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*Original Research*

# *Diadema setosum* Flour to Improve Growth Hormone, Brain Cell Necrosis, and Liver Cell Inflammation in Male Wistar Rats (*Rattus norvegicus*): A Local Food Intervention Model for Chronic Malnutrition

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**ABSTRACT**

**Background:** Chronic malnutrition impairs growth hormone secretion and induces histological damage in vital organs such as the brain and liver. This study aimed to analyze the effects of *Diadema setosum* flour administration on growth hormone levels and the histological profiles of liver and brain tissues in chronically malnourished rats. **Methods:** This experimental study utilized a pretest-posttest control group design involving 15 male *Rattus norvegicus* (aged 5–7 weeks) subjected to chronic malnutrition. Subjects were randomly divided into five groups (n = 3): K+ (standard feed + 1 mL growth hormone injection), K- (standard feed only), F1 (standard feed + 1 g/day *Diadema setosum* flour), F2 (standard feed + 2 g/day *Diadema setosum* flour), and F3 (standard feed + 3 g/day *Diadema setosum* flour). Interventions lasted for 12 days. Blood growth hormone (GH/IGF-1) levels were quantified using ELISA, while liver (central veins, hepatocytes, and inflammation) and brain (neurons, cortex, pyramidal cells, and neuroglia) tissues underwent histological examination. **Results:** Histological evaluations revealed normal cell structures in the K+ group, whereas the negative control (K-) exhibited severe brain cell necrosis, pyknotic neuroglia, and high-grade liver inflammation (+4). Treatment groups showed progressive improvement: F1 displayed necrosis with +3 liver inflammation; F2 showed cortex necrosis with +2 inflammation; and F3 demonstrated completely normal brain cell architecture alongside minimal liver inflammation (+1). **Conclusion:** The administration of *Diadema setosum* flour at an optimal dose of 3 grams per day effectively maintains, prevents, and repairs tissue damage resulting from chronic malnutrition.

**Keywords:** Brain histology, Chronic malnutrition, *Diadema setosum* flour; Growth hormone; Liver histology

## 1. INTRODUCTION

Stunting is a pathological condition resulting from failure in growth and development in children, which is directly caused by chronic malnutrition and infectious diseases, which in the end can affect the quality of life, growth and development of children.[1,2] Growth failure is associated with congenital growth hormone deficiency, can result in

damage to various cells, tissues and organs; including the liver and brain which are at risk of developing pathological conditions.[3,4] The main function of growth hormone (Somatropin) is to promote linear growth such as body composition, cell turnover, and body metabolism that support normal growth. Chronic malnutrition occurs due to the unavailability of chemical elements that play a role in contributing chemical raw materials to biological processes in the body as a whole. Furthermore, cells that do not receive nutritional elements for continued metabolism will gradually die through various cell death mechanisms such as inflammation and necrosis.[4,5]

Necrosis is a response to cells that are injured, resulting in changes in lifestyle and cell death. Necrosis can be caused by internal and external factors. Internal factors, for example infections that cause functional disease which can lead to nerve damage and result in disruption of nutritional distribution; while external factors include trauma and poisoning, such as exposure to chemicals. Cell death through inflammation or necrosis mechanisms will be detrimental to the body, because cells cannot send signals to the body, so they are unable to play a role in immune mechanisms, so the damage becomes more widespread.[6]

The gonads of sea urchins (*Diadema setosum*) are a type of Echinoidea that has been widely used as a source of nutrition for coastal communities and is very beneficial for health. All parts of the body *Diadema setosum* can be used as a source of nutrition, antioxidants and antibacterials.[7,8] Currently, *Diadema setosum* has been developed as an ointment for wound healing, proven to be antidiabetic and a source of collagen.[9,10]

The nutritional content in *Diadema setosum* includes carbohydrates, protein, fat, vitamins, minerals, and bioactive compounds.[7] This wealth of nutrients is known for its benefits in tissue maintenance, as well as repair of cell and tissue damage. Amino acids, fatty acids, vitamins and minerals as well as non-nutritional chemical components have been known to play an important role in the survival of organisms.[11]

Based on the remarkable nutritional and bioactive potential of *Diadema setosum* outlined above, exploring its therapeutic application for tissue maintenance and repair in vital organs, such as the brain and liver, is both timely and essential. Therefore, this study aims to evaluate the efficacy of *Diadema setosum* flour administration on growth hormone levels, brain cell necrosis, and liver cell inflammation in a chronic malnutrition rat model. The findings of this study are of significant importance as they provide robust scientific evidence supporting the utilization of local marine food resources as a sustainable, cost-effective functional intervention to mitigate growth failure and systemic cellular damage caused by chronic malnutrition, ultimately paving the way for novel nutritional strategies in public health and clinical dietary management.

## 2. METHODS

### *2.1 Study Design and Setting*

This study employed an in-vivo experimental laboratory design with a pretest-posttest control group approach. The research was conducted in Kendari, Southeast Sulawesi, Indonesia. Histopathology preparation and microscopic evaluations were performed at the Pathology Laboratory, Universitas Hasanuddin, Makassar, Indonesia.

### *2.2 Population, Sample, and Randomization*

The study population comprised male Wistar rats (*Rattus norvegicus*). A total of 15 healthy male Wistar rats aged 5 to 6 weeks were selected using a simple random sampling method. The rats were acclimatized under standard laboratory environmental conditions (12-hour light/dark cycle, room temperature 25oC).

### *2.3 Inclusion and Exclusion Criteria*

Inclusion criteria: Male Wistar rats aged 5–6 weeks, exhibiting chronic malnutrition defined by a body weight loss 20% lower than the age-matched standard weight (achieved through a 24-day preliminary dietary energy restriction protocol). Exclusion criteria: Rats showing anatomical deformities, active physical signs of non-malnutrition infection, or severe illness prior to intervention. rop-out criteria: Rats that died during the 12-day intervention period.

### *2.4 Intervention Details and Food Formulation*

*Diadema setosum* flour was prepared using standardized conventional procedures. Fresh *Diadema setosum* specimens were harvested from the coastal waters of Soropia around Bokori Island, Konawe Regency, Southeast Sulawesi. The collected sea urchins were retained in shell containers, steam-blanched at 1000C for 5 minutes to prevent degradation, air-cooled, and dried in an electric oven. The dried gonads were pulverized using a dry grinder and sieved to yield fine flour (Figure 1).

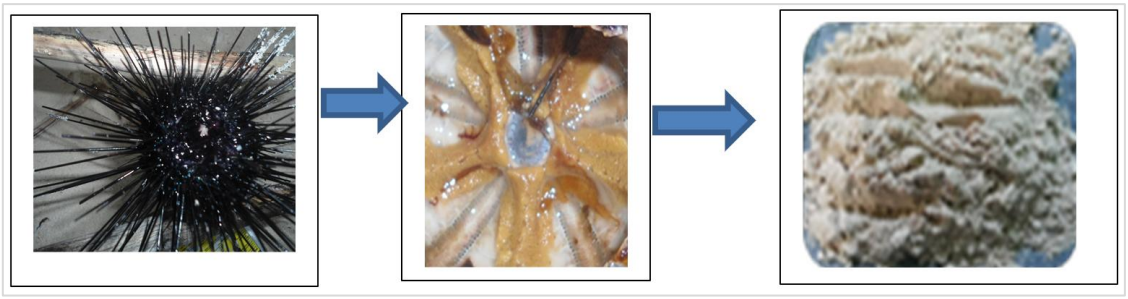


**Figure 1.** Processing flowchart of fresh *Diadema setosum* into functional flour

The 15 malnourished rats were randomly allocated into five equal treatment groups (n=3 per group) and received their respective diets for 12 days:

1. Positive Control (K+): Standard feed + growth hormone injection (1 mL/day).
2. Negative Control (K-): Standard feed only.
3. Intervention 1 (F1): Standard feed + *Diadema setosum* flour at 1 g/day.
4. Intervention 2 (F2): Standard feed + *Diadema setosum* flour at 2 g/day.
5. Intervention 3 (F3): Standard feed + *Diadema setosum* flour at 3 g/day.

### *2.5 Data Collection and Biochemical Measurement*

Following completion of the 12-day intervention, animals were humanely euthanized for organ sampling. Serum samples were collected every 7 days (3 total measurement points across the study) for serum Growth Hormone (GH) quantification using an Enzyme-Linked Immunosorbent Assay (ELISA) kit following the manufacturer's protocol. Briefly, standards and serum samples (50 L) were incubated in antibody-coated microplates for 2 hours at 37oC, washed using wash buffer, incubated with detection antibody-enzyme conjugate for 1 hour, treated with tetramethylbenzidine (TMB) chromogenic substrate for 20 minutes in the dark, and terminated using a stop solution. Absorbance (Optical Density) was measured at 450 nm using a microplate reader.

### *2.6 Outcome Measurement and Histopathological Evaluation*

Brain and liver tissues were harvested immediately post-euthanasia and fixed in 10% buffered neutral formalin (BNF) for 24 hours. Automated tissue processing (Leica TP1020) was conducted over 18.5 hours encompassing dehydration (graded ethanol 70% to absolute), clearing (xylene I–III), liquid paraffin infiltration (57–59oC), and paraffin embedding (Leica EG1160). Paraffin blocks were sectioned at 2–5 m thickness using a microtome, mounted on glass slides, incubated at 50oC, and stained with Hematoxylin and Eosin (H&E).

Microscopic evaluation was conducted in a blinded manner:

**Brain Histology Scoring**

Evaluated across neuroglia, neurons, cortex, and pyramidal cells based on cell integrity:

Score 0: Complete cell necrosis across the observed field.

Score 1: Presence of 1 healthy cell.

Score 2: Presence of 2 healthy cells.

Score 3: Presence of 3 healthy cells.

Score 4: All observed cells demonstrate normal histology.

**Liver Histology Scoring**

Graded microscopically based on the severity/extent of inflammatory cell infiltration:

0: There is no evidence of inflammation

+1: Minimal/localized focal inflammation.

+2: Moderate inflammatory infiltration.

+3: Marked/broad inflammation.

+4: Severe/diffuse necro-inflammatory changes.

### *2.7 Data Analysis and Statistics*

Data were processed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to present mean standard deviation (SD) for quantitative growth hormone levels and ordinal scores for tissue damage. Normality of continuous biochemical data was verified using the Shapiro-Wilk test. Differences in serum growth hormone levels across groups and time points were analyzed using One-Way Analysis of Variance (ANOVA) followed by Tukey's post-hoc test (or Repeated Measures ANOVA for longitudinal time points). Histological ordinal scores (brain necrosis and liver inflammation scores) among groups were evaluated using the non-parametric Kruskal-Walli's test, followed by Mann-Whitney U post-

hoc pairwise comparisons. A p-value <0.05 was considered statistically significant.

### *2.8 Ethical Practice*

All experimental protocols involving animal handling, induction, intervention, and euthanasia strictly complied with the international guidelines for the care and use of laboratory animals (NIH Publication No. 85-23, revised 1985). This research was formally reviewed and granted ethical approval by the Health Research Ethics Committee of University Jendral Sudirman number: 115/EC/KEPK/2020.

## 3. RESULTS

### *Subject Characteristics and Preliminary Model Validation*

Before the main intervention, baseline characteristics of the experimental subjects were evaluated. A preliminary study involving healthy male Wistar rats (n = 75, aged 3–4 months) established a normal baseline growth hormone level of 0.7414 ± 0.255 mcg/mL. After following a 24-day low-energy dietary induction protocol, the rats experienced chronic malnutrition, characterized by a body weight loss of 20% compared to age-matched standards, resulting in a significant reduction in serum growth hormone levels to 0.075 ± 0.078 mcg/mL ($p < 0.05$). This basal reduction confirms the successful establishment of endocrine dysfunction and metabolic stress characteristic of chronic malnutrition.

### *Effects of Diadema setosum Flour on Growth Hormone Levels and Tissue Histology*

Following the 12-day intervention across the five experimental groups, biochemical and histopathological evaluations demonstrated distinct dose-dependent improvements.

**Table 1.** Serum growth hormone levels for 0 day, 7 day and 12 days among experimental groups after 12 days of intervention.

| Group | n | Serum growth hormone level (mcg/mL) | | |
|---|---|---|---|---|
| | | 0 day | 7 days | 12 days |
| K+ (Standard + GH 1 mL) | 3 | 0.059 ± 0.187 | 1.725 ± 0.082 | 1.585 ± 0.307 |
| K- (Standard Feed Only) | 3 | 0.107 ± 0.078 | 0.047 ± 0.005 | 0.230 ± 0.017 |
| F1 (Standard + 1 g/day flour) | 3 | 0.059 ± 0.035 | 1.424 ± 0.074 | 0.731 ± 0.061 |
| F2 (Standard + 2 g/day flour) | 3 | 0.055± 0.015 | 1.5251 ± 0.068 | 0.773 ± 0.061 |
| F3 (Standard + 3 g/day flour) | 3 | 0.051± 0.038 | 1.651± 0.097 | 0.824± 0.001 |
| Mean | 15 | 0.0665±0.0375 | 1.274±0.647 | 0.829±0.465 |
| *p*-value* | | 0.369> sig (0.005) | 0.000< 0.005 | 0.000<0.005 |

*Note: Data analyzed using One-Way ANOVA (for parametric growth hormone levels) Significant difference set at $p < 0.05$ after 7 day and 12 days intervention.

**Table 2.** Brain cell necrosis scores, and liver inflammation grades among experimental groups after 12 days of intervention. (histological interpretation using a single slide)

| Group | Brain cell necrosis score | Description of brain cell necrosis | Liver inflammation grades | Description of liver inflammation |
|---|---|---|---|---|
| K+ (Standard + GH 1 mL) | 4 | All observed cells demonstrate normal histology. | 0 | No evidence of inflammation. |
| K- (Standard Feed Only) | 0 | Complete cell necrosis across the observed field. | +4 | Severe/diffuse necro-inflammatory changes |
| F1 (Standard + 1 g/day flour) | 0 | Complete cell necrosis across the observed field. | +3 | Marked and widespread inflammation. |
| F2 (Standard + 2 g/day flour) | 2 | Two healthy cells were observed. | +2 | Moderate inflammatory cell infiltration |
| F3 (Standard + 3 g/day flour) | 4 | All observed cells demonstrated normal histological features. | +1 | Minimal, localized focal inflammation. |

That the F1 treatment group, which was given standard feed and *Diadema setosum* flour 1 gram/day, could not produce the expected effect in the sense that it was still the same as the negative control group (K-)

which was only given standard feed. In both groups, necrosis was still found in neuron cells, cortex, pyramidal cells and neuroglia. When *Diadema setosum* flour was added to 2 grams/day in the F2 treatment group, normal conditions were found in neuron cells and pyramid cells. Meanwhile, when *Diadema setosum* flour was added again to 3 grams/day, all cells were in normal condition, including neuron cells, pyramid cells, cortex and neuroglia. The condition of the brain cells in the F3 treatment group was completely the same as the condition in the positive control group (K+) which was given standard feed and 1 ml growth hormone injection. Thus, the most effective dose was in the F3 treatment group (Figure 2).

Figure 3 shows that chronic malnutrition causes inflammation in liver tissue, as seen in the negative control group (K-) with extensive inflammation at level 4+. In the positive control group given 1 ml of growth hormone, inflammation was suppressed until it reached level 0 (no visible inflammation in the liver tissue). In the F1 treatment group, which was given standard feed and 1 gram of *Diadema setosum* flour/day, inflammation could be suppressed to level 3+ (slightly better than the K- group which was only given standard feed. When *Diadema setosum* flour was added to 2 grams/day in the treatment group F2, inflammation decreased to level 2+. Meanwhile, when *Diadema setosum* flour was added again to 3 grams/day, inflammation further decreased to level 1+ (almost close to the K+ group).

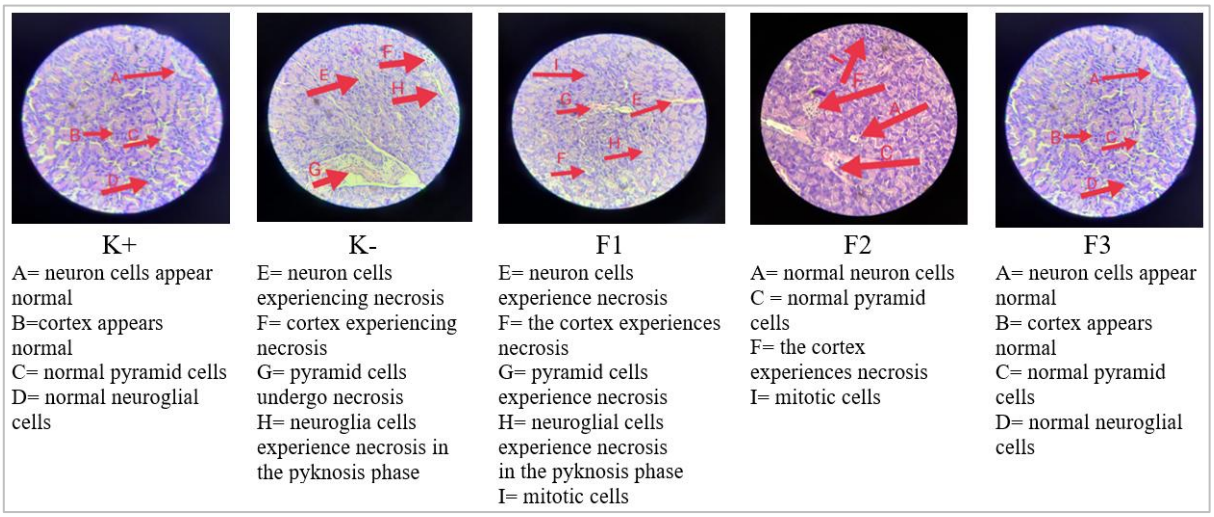



**Figure 2.** Comparison of the incidence of Inflammation in Liver cells between groups

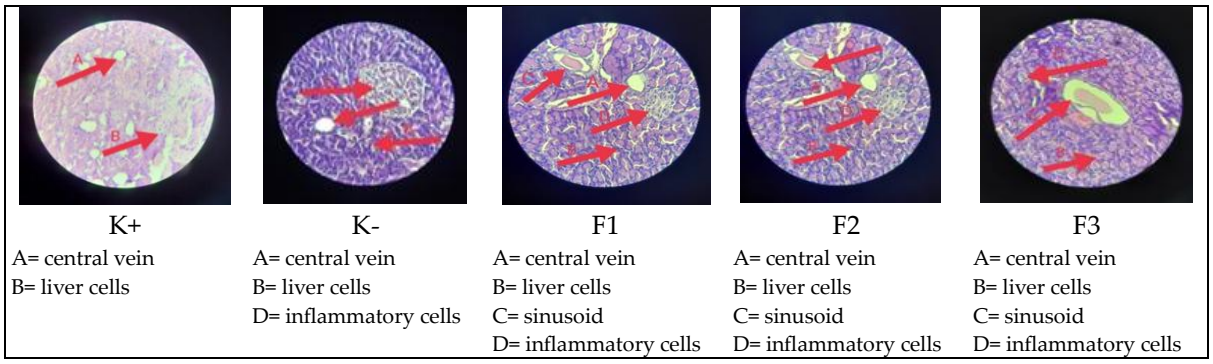



**Figure 3.** Comparison of liver tissue condition between groups

## 4. DISCUSSION

Chronic nutritional deficiency in experimental models is strongly associated with the dysregulation of growth hormone levels, widespread brain cell necrosis, and hepatic tissue inflammation. Cell necrosis and chronic inflammation inevitably trigger cellular demise, culminating in systemic metabolic failure and impaired growth. In this study, the administration of exogenous growth hormone to the positive control group (K+) effectively restored endocrine balance and suppressed tissue injury across neurons, cortical layers, pyramidal cells, and neuroglia, aligning with established endocrine and neuroprotective frameworks.

Conversely, the negative control group (K-), subjected exclusively to standard restricted feeding without intervention, exhibited severe pathological manifestations, including complete neuronal necrosis and extensive, diffuse necro-inflammatory changes in the liver reaching grade +4. The lowest intervention dosage of *Diadema setosum* flour (F1 at 1 g/day) proved insufficient to reverse these degenerative alterations, yielding histological outcomes comparable to the untreated K- group. However, escalating the dosage to 2 g/day (F2) and 3 g/day (F3) elicited dose-dependent tissue recovery. Specifically, F2 restored normal histology in neuronal and pyramidal cells and reduced hepatic inflammation to grade +2, while F3 achieved complete tissue protection across all brain cell types (Score 4) and suppressed liver inflammation down to minimal focal levels (grade +1), mirroring the pristine histological profile observed in the positive control group (K+).

These histological findings are corroborated by the serum Growth Hormone (GH) profiles. While baseline GH levels showed no significant variation across groups ($p > 0.05$), 12 days of intervention revealed a highly significant elevation ($p < 0.001$) in all *Diadema setosum*-supplemented groups compared to K-. Notably, the F3 group achieved mean GH levels closest to the positive control group (K+), demonstrating that an optimal daily dose of 3 grams matches the efficacy of direct hormonal therapy.

At the molecular and biochemical level, *Diadema setosum* flour serves as a rich reservoir of functional nutritional components, including essential amino acids (such as lysine, methionine, threonine, valine, arginine, histidine, tryptophan, and phenylalanine), non-essential amino acids, essential fatty acids (lauric, myristic, palmitic, and oleic acids), and vital growth minerals like calcium and zinc.[12,13] Arginine and histidine are particularly critical for pediatric growth, serving as secretagogues for growth hormone and precursors for tissue synthesis.[14] Chronic malnutrition disrupts cellular survival by depleting these essential substrates, increasing oxidative stress, and up-regulating pro-inflammatory.[15]

Furthermore, the vulnerability of specific neural and hepatic structures dictates the clinical severity of malnutrition. Neurons, particularly vulnerable pyramidal cells within the cerebral cortex, are highly sensitive to energy deprivation, where necrosis leads to irreversible cognitive and functional deficits.[16] Concurrently, the liver acts as the primary metabolic hub responsible for processing macronutrients and synthesizing endocrine mediators such as IGF-1; hepatic inflammation impairs these vital homeostatic pathways.[17] By supplying a comprehensive matrix of antioxidants, essential amino acids, and micronutrients, *Diadema setosum* flour provides the necessary biochemical building blocks to suppress oxidative stress, down-regulate inflammatory cascades, reactivate hepatic protein synthesis, and restore the endocrine axis. Consequently, these findings validate the potential of *Diadema setosum* flour as an effective, food-based therapeutic model for mitigating chronic malnutrition and its systemic neurological and hepatic complications.

Despite the promising findings regarding the therapeutic potential of *Diadema setosum* flour, several methodological limitations of this study must be acknowledged. First, the rats were housed in group cages rather than individually, preventing the precise measurement of individual feed intake and consumption volume for each subject. Second, the histological and molecular analyses were limited to a single sample per group for tissue cross-sectioning without replication across multiple blocks or markers, which restricts the broader quantitative generalizability of the tissue-specific evaluations. Future investigations should incorporate individual housing systems and expanded sample replication to validate these metabolic and histological outcomes more comprehensively.

Ultimately, the dose-dependent efficacy demonstrated by *Diadema setosum* flour in reversing both endocrine dysregulation and multi-organ tissue damage establishes a strong biological foundation for addressing chronic malnutrition, as synthesized in the following conclusion.

## 5. CONCLUSION

A notable finding in this study is that the administration of *Diadema setosum* flour at a dose of 3 grams per day exhibited therapeutic efficacy comparable to that of conventional hormonal intervention in mitigating chronic energy deficiency in Wistar rats. This optimal dosage successfully maintained circulating Growth Hormone (GH) levels, preserved neuronal structure by significantly suppressing brain cell necrosis, and attenuated hepatic inflammation. This equivalence suggests that the complex matrix of macro-nutrients, essential amino acids, and bioactive mineral components (such as zinc and selenium) naturally present *in Diadema*

*setosum* acts synergistically. Rather than merely supplying raw nutritional substrates, these bioactive compounds appear to modulate endocrine feedback loops and down-regulate inflammatory pathways (such as NF-κB) with an efficacy rivaling targeted hormonal therapy, highlighting its strong potential as an accessible, food-based alternative for managing chronic malnutrition and its systemic complications.

## Ethical Approval

This research was formally reviewed and granted ethical approval by the Health Research Ethics Committee of University Jendral Sudirman number: 115/EC/KEPK/2020.

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## Competing Interests

All the authors declare that there are no conflicts of interest.

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## Underlying Data

Derived data supporting the findings of this study are available from the corresponding author on request.

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