Yet the role low levels of nutrients played in altered hepato-renal axis (i.e. a possible association between the two) was not

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investigated. Even though liver is known for its physiologic importance in the metabolism of various metals and abnormal levels of certain elements also induce alterations in physiologic processes in specific organs. The study is aimed at investigating correlation between nutritional parameters (total protein, albumin, calcium, magnesium) and hepato-renal indices (alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, urea and creatinine) at the last trimester of pregnancy.

Study Design: This is a cross-sectional study.

Methods/Participants: Forty pregnant women in the third trimester (29 weeks to term) were recruited as test group while another group of 40 women (age-matched, non-pregnant) served as control. 5 mL of blood was collected and used for estimation of nutritional indices and hepato-renal markers. Information on birth weight was obtained. Data were analyzed using Pearson's correlation coefficient. $P \leq 0.05$ was considered significant.

Results: Data obtained from the study revealed that there were no correlations between any nutritional marker and hepato-renal indices. Similarly, nutritional markers were not correlated with birth weight.

Conclusion: There is no indication that there is a relationship between abnormal nutritional markers and indices of nephro-hepatic activities in third trimester women that had earlier being reported to feature abnormal liver and kidney function.

Keywords: Third trimester pregnancy; correlation; hepato-renal markers; nutritional indices.

1. INTRODUCTION

While mineral depletions during gestation has been linked to inadequate intake in the developing world, data also reveal that in the developed world pregnant women that were studied through various research efforts manifested significantly lower levels of different micronutrients compared with their non-pregnant counterparts in the same environment [1-3]. In many high-income countries, even with year-round dietary diversity, dietary counseling during pregnancy, and widespread intake of fortified foods (especially as it obtains in the USA), few clinical micronutrient deficiencies still exist during pregnancy [4]. Generally, micronutrients are essential physiologically, especially for processes such as bone development, protective effect on the skin and mucosa, and strengthening of the immune system. Their other important roles like maintenance and growth of epithelial tissue, formation of normal teeth and hair, as well as their functions during normal embryonic stage [5-7] cannot be over-emphasized.

Although depletions of nutrients are attributed to fetal demand, especially for processes such as cell differentiation and tissue formation, yet the slight physiologic alteration to organs/tissues as described by Soma-Pillay et al. [8] that characterized different critical stages of pregnancy, may play a role also in low levels of minerals such as Ca, Fe, Cr and Mg. Such background knowledge becomes imperative particularly as both liver and kidney have been linked with micronutrient metabolism. Some of the indispensable roles liver plays in the maintenance of essential trace elements homeostasis include synthesis of protein carriers of trace elements such as zinc (Zn), iron (Fe), copper (Cu) etc, which facilitate transport or distribution of these trace elements and excretion of trace elements such as Cu and magnesium (Mg) through the bile [9-11].

In most cases, comparative statistical (e.g. Student's t test) analyses have been used to understand the depleted micronutrients status of different stages of pregnancy whether in apparently healthy or those with different medical events. Yet it may not be incongruous to understand the relationships between hepato-renal parameters and minerals that are essential during pregnancy such as Fe, Ca, Cr, and Mg by using an ideal statistical analysis like Pearson's correlation coefficient. This study is designed to further fathom the relationship between nephron-hepatic indices and Fe, Ca, Cr, and Mg as well as correlation between birth weight and these mineral at the last trimester of pregnancy

2. MATERIALS AND METHODS

2.1 Ethical Consideration

Consideration was given to ethical concerns as they related with the study carried out on pregnant participants and those in group control. Health Research Ethics Committee of Hospital Management Board Asubiaro, Osogbo Osun state, Nigeria gave approval for the study

implementation. Information obtained from participants were preserved with meticulous confidentiality while informed consents were also gotten individually from participants.

2.2 Sampling Technique

Simple random sampling technique of all participants that presented at study locations.

2.3 Study Design

Cross-sectional comparative study.

2.4 Study Participants

Eighty third-trimester pregnant women partook in the study, consisting of 40 women in each group i.e. test (pregnant) and control (non-pregnant). They were recruited at different study settings i.e. antenatal clinics of maternity centers within Osogbo metropolis. Exclusion criteria were as follows: passive or active exposure of participants to various elements either at home or workplace as well as through lifestyle (passive smoking, cosmetic product); presence of hepatic, renal, or any other existing chronic disease that affects minerals as well as hepatic-renal markers. Those on nutrient supplements were also excluded. Moreover, women in control group were not menstruating at the time of sample collection.

2.5 Collection and Storage of Biological Samples

Each of the participants provided 5 mL of venous blood which was collected with minimum stasis from the antecubital fosa using pyrogen free needle and syringe. This was carefully dispensed into dry, anti-coagulant free bottles. Blood samples were left to clot, retracted and centrifuged at 2000 X g for 10 minutes to obtain sera that were decanted and preserved at -20^0C prior to analyses. Iron, calcium, magnesium and chromium were assayed using Inductive Computerized Plasma Emission Spectrometry while standard photometric methods (kits supplied by Randox) were used to assay hepatic (aspartate and alanine aminotransferases, alkaline phosphatase, bilirubin) and renal (urea, creatinine) parameters. The mineral analyses were done using Inductive Computerized Plasma Emission Spectrometer (Beckam ICP-OES 4000 series, UK).

2.6 Statistical Analysis

Statistical Package for Social Sciences (SPSS), version 15 was used for the inferential statistics. Pearson's correlation coefficient was considered appropriate for correlation study between nutritional indices and birth weight [expressed in kg] or hepato-renal markers. Significance was set at $P \leq 0.05$.

3. RESULTS

Descriptive statistics of parameters used for correlation study are itemized below:

1. Total protein in pregnant women (62.10 ± 0.73 g/L) and control group (75.98 ± 1.15 g/L)
2. Albumin in pregnant women (36.95 ± 1.16 g/L) and control group (44.45 ± 1.05 g/L)
3. Globulin pregnant women (24.98 ± 1.30 g/L) and control group (31.53 ± 1.18 g/L)
4. Iron in pregnant women (57.61 ± 3.59 ug/dL) and control group (118.02± 14.50 ug/dl)
5. Calcium concentration in pregnant women (1.26 ± 0.04 mmol/L) and control group (1.78 ± 0.05 mmol/L)
6. Magnesium in pregnant women (1.71 ± 0.45 mmol/L) and control group (3.60 ± 0.19 mmol/L)
7. Chromium in pregnant women (3.83 ± 0.11 nmol/L) and control group (0.42 ± 0.12 nmol/L)
8. Urea in pregnant women (5.00 ± 0.06 mmol/L) and control group (4.52 ± 0.08 mmol/L)
9. Creatinine in pregnant women (0.88 ± 0.02 mmol/L) and control group (0.73 ± 0.03 mmol/L)
10. Alkaline phosphatase in pregnant women (64.05±18.90 IU/L) and the control group (45.40±18.02 IU/L)
11. Aspartate aminotransferase concentration in pregnant women (21.38 ± 5.70 U/L) and control group (27.63 ± 4.80 U/L)
12. Alanine aminotransferase in pregnant women (18.25± 4.73 U/L) and control group(16.35± 4.11 IU/L)
13. Total bilirubin in pregnant women (2.02 ± 0.67 mg/dl) and control group (0.70 ± 0.03 mg/dl)
14. Birth weight- Range 1.94-2.78 kg

As shown in Table 1, correlation study showed relationship between total protein, albumin and globulin (r=0.703) and (r=0.809) respectively. There was correlation also between albumin and alkaline phosphatases (r =0.451) as well as between urea and creatinine (r = 0.409). Meanwhile, alanine aminotransferase showed

inverse correlation with alkaline phosphatase (r = -0.344) but positive correlation with aspartate aminotransferase (r = 0.372). Iron showed correlation with calcium and magnesium (r= 0.484) and (r =0.484) respectively. Similar correlations were observed in control group as shown in Table 2. For example total protein was positively correlated with albumin and globulin. Other correlations between urea and Mg; ALP and total protein or albumin; AST and ALT or Fe; Ca and Fe as well as Mg and Fe were presented in Table 2.

Correlation of birth weight and hepato-renal markers was not significant for urea (r= .011); creatinine (r= -.099, p= .544), AST (r= -.102; p= .531); ALP (r= -.147, p= .366); ALT (r= .162, p= .317); total protein (r= .033, p= .840); albumin (r= -.092, p= .571); globulin (r= .122, p= .452).

Pearson's correlation study of birth weight and the following nutritional parameters showed no relationship between birth weight and each of the following: total protein, iron, calcium, and chromium as well as globulin as shown in Figs. 1-5 below.

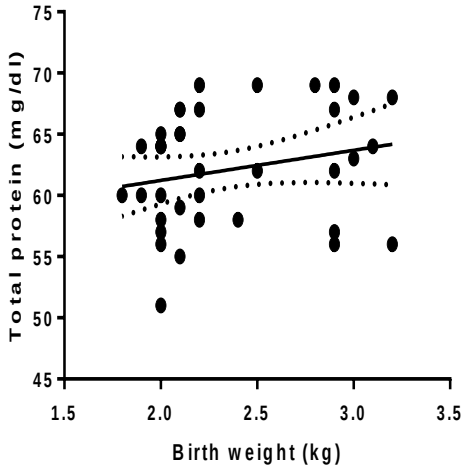

Fig. 1. Correlation between total protein and birth weight
Birth weight and total protein- r= .033; P= .840

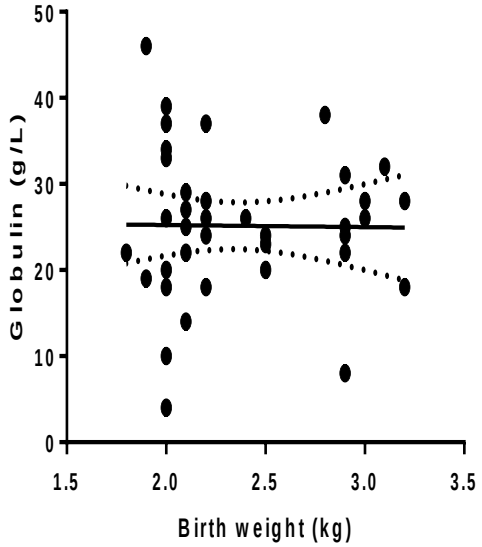

Fig. 2. Correlation between globulin and birth weight
Birth weight and globulin- r= .122; P= .452.

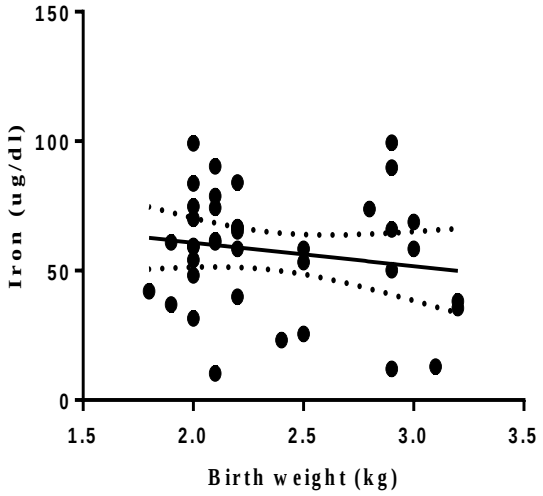

Fig. 3. Correlation between iron and birth weight
Birth weight and Iron- r= .085; P= .864

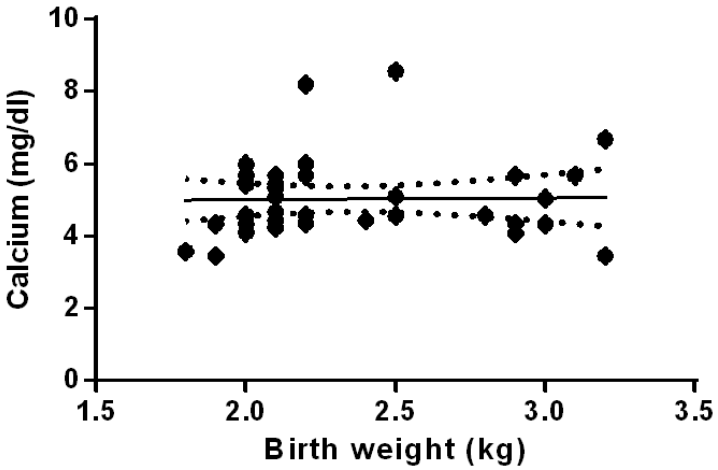

Fig. 4. Correlation between calcium and birth weight
Birth weight and calcium- r= .096; P= .557

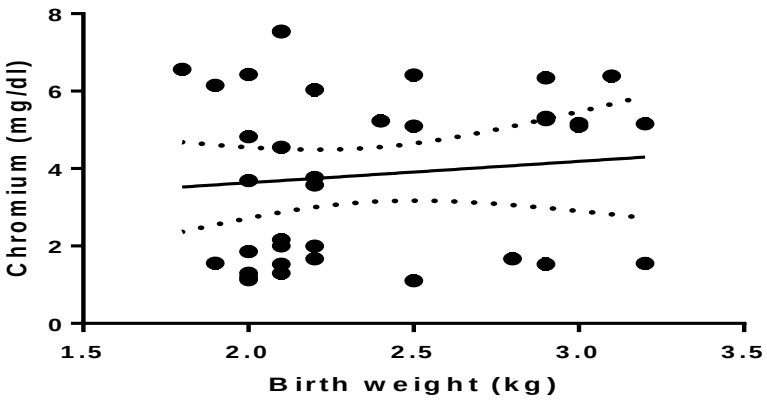

Fig. 5. Correlation between chromium and birth weight
Birth weight and chromium- r= .108; P= .507

Table 1. Correlation study of estimated laboratory parameters among pregnant women

	TP	Alb	Glob	Urea	Creat	ALP	AST	ALT	Fe	Ca	Mg
TP	1										
R		.703**	.809**	.163	-.101	.135	.065	.179	-.233	-.229	-.229
P		.001	.001	.115	.536	.404	.609	.224	.147	.155	.154
Alb		1									
R	703**		.152	242	.101	.451**	-.171	-.042	-.223	-.241	-.241
P	.001		.350	.133	.537	.003	.291	.797	.166	.134	.134
Glob		.152	1								
R	.809**	.350		-.052	-.223	-.184	.232	.002	-.140	-.119	-.119
P	.001			.478	.166	.255	.149	.987	.390	.463	.464
Urea				1							
R	.163	.242	-.052		.490**	.198	-.098	-.035	-.066	-.189	-.189
P	.115	.133	.478		.001	.219	.547	.232	.685	.241	.241
Creat					1						
R	-.101	.101	-.223	.490**		.172	-.060	.145	.065	-.037	-.037
P	.536	.537	.166	.001		.288	.711	.373	.686	.817	.817
ALP					.172	1					
R	.135	451**	-.184	.198	.288		-.272	-.344*	-.092	.076	.817
P	.404	.003	.255	.219			.089	.029	.574	.639	.076
AST							1				
R	.065	-.171	.232	-.098	-.060	-.272		.372*	.241	.149	.148
P	.609	.291	.149	.547	.711	.089		.018	.134	.360	.360
ALT								1			
R	.179	-.042	.002	-.035	.145	-.344*	.372*		.226	.017	.016
P	.224	.797	.987	.232	.373	.029	.018		.161	.917	.917
Fe									1		
R	-.233	-.223	-.140	-.066	.065	-.092	.241	.226		.484**.002	.484**
P	.147	.166	.390	.685	.686	.574	.134	.161			.002
Ca							.149			1	
R	-.229	-.241	-.119	-.189	-.037	.076	.360	.017	484**		1.000*
P	.155	.134	.463	.241	.817	.639		.917	.002		.002
Mg											1
R	-.229	-.241	-.119	-.189	-.037	.817	.148	.016	484**	1.000*	
P	.154	.134	.464	.241	.817	.076	.360	.917	.002	.002	

Abbreviations: TP- total protein; Alb-albumin; Glob- globulin; Creat.- creatinine; ALP- alkaline phosphatase; AST-aspartate aminotransferase; ALT- alanine aminotransferase
***Correlation is significant at the 0.01 level (2-tailed)*
**Correlation is significant at the 0.05 level (2-tailed*

Table 2. Correlation study of estimated laboratory parameters among non-pregnant women

	TP	Alb	Glob	Urea	Creat	ALP	AST	ALT	Fe	Ca	Mg
TP	1										
R		.561**	.797**	-.168	.208	.369*	.039	.182	-.165	-.016	-.095
P		.000	.000	.300	.197	.019	.811	.260	.308	.924	.559
Alb		1									
R	.561**		-.053	-.278	.033	.540**	.015	.075	-.040	.077	-.009
P	.000		.745	.082	.840	.000	.926	.646	.807	.637	.958
Glob			1								
R	.797**	-.053		0.000	.227	.051	.036	.165	-.170	-.075	-.109
P	.000	.745		0.999	.159	.757	.825	.308	.293	.646	.505
Urea				1							
R	-.168	-.278	0.000		.293	-.228	.032 .843	.038	-.271	-.288	-.346*
P	.300	.082	0.999		.066	.156		.815	.091	.071	.029
Creat					1						
R	.208	.033	.227	.293		.021	-.024	036	-.020	068	.019
P	.197	.840	.159	.066		.900	.884	.104	.900	.675	.729
ALP						1	-.074	.127	.024	.025	-.042
R	.369*	.540**	.051	-.228	.021		.651	.434	.883	.887	.796
P	.019	.000	.757	.156	.900						
AST							1				
R	.039	.015	.036	.032 .843	-.024	-.074		346*	-.369*	-.299	-.305
P	.811	.926	.825		.884	.651		.029	.019	061	.056
ALT								1			.207
R	.182	.075	.165	.038	.036	.127	.346*		-.298	-.253	.166
P	.260	.646	.308	.815	.104	.434	.029		.062	.115	
Fe									1		
R	-.165	-.040	-.170	-.271	-.020	.024	-.369*	-.298		.725**	.094
P	.308	.807	.293	.091	.900	.883	.019	.062		.000	.780
Ca					-.068					1	
R	-.016	.077	-.075	-.288	.675	.025	-.299	-.253	725**		.815**
P	.924	.637	.646	.071		.887	061	.115	.000		.000
Mg								.207	.094		1
R	-.095	-.009	-.109	-.346*	.019	-.042	-.305	.166	.780	.815**	
P	.559	.958	.505	.029	.729	.796	.056			.000	

Abbreviations: TP- total protein; Alb-albumin; Glob- globulin; Creat.- creatinine; ALP- alkaline phosphatase; AST-aspartate aminotransferase; ALT- alanine aminotransferase
***Correlation is significant at the 0.01 level (2-tailed)*
**Correlation is significant at the 0.05 level (2-tailed*

4. DISCUSSION AND CONCLUSION

Earlier report on the same set of participants, (using comparative inferential statistics), revealed that significantly lower levels (albumin, total protein) or higher activities (AST, ALT, ALP) of hepatic markers existed among the pregnant participants compared with control, which was assumed or postulated to occur from anatomical and physiological changes that characterize gestation, an important process during pregnancy required in order for the mother to nurture and accommodate the developing foetus. These alterations start after conception and impact not only liver and kidney but all the organs of the body. Especially for the kidney, anatomical changes were reported by Soma-Pillay et al. [8] to involve altered renal blood flow which sometimes results in an increase in renal size of 1–1.5 cm that reaches maximal size by mid-pregnancy.

While this is mostly speculative, there is sufficient evidence that anatomical changes induced during gestation have been linked with modifications in certain metabolic activities or processes. For example, during gestation, arterial under-filling in pregnancy leads to the stimulation of arterial baroreceptors, activating the renin–angiotensin–aldosterone and the sympathetic nervous systems, which in turn causes non-osmotic release of arginine vasopressin from the hypothalamus. A situation that has been described to give rise to water and (the cation)-sodium retention by the kidneys and produce a hypervolaemic, hypoosmolar condition that is a common feature of gestation [12]. Yet no correlation was observed between urea and cations such as Fe, Ca, and Mg.

Studies have shown that women from Nigeria and other low-income countries begin first trimester malnourished, and that the requirement of gestation can aggravate micronutrient deficiencies suggest a probable cause of significantly low levels of several nutrients during gestation as several studies have revealed [13-16]. Birth weight was the only birth outcome explored in the study, some other studies though incorporated a more elaborate panel of birth outcomes to better understand the dynamics between maternal health (specifically essential element levels) and birth outcomes. While the significant low birth weight co-existed with depleted Fe, Mg, Cr and Mg status as previous described [16] and have been widely speculated to occur as a result of the fetal demand, the present report study did not reveal a correlation between birth weight and any of the essential elements. That there was no relationship between abnormal birth weight and each of the minerals using Pearson's correlation analysis does not mean the combined effects of all could not have given rise to such observation i.e. depleted levels of Cr, Fe, and Ca eliciting low birth weight among the neonates.

Although the present data did not show that there was a relationship between low mineral levels and low birth weight, the implication of low birth weight are diverse. Low birth weight (LBW, <2.5 kg) which can result from decrements in either fetal growth or length of gestation, increases the risk of infant morbidity and mortality [17]. The functions of the elements such as cell signaling, motility, proliferation, differentiation and apoptosis that regulate tissue growth, function and homeostasis, etc, may have significant implications if not on birth weight but on other indicators of fetal health.

Yet there is need to exercise caution as concentrations of micronutrient frequently employed as biomarkers that guide estimation of status and therefore physiological need, can be affected by plasma volume expansion and other adaptations to the pregnant state. Contrary to the present study, Eshak et al. [18] reported that unsatisfactory maternal micronutrient nourishment might reduce birth size. Further evidence for a role for depleted micronutrient levels in the processes that give rise to low birth weight was also offered by Wang et al. [19]. Their study revealed that antenatal supplement trials, sometimes of a single nutrient e.g. iron or folic acid, had significant effects on birth weight. While low birth weight has been linked with increase in infant morbidity and mortality in the short term, increase risk of certain chronic disease later during adulthood has been speculated also.

This small pilot study becomes expedient, in part because the costs of assessing biochemical indicators of individual micronutrients are exorbitant which have led to few population estimates of deficiencies during pregnancy. This unfortunate situation has given rise to the term 'hidden hunger', [20], referring to a lack of knowledge as to the extent and consequences of this nutritional burden. Additionally, while in literature there is well established relationship between the liver and essential elements, there were no correlation between any of the hepatic

parameters and the estimated elements. This suggests that co-existence of two abnormal conditions does not indicate that a correlation or even association between them really exists. This is despite the fact that AST and Fe and urea and Mg featured correlation among non-pregnant control group.

The fact that there were comparable correlation results between similar sets of parameters in both test and control group suggest that such correlations have nothing to do with gestation but may be a reflection of normal natural interaction that take place among biomolecules. The positive correlation between albumin and alkaline phosphatase as well as between AST and ALT is quite understandable, they are hepatic markers and it therefore shows a relationship with liver function, and may also explain the correlation between urea and creatinine with respect renal function. Meanwhile the inverse relationship between ALP and AST is difficult to interpret

It is quite understandable that there is correlation between ALT and AST or ALP, these respond to hepatic manifestations similarly. The correlation between Fe and Ca as well as Mg while it may have nothing to do with hepatic function (no correlation between any element was observed with hepato-renal marker), it is quite understandable they are all diet-derived. This is best supported by similar correlational observations present in control group.

The fact that there were no correlations between hepato-renal markers and birth weight suggest that the hepatic and renal indices played no role in the birth range of 1.94-2.78 kg observed among the neonates. Moreover, it seems reasonable to speculate that lack of correlation between nutritional markers and birth-weight indicate that the maternal nutritional status probably did not play direct role in birth weight range observed. And while hepatic and renal axis play significant role in metabolism of many elements, no correlation was observed. The study revealed no correlation between nutritional indices and hepato-renal markers on one hand as well as birth weight on the other, signifying that the low birth weight range may not be related with the levels of nutritional markers.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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